[Frontiers in Bioscience 8, d306-356, January 1, 2003]

THE CADHERIN SUPERFAMILY IN NEURAL DEVELOPMENT: DIVERSITY, FUNCTION AND INTERACTION WITH OTHER MOLECULES

Shinji Hirano [1, 2, 4], Shintaro T. Suzuki [3, 4] and Christoph Redies [5]

[1] "Recognition and Formation" PRESTO, Japan Science and Technology Corporation (JST), Saitama 332-0012, Japan, [2] Institute for Developmental Biology, Kobe RIKEN, 2-2-3 Minatojima-minamimachi, Chuou-ku, Kobe-City 650-0047, Japan, [3] Department of Bioscience, School of Science and Technology, Kwanseigakuin University, Sanda-City 669-1337, Japan, [4] Institute for Developmental Research, Aichi Human Service Center, Kasugai-city Aichi 480-0392, Japan, [5] Institute of Anatomy, University Hospital Essen, Hufelandstrasse 55, D-45122 Essen, Germany

TABLE OF CONTENTS

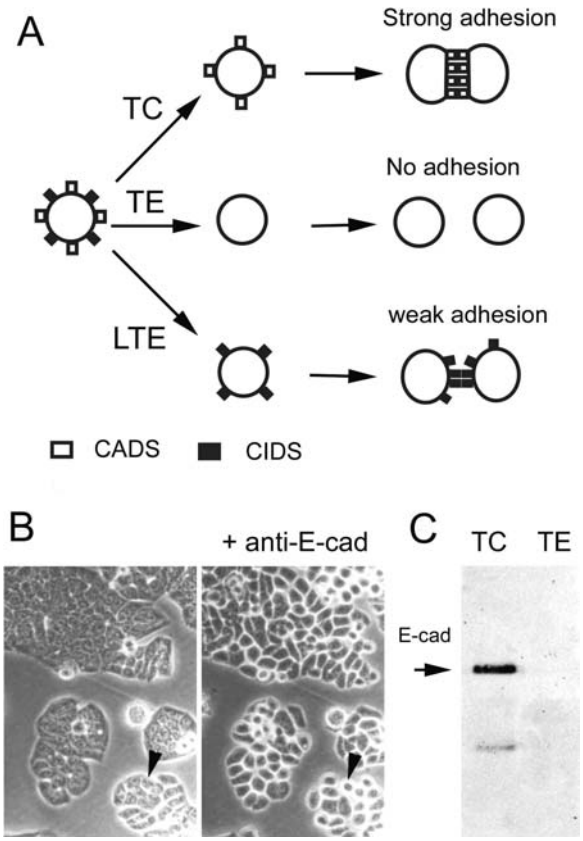

Figure 1. Discovery of classic cadherins. (A) Assays using differential sensitivity to trypsin revealed the existence of two independent adhesion systems (CADS, calcium-dependent adhesion system; CIDS, calcium-independent adhesion system). Cells treated with trypsin in the presence of Ca^{2+} (TC) adhere strongly to one another, whereas cells treated with low concentrations of trypsin in the absence of Ca^{2+} (LTE) adhere only weakly. Cells treated with trypsin in the absence of Ca^{2+} (TE) do not show adhesive activity. (B) Anti-human E-cadherin antibody (HECD-1) inhibits cell-cell adhesion of colon cancer HT29 cells (right panel). The adhesion of HT29 cells in the absence of HECD-1 is very tight and results in a smooth surface for each colony (left). In contrast, cell-cell junctions are weakened in the presence of HECD-1 antibody, resulting in clear outline for individual cells (right). The arrowheads point to a cell that has rounded up due to indirect inhibition of cell-substrate adhesion with the antibody. (C) Immunoblot analysis shows that HECD-1 detects E-cadherin only in the sample treated with TC, but not in the sample treated with TE. The lower band is an 80-kDa proteolytic fragment of E-cadherin.

1. ABSTRACT

Cell-cell interactions are crucial steps for the development of the highly complex nervous system. A variety of cell-cell adhesion molecules of the cadherin superfamily have been found to be expressed in the developing nervous system. Recently it was proposed classic cadherins are involved in various aspects of neural development such as regionalization, brain nucleus formation, neurite outgrowth, target recognition and synaptogenesis. Classic cadherins preferentially bind to the same cadherin subtype ("homophilic adhesion"), and this binding specificity can provide an “adhesive code” that can account for various aspects of neural morphogenesis. In addition, novel members of the cadherin superfamily are also involved in various steps of neural development. The function of these cadherins molecules is orchestrated in the cellular context by a complex network of signaling pathways such as the small GTPase pathway. Here, we will review the molecular properties of the cadherin superfamily and their coordinated roles in the formation of the nervous system along with the accumulated knowledge in non-neuronal systems.

2. INTRODUCTION

Cell-cell interactions are indispensable in the development of multicellular organisms. Before cell adhesion molecules were identified, a number of pioneering studies using various experimental, and theoretical approaches had been performed to reveal the importance of cell-cell adhesion and possible principles of adhesion mechanisms (see reviews, for example, 1-4). Since then, various types of cell adhesion molecules have been discovered including selectins, molecules of the immunoglobulin (Ig) family and cadherins.

The molecules, which today are called (classic) cadherins, were identified independently by several groups in the early 80’s using various approaches (see Table I). Edelman and coworkers identified L-CAM (chicken E-cadherin) by using an antibody that inhibited cell adhesion (5). Jacob and Kemler’s group discovered uvomorulin (now called E-cadherin) as a cell-adhesion molecule that mediates compaction in early embryos (6). Similarly, Birchmeier and Beherens’ group discovered Arc-1 using a blocking antibody specific for canine epithelial cells (7). On the other hand, Lilien’s group identified a 130-kDa molecule (now called N-cadherin) in the chick neural retina that was protected by Ca^{2+} from proteolysis (8). Damsky’s group also identified Cell-CAM 120/80 from a peptide released into the culture medium (9). Geiger and coworkers then identified A-CAM (now called N-cadherin) as a molecule that was localized at adherens junctions (10).

Takeichi found differences in trypsin resistance between different cell types, depending on whether calcium ions were present in the culture medium or not (Figure 1; 11). Consequently, he proposed that there are 2 adhesion systems, a calcium-dependent cell adhesion system (CADS) and a calcium-independent adhesion system (CIDS; 3, 11). It was revealed that CADS mediates strong adhesion and is temperature sensitive (3, 11). He noticed also that there was specificity in binding among different cell types (12). As a result of a quest for the molecules responsible for these differences, his group was able to show that a molecule termed E-cadherin was responsible for the calcium-dependent aggregation of the F9 teratocarcinoma cell line (13). In the course of their studies, they also identified other cadherin subtypes in different tissues, e.g., in neural tissue: N-cadherin; in

Table 1. Members of the cadherin superfamily

Type	Protein name	Synonymous of protein name or aliases of gene name	Human gene name
CLASSIC CADHERINS			
Type I			
	E-cadherin	uvomorulin , L-CAM, Cell CAM120/80 , Arc-1, cadherin-1	CDH1
	N-cadherin	ACAM, N-Cal-CAM, cahderin-2	CDH2
	P-cadherin	B-cadherin, XB/U-cadherin, cadherin-3	CDH3
	R-cadherin	cadherin-4	CDH4
	M-cadherin	cadherin-15	CDH15
	C-cadherin	EP-cadherin (Xenopus specific), close to E-cadheirn and P-cadherin	
Type II			
	Cadherin-5	VE-cadherin	CDH5
	Cadherin-6	K-cadherin	CDH6
	Cadherin-7	chicken cadherin-7 ortholog	CDH7
	Cadherin-8		CDH8
	Cadherin-9	T1-cadherin	CDH9
	Cadherin-10	T2-cadherin	CDH10
	Cadherin-11	OB-cadherin, VN-cadherin	CDH11
	Cadherin-12	BR-cadherin, N-cadherin 2	CDH12
	Cadherin-18	Cadherin-14, EY-cadherin	CDH18
	Cadherin-19	similar to cadherin-7	CDH19
	Cadherin-20	F-cadherin, mouse cadherin-7 ortholog, FIB2	CDH20
	Cadherin-22	PB-cadherin ?, LOC58532	CDH22
T-CADHERIN			
	T-cadherin	cadherin-13, H-cadherin	CDH13
PROTOCADHERINS			
7-repeat-type			
	Protocadherin 1	Protocadherin42	PCDH1
	NF-protocadherin	BH-protocadherin	PCDH7
	Protocadherin 9		PCDH9
	Protocadherin-X	PCDHX, PCDHY	PCDH11
6-repeat-type			
Protocadherin 2 family *		**Protocadherin γ family**	
	Protocadherin 2A	Protocadherin 2, Protocadherin 43, Protocadherin γC3	PCDHGC3
	Protocadherin 2B	Protocadherin 4	
	Protocadherin 2C		
	FIB3	Protocadherin γ A12	CDH21
	*Total: γ A subfamily 12 members (in human); γ B subfamily 7 members (in human); γ C subfamily 3 members (in human)		
Protocadherin 3 family **		**Protocadherin β family**	
	Protocadherin 3		
	**Total: 15 members (in human)		
CNR family***		**Protocadherin α family**	
	*** Total: 13 members (in human)		
Ohters			
	OL-protocadherin	Protocadherin-10, KIAA1400	PCDH10
	PAPC	Arcadlin, Protocadherin 8	PCDH8
	VE-cadherin-2	Protocadherin-12, LOC51294	PCDH12
	Protocadherin 16	FIB1 (partial), CDH19	PCDH16
	Protocadherin 17	Protocadherin 68	PCDH17
	Protocadherin 18	KIAA1562	PCDH18
	PrCAD		
	MT-protocadherin	KIAA1775	
LARGE CADHERINS			
	FAT	CDHF7, ME5	FAT
	FAT2	MEGF1, CDHF8,	FAT2
	Cadherin 23	USH1D, DFNB12	CDH24
	Protocadherin 15		PCDHA15
	ProtocadherinLKC	FLJ20124	FLJ20124
FLAMINGO			
	Flamingo	CELSR3, MEGF2, CDHF11, EGFL1	HFMI1
	Celsr1	FMI2, CDHF9, ME2	CELSR1
	MEGF3	CELSR2, KIAA0279, CDHF10, EGFL2	CELSR2
DESMOSOMAL CADHERINS			
Desmogleins			
	Desmoglein I	CDHF4, DG1, DSG	DSG1
	Desmoglein II	CDHF5, HDGC	DSG2
	Desmoglein III	pemphigius vulgaris antigen, CDHR7	DSG3
Desmocollins			
	Desmocollin I	DG2/DG3, CDHF1	DSC1
	Desmocollin II	DG2, DSC3, DGII/III, CDHF2	DSC2
	Desmocollin III	DSC4, DSC2, CDHF3, HT-CP	DSC3
ret			
	ret	MEN2A, HSCR1, MEN2B, MTC1, PTC, CDHF12	RET
LI-CADHERIN			
	LI-cadherin	cadherin-17	CDH17
	Ksp-cadherin	cadherin-16	CDH16
CALSYNTENIN			
	Calsyntenin-1		KIAA0911
	Calsyntenin-2		CS2
	Calsyntenin-like protein		KIAA0726
OTHERS OR UNCLASSIFIED			
	μ-protocadherin		MUCDHL
	Cadherin-like 24	CDH25	CDH24
	Cadherin-like protein VR20	FLJ20047	VR20
	Cadherin-like 22		data not available

placental tissue: P-cadherin and in retina: R-cadherin (14-16). By sequence analysis, it turned out that these cadherins (now called classic cadherins) constitute a molecular family (Table I).

With the development of molecular biological techniques, in particular the polymerase chain reaction (PCR) method, more and more cadherins were discovered (17). In addition, the notion of the cadherin superfamily has been established by the finding of novel classes of cadherin-like molecules, including desmosomal cadherins, Fat and protocadherins (Figure 2, Table I; see section 5 for each molecule; 18-20). To discriminate these molecules from "classic" cadherins, we call them "non-classic cadherins" collectively. Most types of these cadherins are expressed in the nervous system.

In this review, we will first give a brief overview of the cadherin superfamily (section 3) and then describe classical cadherins (section 4) and other molecules in the cadherin superfamily (section 5) in more detail. However, because a vast amount of knowledge about classical cadherins has been accumulated over the past 20 years, we will use almost half of this review to deal with this type of cadherin molecules. However, at this point we would like to point out that we will also present a description of cadherin properties revealed from studies using non-neuronal systems. We believe that the basic properties of cadherins in these non-neuronal systems are also important for the understanding of the neural functions of cadherins.

3. OVERVIEW OF THE CADHERIN SUPERFAMILY

3.1. Members of the cadherin superfamily

The cadherin superfamily includes a variety of molecules that are all characterized by so-called "cadherin domains" or "cadherin repeats" in their extracellular domain (Figure 2 and Table 1; see section 4.2.1 for cadherin domain). The different cadherins are classified according to the gross organization of their extracellular cadherin motifs as well as to sequence similarities in their extracellular and cytoplasmic domains (21-25). For historical reasons, cadherins have been divided into 2 classes: classic cadherins (see section 4) and nonclassic cadherins (see section 5). The word "cadherin" is often used for only classic cadherins, whereas the nonclassic ones have been subsumed under various other names (see Table I). Classic cadherin is so defined by its characteristic cytoplasmic sequence for binding to catenins (see section 4.2.3. for catenins). Non-classic cadherins comprise a variety of molecules (Figure 2 and Table 1; 23, 25). Major subfamilies are the desmosomal cadherins, Fat-type cadherins, Ret, protocadherins, flamingo and calsyntenin (CDH11 in *C. elegans*; 23, 25). Protocadherins are cadherins with 6 or 7 consecutive cadherin repeats (section 5.2). Fat-type cadherins are huge cadherins with many cadherin-repeats (section 5.3). Flamingos are cadherins with a seven-pass transmembrane domain and a huge extracellular domain (section 5.4). Desmosomal cadherins (desmocollins and desmogleins) are cadherins localized at desmosomes (section 5.5.). Ret is a unique cadherin with a tyrosine kinase domain (section 5.6). Calsyntenin is a unique cadherin with 2 cadherin motifs (section 5.8). Each member of the non-classic cadherin family has a considerably different cytoplasmic region, suggesting that these cadherins have also functions different from those of the classic cadherins. Thus, it may be better to regard these molecules as independent subfamilies within the non-classic cadherin family. Accordingly, we will now discuss the roles of each of the types of cadherin independently.

3.2. Evolution of cadherins

The evolution of cadherin molecules can be deduced from their molecular structure and genomic organization. The genes of classic cadherins have many introns at positions that vary with respect to the extracellular cadherin domains (Figure 3; 26). In contrast, the genomic structure of nonclassic cadherins shows that their extracellular domain has few introns (27). In particular, it is notable that the extracellular domain of most protocadherins is encoded by a single exon (Figure 3; 28). Therefore, it has been speculated that the cadherin domains were multiplied first to generate the various cadherin molecules, and that introns were introduced after the emergence of the classic cadherins (22, 26).

Cadherins must have evolved when or before the animal kingdom appeared, because cadherins are found throughout all of the animal kingdom. However, the precise origin of cadherins has not been determined yet. Cadherin-like molecules have been found also in the slime mold *Dictyostelium* (29). Moreover, β-catenin also exists in *Dictyostelium*, and it is responsible for the formation of adherens junction (AJ)-like junctions in this species (30). It has been difficult, however, to demonstrate how the cadherins of *Dictyostelium* and animals might have evolved from a common ancestor (29).

Although their evolutionary origin is unknown, cadherins have expanded very successfully in the animal kingdom. At least 15 and 13 cadherins have been found in the genome of *C. elegans* and *D. melanogaster*, respectively (25). About one-third of the cadherins in these species can be classified into the several major subgroups mentioned above, whereas the other two-thirds represent very diverged members of the cadherin superfamily, suggesting species/lineage-specific evolution (24, 25). It is notable that *C. elegans* has only 2 classic cadherins and that *D. melanogaster* has only 3 of them. This finding indicates that classic cadherins alone cannot account for all the specificities of cell-cell adhesion in animal morphogenesis. Cadherins, which are common to vertebrate and invertebrate species, include classic cadherins, Fat-type cadherins, flamingo cadherins, calsyntenin and Ret (23-25, 31). These cadherins seem to have evolved in the early phase of evolution. In contrast, desmosomal cadherins and protocadherins are found only in the vertebrate lineage, suggesting their specific function in vertebrate development (24, 25, 31). Desmosomal cadherins seem to have evolved from the common ancestor of the vertebrate classic cadherins because they show a substantial sequence similarity (23). Protocadherins seem to have evolved rapidly within the vertebrate lineage because more than 50 protocadherins are arranged in 3 clusters

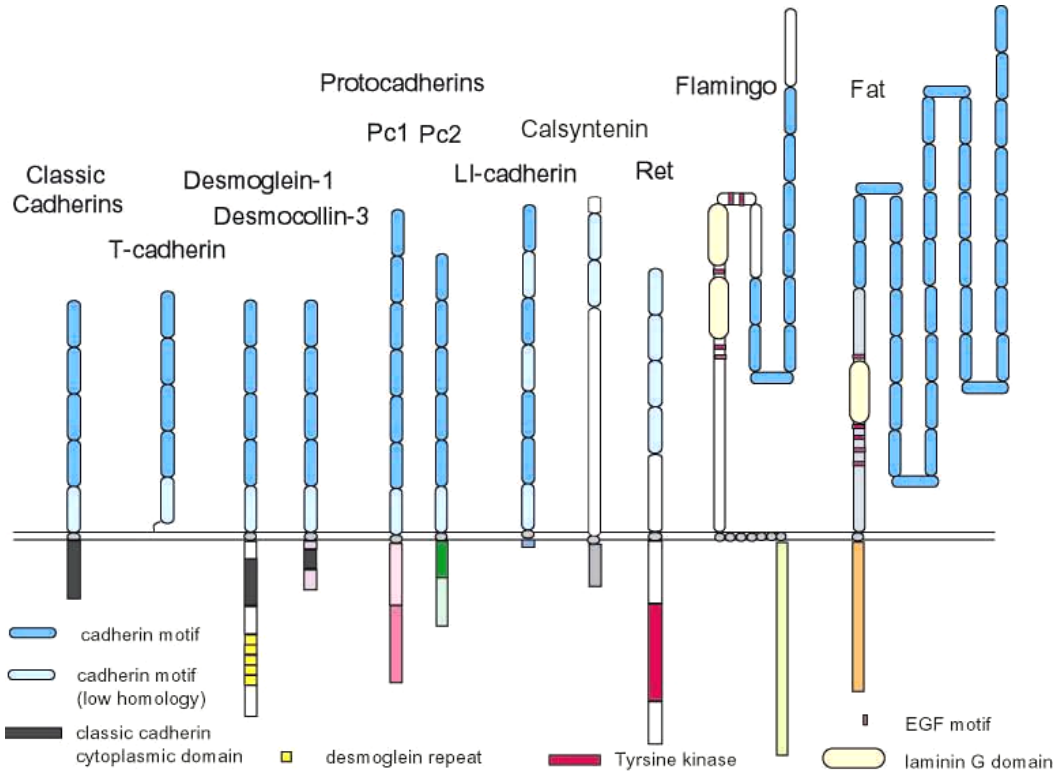

Figure 2. Members of the cadherin superfamily. Shown are the domain structures of representative members of the cadherin superfamily in the vertebrates. Note that in most cases the cytoplasmic domains are completely different from each other. This feature suggests that they participate in distinct signaling pathways and protein interactions. For the structures of the invertebrate cadherins see Hill *et al.* (25).

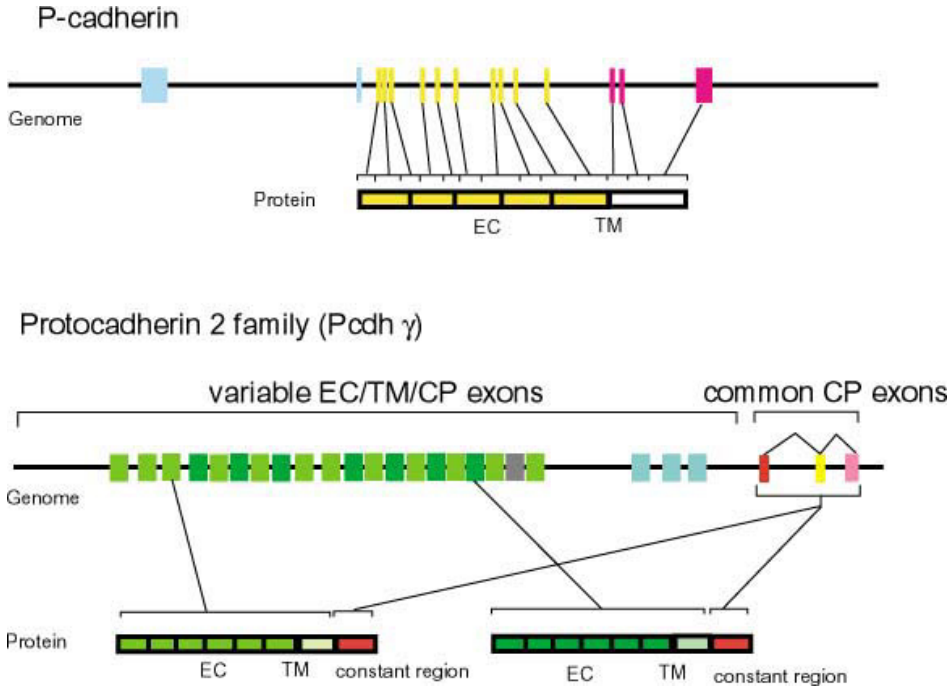

Figure 3. Genomic structures of P-cadherin gene and the protocadherin 2 subfamily gene cluster. The upper panel shows the genomic structure of the P-cadherin gene. The extracellular part of P-cadherin is encoded by 10 exons. It should be noted that exon/intron boundaries are not in register with the boundaries of cadherin protein domains. The lower panel shows the genomic organization of the protocadherin 2 family gene clusters. Note that extracellular domain of protocadherin is encoded by 1 exon and that a set of common exons is used by many protocadherin genes.

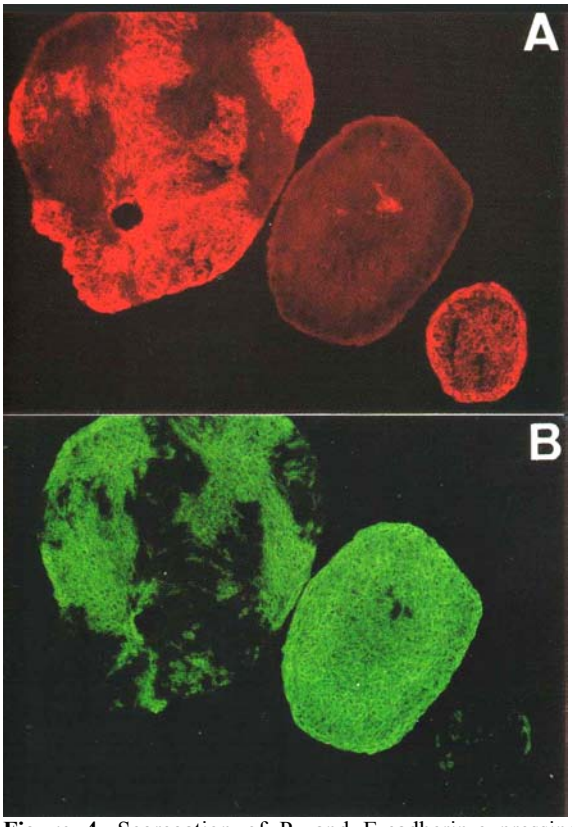

Figure 4. Segregation of P- and E-cadherin-expressing cells in culture. P-cadherin transfected cells and E-cadherin transfected cells were dissociated by TE-treatment, mixed at a 1:1 ratio and co-cultured. The resultant aggregates were sectioned and stained with anti-P-cadherin antibody (red) and with anti-E-cadherin antibody (green). Note that the 2 types of transfected cells either aggregate into separate cell clusters or form segregated domains in mixed cell aggregates. Reproduced from the work by Nose *et al.* (35) with permission of Elsevier Science.

on a single chromosome of the human genome (Figure 3 and see section 5.2; 28, 32). Taken together, the data indicate that there are common as well as species/lineage-specific members of the cadherins in the animal kingdom. However, the structure of some cadherin subfamilies has so diverged that their evolutionary relationship cannot be determined precisely at present. In the following sections, we will overview each family of the cadherin superfamily.

4. CLASSIC CADHERINS

4.1. Overview and classification

Classic cadherins are type I membrane proteins (Figure 2). The extracellular domain has 5 cadherin repeats of which the 5th repeat has diverged the most (33). The cytoplasmic region is highly conserved among classic cadherins and interacts with the actin-based cytoskeleton through cadherin-binding molecules such as the catenins (see sections 4.2.3 and 4.2.4., Figure 5). The binding to catenins and to elements of the actin-based cytoskeleton is a critical feature of cadherin-mediated adhesion (see for example 34). Thus, catenin binding (i.e., conservation of the β-catenin-binding sequence in the cytoplasmic region) is an important function that defines classic cadherins.

So far, over 20 different classic cadherin subtypes have been found in a single vertebrate species (Table 1). On the basis of characteristic amino acid sequences of the cytoplasmic domain, classic cadherins can be further divided into 2 subfamilies: type I and type II classic cadherins (17). Type I cadherins comprise E-, P-, N- and R-cadherin, which were each named according to the organ or tissue in which they were first identified (i.e., epithelium, placenta, neural tissue and retina, respectively). Type I cadherins have also been numbered cadherin-1 to cadherin-4 (Table 1; 17, 23). The difference of subtype is critical for binding specificity, and it also give rise to some functional differences (35, 36). Type II cadherins include such molecules as cadherin-5 and cadherin-6, which were numbered by the order of their discovery. It has been speculated that type I cadherins are involved mainly in the formation of epithelial tissues, that their expression inhibits cell scattering and that type II cadherins are also synthesized by migratory cells (37). In fact, N-cadherin and cadherin-7 were shown to function differently in cell scattering in transfected cells (37). However, at least in the developing central nervous system (CNS), such differences in expression patterns are not understood. It was also reported that cadherin-8 is sensitive to trypsin digestion even in the presence of Ca^{2+} (38). However, such protease sensitivity was not found for other type II cadherins. More experimental studies are needed to determine the functional difference between type I and type II classic cadherins.

In addition to their original forms, at least cadherin-8 and cadherin-11 have splice variants that lack a cytoplasmic domain (38). Cadherin-8 is spliced in its EC5 domain, whereas the cadherin-11 isoform has an insertion in its transmembrane region, generating a stop codon (38). The truncated cadherin-11 isoform did not show adhesive activity in a transfected cell line (39). However, it was shown to become localized at the cell surface and to enhance cadherin-11-mediated adhesion by stabilizing the interaction between the intact form and β-catenin (39). Thus, the truncated cadherin isoform may modify and regulate cadherin-mediated adhesion.

4.2. Structural aspects of cadherins and cadherin-based adhesion apparatus

4.2.1. Structure of the cadherin extracellular domain

One of the structural bases of cadherin-dependent adhesion is the so-called cadherin domain, the structure responsible for some crucial molecular interactions and calcium binding (40, 41). The cadherin domain consists of about 110 amino acid residues and is tandemly repeated. These repeats are usually called EC1 (extracellular domain1), EC2, EC3 and EC4, with the numbering starting at the N terminus. Basically, the cadherin domain is characterized by a number of conserved amino acid sequences such as PE, LDRE, DXNDN and DXD (33). In a cooperative manner, these motifs can bind 3 Ca^{2+} at each interdomain boundary (40, 42). Although the DXD motif is found consistently in almost all domains, not all of these motifs are present in each cadherin domain (33).

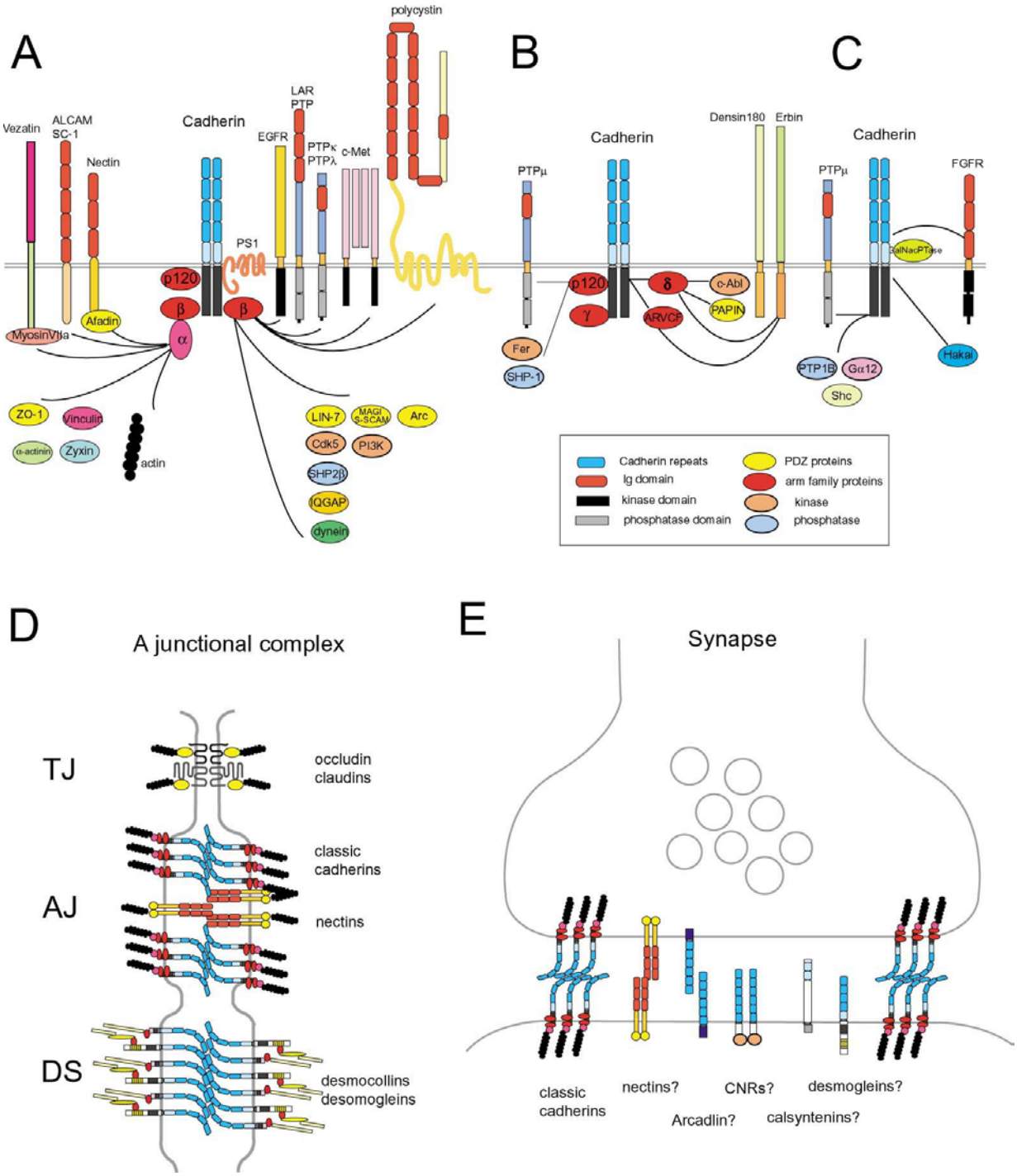

Figure 5. Schematic diagrams of cadherin-associated molecules and a junctional complex between epithelial cells and a synaptic junction between neurons. (A) Molecules that associate with the cadherin/catenin complex via α-catenin (left side of the cadherin) or via β-catenin (right side of the cadherin). (B) Molecules associated with the cadherin/catenin complex via members of the p120ctn subfamily (p120ctn, δ-catenin, ARVCF). (C) Associated molecules directly binding to cadherin. (D) In epithelial tissues, classical cadherins are localized at the AJ, whereas desmosomal cadherins are found in desmosomes (DS). Each integral adhesive membrane protein links to the cytoskeleton via associated proteins. Many details of the molecular architecture of these junctions still remain to be elucidated. (E) The synapse is a specialized AJ with an asymmetric structure. Classic cadherins are localized in ring-like regions adjacent to the neurotransmitter release zones. Although several cadherins appear to be localized at synapses, the molecular details of their subcellular localization are largely unknown.

Analysis of crystal structure has revealed the 3-dimensional structure of cadherin molecules and possible mechanisms of cadherin-mediated adhesion (40-46). The cadherin domain folds in a manner similar to that of the Ig domain, although Ig's emerged independently in evolution (41). Cadherin domains form a barrel-like structure (40); the tandem array of barrels is flexible when the concentration of Ca^{2+} is low, whereas it is rigid in the presence high Ca^{2+} concentrations (40, 43).

The molecular mechanisms of cadherin interaction are still elusive. It is proposed first that two cadherin molecules can interact at their EC1 to form an X-shaped "strand dimer" (also called *cis*-dimer) as a functional unit (41, 43). This dimer can interact in *trans* configuration with an opposing strand dimer on another cell, thus forming the so-called "adhesion dimer." The strand and adhesion dimers form a zipper-like array of cadherin molecules (so-called "cadherin zipper"), (41). In this model, EC1 is responsible for the *trans* interaction. A second model proposes that a variable number of EC domains are involved in the *trans* interaction (47, 48). In addition, it has also been proposed that cadherin molecules form a cluster by lateral interaction at the cell surface (49-52). Furthermore, a novel configuration of interaction was proposed that would abort the original model offered by the same group (46). In this model, the strand dimer interface is used for trans-interaction rather than the cis-dimer and cis-interaction occurs between EC1 of one molecule and EC2 of another molecule (see Figure 5D and E), resulting in the formation of a lattice of supramolecular complex. It is argued that this model is consistent with the results of previous studies using electron microscopy and also with functional analysis of C-cadherin (46). The currently discussed models thus differ in details regarding the molecular interaction for *cis*-dimer formation, trans-dimer formation and lateral clustering. These differences may be partially due to the differences in cadherin subclasses, experimental conditions and/or interpretation of the observations, in the different studies (42, 46, 53). By some molecular interactions of ectodomains along with transmembrane and cytoplasmic domains, cadherin molecules assemble for the formation of mature junctional complexes (see section 4.2.4 for junctional organization).

4.2.2. Adhesion specificity of classic cadherins

Specificity of adhesion is a fundamental feature mediated by classic cadherins in morphogenesis (3, 54, 55). Cadherin-mediated adhesion is basically homophilic, i.e., cadherin molecules of the same subtype bind to each other but not to cadherin molecules of another subtype (35). For example, N-cadherin interacts with N-cadherin, whereas E-cadherin interacts with E-cadherin. This binding specificity is thought to provide a molecular basis for the sorting of cells (Figure 4), the fasciculation of axons and neural circuit formation (see section 4.5.13) and probably for many other cadherin-related phenomena.

Cell sorting is an important process in animal morphogenesis (1). It may be regulated not only by qualitative differences in the subtype of cadherin expressed by cells but also by quantitative differences; i.e., two cell populations that express the same cadherin but at different levels also sort out (Figure 4; 35, 56). The first direct evidence that cadherins are involved in sorting *in vivo* came from observations on DE-cadherin in *Drosophila* (57). The oocyte preferentially contacts posterior follicle cells that express higher levels of DE-cadherin. In the absence of DE-cadherin in either the oocyte or the follicle cells, the oocyte often becomes mislocalized at the central or anterior part of the follicle. Given the fact that neural morphogenesis involves very complex cell-cell interactions, it is not surprising that cadherin-mediated sorting is involved extensively also in neural development. The importance of cadherins in cell sorting has also been shown by overexpression or by dominant-negative inhibition of cadherins in *Xenopus* (58-62). Here, the genetically altered tissue segregates from the surrounding tissue that expresses different type of cadherins. A similar segregation of N-cadherin-deficient cells was observed in chimeric mouse embryos (63). Although it is reported that cell sorting is not determined by a simple specificity of adhesion (64), specificity of cadherins seems to contribute to cell-sorting at least in part.

Besides homophilic binding, heterotypic adhesion between different cadherin subtypes can also be observed *in vitro* in some situations. For example, N-cadherin can interact with R-cadherin *in vitro* (16). Similarly, other combinations, such as cadherin-7 and cadherin-6B, B-cadherin and E-cadherin and E-cadherin and N-cadherin, have been observed to mediate heterotypic cell binding (65-69). With some exceptions (69,70), heterophilic binding is weaker than homophilic binding. The functional significance of heterophilic binding *in vivo* remains to be elucidated.

Moreover, N-cadherin and R-cadherin can produce a heterotypic strand dimer, which can give even more variety to adhesive specificity (71). It is thought that many cells, including neurons, express more than 1 type of cadherin (16, 72, 73). This kind of heterotypic strand dimer formation could exist *in vivo* (71).

In addition, cadherins can interact with other types of molecules, although it is not known know how general this kind of interaction is in developmental processes. For example, E-cadherin expressed by epithelial cells can interact with αEβ7 integrin expressed on T lymphocytes (74, 75). Also, cadherin-5 (VE-cadherin) interacts with fibrin (76).

In summary, the following factors contribute to the diversity of cell-cell interactions mediated by cadherins: [1] Expression of different cadherin subtypes. [2] Quantitative differences in cadherin expression level. [3] Combinatorial expression of cadherin subtypes in the same cell. [4] Combination of cadherin subtypes in heterotypic *cis*-dimers. [5] Heterotypic interaction of different cadherin subtypes in *trans* configuration. [6] Interaction of cadherins with non-cadherin molecules. Although it is difficult to estimate the relative importance of each of these factors at the present, it is clear that the expression of cadherins in the nervous system has the potential of generating a very high degree of complexity.

4.2.3. Catenins: major cadherin-associated molecules

Recent studies have revealed complex interrelations of cadherins with other molecules, including cytoskeletal elements and signaling molecules (Figure 5; 77, 78). The reality of this complexity steadily increases, as new types of interactions are identified. Cadherin-associated molecules are direct binding partners of cadherins, and they are considered to regulate cadherin-based adhesion. Six so-called "catenins" (α-catenin, β-catenin, γ-catenin [plakoglobin], $p120^{ctn}$, δ-catenin and ARVCF (armadillo repeat gene deleted in Velo-cardio-facial syndrome) interact directly or indirectly with the cytoplasmic domain of classic cadherins (79-81). All catenins except α-catenin belong to the armadillo family of molecules (82).

β-catenin and γ-catenin bind competitively to the C-terminal region of classic cadherins (83, 84). The analysis of the structure of the β-catenin/E-cadherin complex shows the importance of phosphorylation of cadherins for this binding (85). Various molecules are known to interact with the cadherin/catenin complex via β-catenin (Figure 5A). Gα12 and Gα13 G proteins interact with the cytoplasmic domain of cadherin and cause release of β-catenin and thereby reduce cadherin function (86-88). On the other hand, it is well known that β-catenin participates also in the Wnt-signaling pathway (see section 4.3.3). γ-Catenin is also localized at the desmosome (83).

α-Catenin links cadherins to the actin cytoskeleton and is essential for strong adhesion (34, 89). α-Catenin does not bind cadherins directly but binds it via β-catenin (79). To link to the actin cytoskeleton, α-catenin is involved in the recruitment of various molecules including vinculin, zyxin, VASP and Mena in the initial phase of the AJ formation (90). It is known that αN-catenin is a neural type of α-catenin and has a splice variant (34, 91). The molecule originally called α-catenin is now often called αE-catenin to distinguish it from αN-catenin. In the mouse, αN-catenin is specifically abundant in axons, whereas αE-catenin is expressed only in the ependymal lining, suggesting a differential role of these 2 molecules in the nervous system (91). However, the functional difference between the role of αE-catenin and that of αN-catenin remains to be determined. Recently, it was also reported that another member of α-catenin, named αT-catenin, is expressed in specific tissues such as the heart, testis and brain (92).

At the juxtamembrane region, $p120^{ctn}$, δ-catenin and ARVCF are known to bind (Figure 5B; 79, 93-95). These are close members in the $p120^{ctn}$ subfamily. $p120^{ctn}$ regulates cadherin clustering as a negative regulator (96, 97) or as a positive regulator (49). It is reported that $p120^{ctn}$ is involved in the regulation of adhesive or motile cellular phenotypes through controlling cadherin activity via Rho GTPases (98, 99, 100). δ-Catenin is specifically expressed in the nervous system and undergoes dynamic relocalization during development (101). It enhanced dendritic morphology in primary hippocampal neurons and accelerated neurite extension of PC12 cells (102, 103). It is suggested that δ-catenin acts downstream of Abl, a molecule involved in axogenesis (for Abl see section 4.5.9, 103). In addition, δ-catenin interacts with various molecules such as densin-180 (originally found from postsynaptic density [PSD]; 104), Erbin (similar to densin 180; 105) and PAPIN (plakophilin-related armadillo repeat protein-interacting PSD-95/Dlg-A/ZO-1 protein; Figure 5B; 106). ARVCF was originally found as a candidate gene for the Velo-cario-facial syndrome (81). Interestingly, the amount of ARVCF is at least tenfold less than that of $p120^{ctn}$ in cells, and it is more nucleophilic than $p120^{ctn}$ (95).

4.2.4. Other cadherin-associated molecules and adherens junction (AJ)

When a cadherin-mediated adhesion site matures by recruiting various molecules, it becomes a highly specialized cell-cell junction, the so-called adherens junction (AJ, Figure 5D; in this review we will use the term AJ for cadherin-based adherens junctions). About half of the total amount of cadherins in a cell seems to be incorporated in AJ's as an insoluble component (66, 107). In epithelial cells, the AJ is highly developed and forms the *zonula adherens* (also called the belt desmosome or intermediate junction; Figure 5D). In cardiac myocytes, this structure is present in the form of the *fascia adherens* (intercalated discs). In the paranodal loops of the myelin sheet, there are autotypic AJ's (108). Synaptic junctions can also be viewed as a specialized form of AJ (Figure 5E, see also section 4.5.14. for cadherins in synaptic function; 109, 110). In the synaptic glomerulus of the granular layer in the cerebellum, the AJ is called the contactus adherens (*puncta adherentia*) and contains M-cadherin as an integral component (111, 112). AJ's are highly dynamic structures that break and form during morphogenesis and give rise to strong forces, which induce cell and tissue rearrangement.

Many molecules have been found identified to be localized at the AJ (Figure 5; 77, 79, 80, 113-117; see also next section). Beside various catenins as described above, the AJ contains various cytoskeletal proteins such as vinculin, α-actinin, radixin, ZO-1, ankyrin, fodrin, actin, myosin, LIN-7, Arc and tenuin. LIN-7 (named MALS/Velis in mammals) is a protein containing the PDZ domain and clusters together with PSD-95 and NMDA receptors (118, 119). In addition, N-cadherin is required for recruitment of the kainate receptor (120). Moreover, S-SCAM (synaptic scaffolding molecule, also called MAGI) interacts with β-catenin and also with the NMDA receptor in synapses (121, 122). In addition, the AJ contains some regulatory proteins including SFK (Src family kinase), phophatases (see section 4.3.1. for kinases and phosphatases), crumbs (*Drosophila*), Rap1 GTPase (*Drosophila*) and Adenomatous polyposis coli (APC) gene product (123-126). For example, it was shown that APC and microtubule-associated EB1 in the AJ govern planar polarity cues in the asymmetric division of neuroblasts (126).

Recently, another adhesion system named the "nectin-afadin system" has also been shown to be an integral component of the AJ (Figure 5D; 127-129). Nectins are transmembrane proteins of the Ig superfamily, (128) and

nectins and cadherins interact, probably through □-catenin (130). Among the 3 known isoforms, nectin-1 is mainly expressed in the nervous system (131). Afadin (also called AF-6) binds to the cytoplasmic region of nectin (128). l-Afadin, a long isoform, is expressed ubiquitously; whereas s-afadin, a short isoform, is abundantly expressed only in neural tissue (127). s-Afadin interacts and clusters with the Eph receptor tyrosine kinases in the brain (132). The nectin-afadin system is involved in the formation of AJ's and tight junctions (133, 130). In afadin knock-out mice, the embryonic ectoderm is disorganized during gastrulation (133).

Furthermore, other membrane and transmembrane proteins seem to interact with the cadherin-catenin complex (Figure 5A-C). The novel transmembrane protein vezatin is ubiquitously present in the AJ and this molecule bridges myosin VIIA to the E-cadherin/catenin complex to create tension force (134). Moreover, other molecules such as epithelial cell adhesion molecule (Ep-CAM), activated leukocyte cell adhesion molecule (ALCAM) and polycystin, a causal gene product of autosomal dominant polycystic kidney disease (ADPKD), seem to interact with cadherin-catenin complexes (135-137). It is likely that more molecules will be identified in the near future, providing an even more complex image of the AJ (see also section 4.3.5. for presenilin).

4.3. Cadherin regulation and cadherin signaling in various cellular processes

Cadherin-mediated adhesion is dynamically regulated during morphogenesis. Its regulation is achieved not only through transcriptional control, but also by intracellular signaling. As described above, there are a large number of molecules that participate in cadherin-based adhesion. They must be regulated and some may be involved in signal transduction. In the regulation of cadherin-mediated adhesion, signaling runs in the inside-out direction from signaling molecule to cadherins.

Conversely, we can consider that cadherins can give rise to signals in the outside-in direction ("cadherin signaling"), because cadherin-mediated adhesion induces various processes, such as junctional assembly, reorganization of the actin cytoskeleton, cell proliferation (section 4.4.2.), cell differentiation (section 4.4.2) and neurite outgrowth (section 4.5.9; and for references see 89, 138-143). For example, it is reported that cadherin engagement stimulates tyrosine phosphorylation of junctional proteins (144). Thus, cadherin-mediated adhesion is not a simple mechanical adhesion.

These signaling mechanisms in both directions make it possible for cadherin-mediated adhesion to play roles in and coordinate dynamic cellular processes such as growth cone navigation. Accordingly, the signaling network is a critical to link cadherin-mediated adhesion and various processes. In the following sections, we will summarize what is known about the role of each of these molecular systems in cadherin-mediated adhesive function and signal transduction.

4.3.1. Phosphorylation-mediated regulation of cadherins and catenins

Phosphorylation/dephosphorylation of cadherins and cadherin-associated molecules is a key regulatiory event for proper cadherin function (78, 145). Here, we summarize the general aspects of phosphorylation in cadherin-mediated adhesion. (see also sections 4.3.4., 4.3.7., 4.5.9. and 4.5.14. for phosphorylation in relation to the nervous system.)

Many kinases, phosphatases and their substrates are abundant in cadherin-based adhesion sites (Figure 5A-C; 145). For example, src family kinases (SFK: src, yes, lyn; 123), EGFR (146), Fer, phosphatidylinositol 3-kinases (PI 3-kinase; 147), Abl (103), PTPμ (148, 149), PTPκ (150), PTPλ (151), PTP1B (152, 153), SHP-1 (154), SHP2 (155), c-Met (156) and leukocyte antigen-related protein (LAR) PTP (157) are bound to cadherin-catenin complexes (78, 145). In addition, these molecules seem to control AJ assembly and its function. For example, PTPμ recruits scaffolding protein PACK1 that binds PKC, src kinases, etc. to the AJ (158).

Regulation of cadherin-mediated adhesion by phosphorylation is known to occur in various cases. Major targets of kinases/phosphatases are the tyrosine residues of the armadillo family proteins, including β-catenin, δ-catenin and $p120^{ctn}$ (78, 79, 145). Phosphorylation of β-catenin decreases the binding of β-catenin to E-cadherin (146, 159, 160), whereas that of $p120^{ctn}$ increases its binding to cadherins and reduce adhesion activity (160, 161). It is reported that phosphorylation of β-catenin by Fyn kinase is under the control of Rho GTPase through the PRK2 effector in keratinocytes (162). In addition, receptor-type kinases (RTK), such as receptors for EGF (epidermal growth factor), TGFα (transforming growth factor α), PDGF(platelet-derived growth factor), CSF-1 (colony stimulating factor-1) and HGF, also cause phosphorylation of catenins (145). For example, HGF/c-Met activate MAP kinase and PI3 kinase via Ras and Rac, resulting in disassembly of the AJ (163). It was also reported that there is a genetic interaction between EGFR and DE-cadherin in *Drosophila* (164). Conversely, protein tyrosine phosphatases (PTPs), such as PTP-μ, PTPκ, PTP1B, PTPβ/ζ, and LAR-PTP are involved in the dephosphorylation of catenins and cadherins and thereby facilitate cadherin-mediated adhesion (78, 145, 148, 149, 153, 157, 165-168).

Other mechanisms of phosphorylation are reported to be involved in cadherin regulation. For example, Shc, an adapter protein, binds to cadherins, but only when tyrosine residues of cadherins are phorphorylated; the binding of Shc to cadherins, in turn, has an inhibitory influence on the binding of β-catenin to cadherins (169). In addition, cadherin-mediated adhesion is also regulated by phosphorylation of serine/threonine residues. For example, protein kinase C (PKC) seems to be involved in the regulation of cadherins in various contexts such as junctional assembly or disassembly and activation of E-cadherin, (170-173). Similarly, casein kinases 2, MAPK and glycogen syntethase kinase (GSK3β) are also reported to be involved in the modulation of cadherin-based adhesion (174-177).

On the other hand, it has also been revealed that cadherin-mediated adhesion activates cause signaling

pathways via a phosphorylation mechanism. For example, homophilic interaction of cadherin molecules recruited PI3-kinase to the cadherin complex and stimulated Akt/MPAK pathway in a PI3K-dependent manner (147, 178-180). Similarly, cadherin-mediated adhesion induced phosphorylation of Gab-1, a docking protein, by src, resulting in activation of Ras/MAP kinase and the PI3-kinase/Akt cascade (181).

Taken together, these cited studies demonstrate the possibility that cadherin function is regulated by phosphorylation/dephosphorylation and that cadherin-mediated adhesion triggers phosphorylation/ dephosphorylation. Because phosphorylation is well adopted in various signaling mechanisms, it links cadherin-based adhesion and other signaling pathways such as Rho GTPase. Thus, cadherin-mediated adhesion is integrated in various cellular phenomena through a complex signaling network. The signaling cascade in neurite outgrowth and growth cone motility is described in section 4.5.9.

4.3.2. Interaction with Rho small GTPase and IQGAP

Rho small GTPases are key regulators of the actin and also microtubule cytoskeleton, and they are involved in various dynamic cellular processes such as epithelio-mesenchymal transition, cell motility, membrane ruffling and neurite retraction through many effectors (182-184). In neural circuit formation, the importance of RhoGTPases in growth cone navigation and collapse has been emphasized (185).

It is known that Rac1, Cdc42 and RhoA types of GTPases are required for the regulation of cadherin-mediated cell-cell adhesion. For example, Rac1 and RhoA are involved in the accumulation of cadherins at sites of cell-cell contact (186). In addition, RhoA is required in junctional remodeling (187). The effect depends on cell type, junctional maturation and cellular context (188, 189). In *Drosophila*, it was reported that Rho 1 binds directly to α-catenin and $p120^{ctn}$ *in vitro* (190). The molecular mechanism of cadherin regulation by small GTPases has been partly unveiled. IQGAP, an effector of Cdc42 and Rac1, regulates cadherin-mediated adhesion by causing a dissociation of α-catenin from the cadherin-catenin complex (191). Rac1-Cdc42-IQGAP1 system is involved in HGF-induced scattering (192). It is speculated that the dynamic equilibrium between IQGAP-1-bound cadherin complex and IQGAP-unbound cadherin complex regulates the strength of cell-cell adhesions (184). IQGAP1 itself is regulated in its association with Cdc42 and actin by calmodulin (193). Despite the possible importance of IQGAP1, IQGAP1 null mutants show no obvious defects in development, probably due to the redundancy of the IQGAP-1 function by IQGAP-2 and IQGAP-3 (184, 194). Beside direct regulation, Rho GTPases could also regulate cadherin function indirectly. For example, endocytosis of cadherin and degradation of cadherins by metalloproteinases may be regulated by Rho GTPases (184).

Conversely, cadherin-mediated adhesion affects Rho GTPase activity. For example, direct interaction of C-cadherin molecules inhibits RhoA activity but increases Rac 1 activity (195). In addition, homophilic interaction of E-cadherin recruited Rac and PI3-kinase to contact sites and stimulated Rac signaling (178, 196). Regulation of Rho GTPase activity by E-cadherin is partly mediated through PI3K, which is an upstream molecule of Rac1 and interacts with E-cadherin and β-catenin (147, 178, 196, 197). In addition, it was shown that $p120^{ctn}$ can inhibit RhoA and activate Rac and Cdc42 (98-100). Thus, it is possible that cadherins are involved in regulation of Rho GTPases, thus controlling the amount of the cytoplasmic pool of $p120^{ctn}$. Taken together, the Rho family of small GTPases plays a role as a mediator of cadherin-signaling to coordinate the dynamics of cell-cell adhesion and various cellular processes.

4.3.3. Relation with the Wnt signaling pathway

Wnt signaling is important in cell fate decisions and patterning during development. Examples of processes in which Wnt signaling plays a role include neural induction, determination of the neural crest and brain patterning (198). At least 4 pathways are known to be regulated downstream of Wnt signaling (199). One pathway is involved in TCF/LEF-mediated transcriptional regulation. The other pathways include the JNK pathway, Ca^{2+} pathway and the pathway involved in asymmetric cell division. Because Wnt signaling and the cadherin/catenin complex share β-catenin as a mutual constitutive component, it is possible that each system is affected by the other (200). In Wnt-1 mutant mice, the expression of E-cadherin and αN-catenin in the brain are both affected (201). *In vitro*, the introduction of Wnt-1 protein induces strong adhesion by stabilizing β-catenin and γ-catenin binding to cadherin (202). On the other hand, high levels of cadherin expression can influence Wnt signaling by sequestering free β-catenin (203). It has been speculated that β-catenin is transported between the cadherin-based AJ and the nucleus by APC (adenomatous polyposis coli protein; 204). In addition, as described below, presenilin increases the level of free cytosolic β-catenin and also cadherin stabs by its γ-secretase activity (section 4.3.5; 205). Thus, it is possible that presenilin may link cadherin-based adhesion and the Wnt-1 signaling pathway. However, the exact nature and extent of these interactions between cadherin system and Wnt signaling pathway *in vivo* remains to be determined (206). In addition, other arm family molecules including γ-catenin and $p120^{ctn}$ are also involved in transcriptional regulation in a similar manner as β-catenin (204), although the details are not known in relation to cadherin-mediated adhesion.

4.3.4. Interaction with the reelin signaling pathway

Reelin is a large extracellular matrix protein that is involved in cortical development of the brain (207, 208). Receptors for reelin include VLDLR (very-low-density lipoprotein receptor), ApoER2 (apolipoprotein E receptor 2), α3β1 integrin and CNR (cadherin-like neural receptors, see section 5.2.6.), and its intracellular signaling is mediated by molecules such as Dabl and Cdk5 (207-209). Interestingly, it has been reported that p35-Cdk5 kinase is associated with the β-catenin/N-cadherin complex in the mouse cortex (210). Moreover, overexpression of p35 in

COS cells causes dissociation of the β-catenin/N-cadherin complex and results in a reduction in N-cadherin-mediated adhesion (210). Based on these observations, it is hypothesized that N-cadherin is down-regulated during migration of neuroblasts by the activity of p35/Cdk5 and that neuroblast migration is terminated with the down-regulation of p35/Cdk5 by reelin (211). This hypothesis can explain how N-cadherin-mediated adhesion of migrating neurons may be regulated by the reelin signaling cascade.

4.3.5. Interaction with presenilin

Presenilin-1 (PS-1) is a transmembrane protein that is responsible for most of the cases of early-onset familial Alzheimer's disease. PS-1 is concentrated at synaptic and epithelial cell-cell contact sites (212) and binds to E-cadherin competitively with $p120^{ctn}$ (213). Two distinctive effects of PS-1 on cadherin-catenin complex were reported. One study showed that PS-1 stimulated E-cadherin binding to β- or γ- catenin, promoting cell-cell adhesion (213). Another showed PS-1 to stimulate the disassembly of E-cadherin/catenin complexes by cleaving E-cadherin via its γ-secretase activity (205). Its cleavage was stimulated by apoptosis or calcium influx; and E-cadherin, β-catenin and α-catenin were released from the cytoskeleton, increasing the cytosolic pool of β-catenin (see also section 4.3.3. for Wnt signaling; 205). In addition, it is known that PS-1 and PS-2 modulate the Notch signaling pathway, which is crucial for cell-fate decisions during neural development (214). Thus, it is possible that PS-1 may be important in dynamic processes such as synaptic plasticity by regulating cadherin-mediated adhesion and modulation of Wnt signaling pathways.

4.3.6. Eph receptors/ephrin

The mechanism opposite to cell adhesion is the repulsion between cells. These two mechanisms cooperate antagonistically with each other during the development of complex multicellular systems. Among the repulsive factors, ephrins and Eph receptors are key regulators of brain morphogenesis, regulating processes such as neuromere formation, axonal pathfinding and neuroblast migration (215, 216). Eph receptors are receptor-type kinases (RTKs). There is some evidence that cadherin function is related to Eph/ephrin signaling. For example, E-cadherin was required for the cellular localization of the EphA2 receptor and activation of this receptor by E-cadherin expression decreased cell-substrate adhesion and cell growth (217). In addition, the expression of specific Eph receptors and ephrins was shown to be regulated differentially by E-cadherin (218). Moreover, afadin also interacted with a subgroup of Eph receptors at the postsynaptic membrane, where it was considered to control clustering of Eph receptors (132). In addition, afadin has been shown to be a substrate of Eph receptors (132). Thus, Eph signaling and adhesion mediated by the nectin-afadin system and cadherins may be closely related (see section 4.2.4. for the AJ).

4.3.7. Cross-talk with cell-substrate adhesion

Cross-talk between the cadherin and the cell-substrate system is important when cells need to coordinate behavior such as neuroblast migration and growth cone navigation. This cross-talk was speculated to exist by the old observation that inhibition of cadherins by antibodies often causes loss of cell-substrate adhesion (for example, see Figure 1B). Today, evidence for such cross-talk has been accumulating. For example, a cross-regulation between E-cadherin and αV integrins can be seen in the migration of carcinoma cells (219). Expression of β1 integrins results in a decrease in cadherin and α-catenin expression and function (220). Recently, a direct interaction between these two molecular systems was demonstrated. The interaction of the proteoglycan neurocan with its receptor, GalNAcPTase, inhibits both N-cadherin- and β1-integrin-mediated adhesion and neurite outgrowth (221). The effect of neurocan on the cadherin complex seems to be mediated by the Fer protein tyrosine kinase (222). The neurocan signal is transferred to GalNAcPTase, which, in return, causes Fer to phosphorylate the β-catenin and integrin adhesion components (222). PTP1B, which is involved in the regulation of N-cadherin and β-integrin-mediated axon growth, is a possible antagonist of Fer (221, 223). Because neurocan is restricted to the inner plexiform layer and the ganglion cell layer in the retina, it is speculated that neurocan may be used for inhibition of neurite extension across boundaries (221).

Other proteoglycans are also possibly linked to cadherin-based adhesion (224, 225). Syndecan-1, a transmembrane-type proteoglycan, is localized at the cell-cell adhesion sites on epithelial cells, whereas syndecan-2 is present at neuronal synapses (226). It has been speculated that syndecan signaling, including the syndecan-binding protein CASK, may affect cadherin/β-catenin signaling (224). On the other hand, it is known that proteoglycans abolish E-cadherin function by inhibiting homophilic cadherin interactions in tumor cells (225).

4.3.8 Interaction with microtubules

The microtubule is another major part of the cytoskeleton and is important not only for cell shape but also for axon elongation and maintenance of AJ's (227). Although the relationship between cadherins and microtubules is elusive, recent studies suggest that they may be indeed connected. For example, it was reported that the M-cadherin-catenin complex interacts with microtubules and that dynein binds to β-catenin, suggesting microtubules are anchored at the AJ (228, 229). Moreover, cadherin-mediated adhesion affects microtubule dynamics and organization (230). It is also reported that APC in AJ and microtubule-associated molecule EB1 are required for symmetric division of the *Drosophila* neuroepithelium (126). On the other hand, it is known that microtubules affect E-cadherin-mediated adhesion positively or negatively (227, 231). Thus, cadherin-mediated adhesion has a potential to link microtubule organization.

4.3.9. Relation with membrane trafficking and polarity

Membrane trafficking including endocytosis and vesicle transport contributes to regulation of cadherin-mediated adhesion. For example, if cell adhesion is disrupted by HGF, the HGF receptor (c-met) and cadherins

are sequestered together by endocytosis (232). Endocytosis itself is controlled in a coordinated manner by members of the Rho and Rab families of molecules: the Rho family is involved in the rearrangement of the actin-based cytoskeleton, whereas the Rab/Arf family regulates vesicle transport, and members of both families cooperate to coordinate the motility of cells (183, 232). RAC1 also regulates the AJ through endocytosis of E-cadherin (233). In addition, it was reported that ARF6 GTPase, a Ras-related GTPase, is involved in HGF-induced E-cadherin internalization (234). Moreover, another mechanism of endocytosis was reported recently (235). Hakai, a c-Cbl-like E3 ubiquitin-ligase, interacts with E-cadherin in a tyrosine phosphorylation-dependent manner and induces endocytosis of E-cadherin complexes (235).

It is known that cadherin-mediated adhesion is important in the establishment of apico-basal cell polarity, based on the observation that introduction of E-cadherin into fibroblasts induces epithelial morphology (236). Then, it was revealed that E-cadherin induces cell polarity, resulting in a distinct subcellular distribution of particular proteins, such as Na^+-K^+ ATPase (237). Interestingly, the mammalian Sec6/8 complex, which is known to be responsible for delivery of secretory vesicles to the axon terminal, is recruited from the cytosol to cell-cell contact sites in a cadherin-dependent manner, suggesting that the induction of polarity by cadherin-mediated adhesion may be mediated by this sec6/8 complex (238). In addition, it is speculated that target delivery of vesicles by sec6/8 is important in synapse formation (239). Thus, target delivery of vesicles by these molecules and cadherin-mediated adhesion may play a role in synaptogenesis cooperatively. It should be noted, however, that other mechanisms are also known to be involved in the establishment of cell polarity (planar polarity) by cadherin-mediated adhesion (126, 464).

4.3.10. Interaction of the AJ with tight junctions, desmosomes and gap junctions

The tight junction (TJ), AJ and desmosomes form a junctional complex in epithelial cells (Figure 5D). The TJ is usually found just apical to the AJ. Integral membrane proteins of the TJ include occludin and claudins, but not cadherins (240). Occludin and the claudins are linked to skeletal proteins such as ZO-1, ZO-2 and ZO-3, which, in turn, provide a link to the actin cytoskeleton (240). In fibroblasts, which do not have TJ's, ZO-1 and ZO-2 are localized at the AJ, and they interact with α-catenin, suggesting a close molecular interrelation between the TJ and the AJ (241, 242). Thus, ZO-1 may be a key switch in the formation of the TJ or the AJ (77). In addition, the assembly of the TJ seems to be regulated by the AJ. For example, the addition of anti-E-cadherin antibodies disrupts cell-cell adhesion as well as formation of TJ's. The restoration of cadherin-based adhesion re-induces the formation of the TJ (89). TJ formation is also controlled by the nectin-afadin system that plays a role also in AJ formation (see section 4.2.4; 133). In a similar way, cadherin-mediated adhesion also regulates the formation of desmosomes and gap junctions (89, 243-246). Antibodies to gap junction proteins such as connexins inhibit AJ formation, suggesting an interdependency of these two types of junctions (245). Dynamics of the gap junction and AJ may be coordinated by $p120^{ctn}$, because this protein is also colocalized with connexin 43 (247).

4.3.11 Transcriptional control of cadherins and other molecules

The expression of cell-adhesion molecules is regulated by morphoregulatory transcription factors, although not many examples have been reported. For example, in *Drosophila*, twist and snail are involved in the switch of expression from DE-cadherin to DN-cadherin (248). Similarly, it was reported that MSh, SIP1, E2A gene product, SIP1 and C/EBP transcription factors are involved in the expression of mammalian E-cadherin or *Drosophila* DE-cadherin (249-252). The transcriptional control of cadherins in neural tissue is particularly interesting. For example, misexpression of Xgbx-2 prevents N-cadherin expression during early neurulation and the resulting phenotype is strikingly similar to that of a dominant-negative mutant of N-cadherin in *Xenopus* (253). In zebrafish, segmental expression of R-cadherin in the hindbrain and spinal cord is regulated at least in part by sonic hedgehog and pax6.1 (254). It is known that the promoter of N-cadherin has a Maf binding site (255). Null mutants of the genes Emx-2 and Pax-6.2 transcription factors, which control area identity in the mammalian neocortex, show an altered expression of cadherin-6 and cadherin-8 in the neocortex (256). In addition, expression of R-cadherin is affected in Pax-6-deficient mouse mutants (257). In the HoxA-1 null mutant, the restricted expression of cadherin-6 in rhombomeres 4 to 6 is suppressed transiently (258).

In addition, molecules other than transcription factors also affect cadherin expression. As noted before, E-cadherin expression is altered in Wnt-1 mutant mice (201). Molecules such as progesterone, esradiol and TrkB, an EGF receptor-like molecule, are also known to affect cadherin transcription in various cells (259-262).

Conversely, cadherins often affect the expression of other molecules. For example, E-cadherin affects the expression of some Eph receptors and ephrins (218). Syndecan expression also depends on E-cadherin (263). In addition, cadherin-mediated cell interactions are necessary for the activation of MyoD expression during muscle differentiation (264). These are just a few examples of the involvement of cadherins in complex transcriptional regulation that takes place during development.

4.4. General roles of cadherins

The principal role of classic cadherins is in cell-cell adhesion. As described in the previous sections, cadherin-based adhesion is strong because of the linkage of those molecules to the actin cytoskeleton. In addition, as a result of interaction with various signaling pathways, cadherins are not only involved in cell-cell adhesion, but also in many basic processes such as cell locomotion, proliferation and differentiation. In the following subsections we will discuss the general roles of cadherins in cell adhesion, in cell proliferation and in cell differentiation (see the next section for roles of cadherins in the nervous system).

4.4.1. General roles of cadherins in cell-cell adhesion

Since the major role of cadherins is in cell-cell adhesion, it is not surprising that these molecules are expressed in all cohesive tissues. Often, multiple cadherins are expressed by a single tissue. A good example for the importance of cadherins in histogenesis can be found in somitogenesis (265, 266). N-cadherin is expressed rather uniformly at the cell-cell junctions in the paraxial mesoderm (267). As the mesoderm begins to aggregate, N-cadherin becomes localized at the inner side of the mesenchymal condensation. During somite vesicle formation, an epithelial-mesenchymal transition occurs as N-cadherin becomes concentrated at the apical region of the epithelium. If N-cadherin function is blocked by antibodies or gene targeting, the somite structure becomes disorganized (265, 266). In N-cadherin-deficient mutants, the cell mass of the somites has a tendency to be split into an anterior part and a posterior part, but the somites are not destroyed completely (266, 268). Although cadherin-11 is also expressed in the somites, a null mutation of cadherin-11 in mouse shows normal somite phenotype (266). Double knock-out mice of N-cadherin and cadherin-11 show a more severe phenotype with a more complete fragmentation of somite epithelia than the N-cadherin null mutation alone (266). Thus, N-cadherin plays a major role in somitogenesis, while cadherin-11 plays a minor one.

Similar roles of cadherins in histogenesis were experimentally demonstrated in other tissues, including the lung epithelium, skin, limb cartilage, neural tube, retina, tectum and the early embryo (269-276). In all cases, blocking cadherin function causes disorganization of tissue structure.

4.4.2. Roles of cadherins in cell proliferation and differentiation

Cadherin-mediated adhesion can regulate cell proliferation in a positive or negative fashion. For example, when cadherin-mediated adhesion is restored by exogenous α-catenin in an α-catenin-deficient dispersed carcinoma line, cell proliferation is enhanced (89). In addition, soluble N-cadherin is mitogenic for oligodendrocyte precursor cell lines (277). It is speculated that this might be important for the repopulation of demyelinated lesions during regeneration. On the other hand, cell growth is suppressed in various other examples of N-cadherin, VE-cadherin and P-cadherin action (278-280). The N-cadherin-mediated contact inhibition of cell growth seems to involve the cyclin-dependent kinase (cdk) system (281). In null mutants of P-cadherin, the mammary glands show hyperplasia and dysplasia, suggesting P-cadherin to be a negative regulator of mammary gland cell growth (282). Similarly, it was reported that loss of N-cadherin function caused increased mitosis in the dorsal midbrain and hindbrain in the zebrafish (283).

Cadherin-mediated adhesion is also involved in cell differentiation. For example, N-cadherin signaling is important for muscle differentiation (284, 285). In addition, E-cadherin induces enterocyte differentiation through the MAPK pathway (179). Another example of cadherin function in differentiation comes from experiments using E-cadherin -/- ES cells (284, 286). The constitutive expression of E-cadherin in E-cadherin -/- ES cells resulted exclusively in the formation of epithelia in teratomas, whereas the expression of N-cadherin led to the formation of cartilage and neuroepithelium. R-cadherin expression in E-cadherin -/- ES cells resulted in the formation of teratomas containing striated muscle and epithelia (284, 286). Note that these tissues express the respective cadherins during normal development. Similar results for N-cadherin were obtained by using P19 carcinoma cells (287). In general, the role of cadherins in neural differentiation has not been studied well. It is reported that N-cadherin is involved in the differentiation of O-2A oligodentocyte precursors (288). However, overall differentiation seemed to be normal in an N-cadherin null mutant, at least at an early stage, possibly due to the redundancy of cadherin signaling (268).

4.5 The role of classic cadherins in neural development

The molecular properties of cadherins and their function in cadherin-based adhesion suggest that cadherins are potentially involved in multiple aspects of cellular behavior. In the past decade, extensive studies have been carried out to describe also the expression patterns of cadherins in the nervous system. Most of the cadherins, which have been studied so far, are expressed in a regionally restricted fashion and are expressed at different levels during nervous system development, e.g., by embryonic subdivisions, brain nuclei, fiber tracts, neural circuits and synapses. Here, we will only briefly discuss the anatomical work on cadherin expression to illustrate its relation to the role of cadherins in nervous system development. For a more detailed review on the expression patterns, see Redies (2000) (55). The expression patterns have been taken as preliminary evidence to suggest specific functional roles of cadherins in neural development (3, 79, 289, 290, 291). Although several of the postulated roles of cadherins in neural development remain speculative, recent experimental evidence supports some of the insights that have been deduced from such expression studies.

In this section, we will describe the roles of cadherins in the development of the nervous system, with a special focus on vertebrate development. We will discuss separately several processes in which cadherins may be involved.

4.5.1. The “adhesive code” based on cadherins in neural development

Neural development is the process during which the relatively simple neuroepithelium of the neural tube is transformed into highly complex divisions that become functionally connected to form information-processing neural networks. In vertebrates, this transformation involves multiple events of pattern formation. First, the early embryonic neuroepithelium becomes parcellated into embryonic divisions or segments. The primary transverse segments are the so-called neuromeres. There are also longitudinal divisions, such as the roof, alar, basal and floor plates of the neural tube. Each primary division is regionalized secondarily into further subdivisions, which finally give rise to various gray matter structures, such as

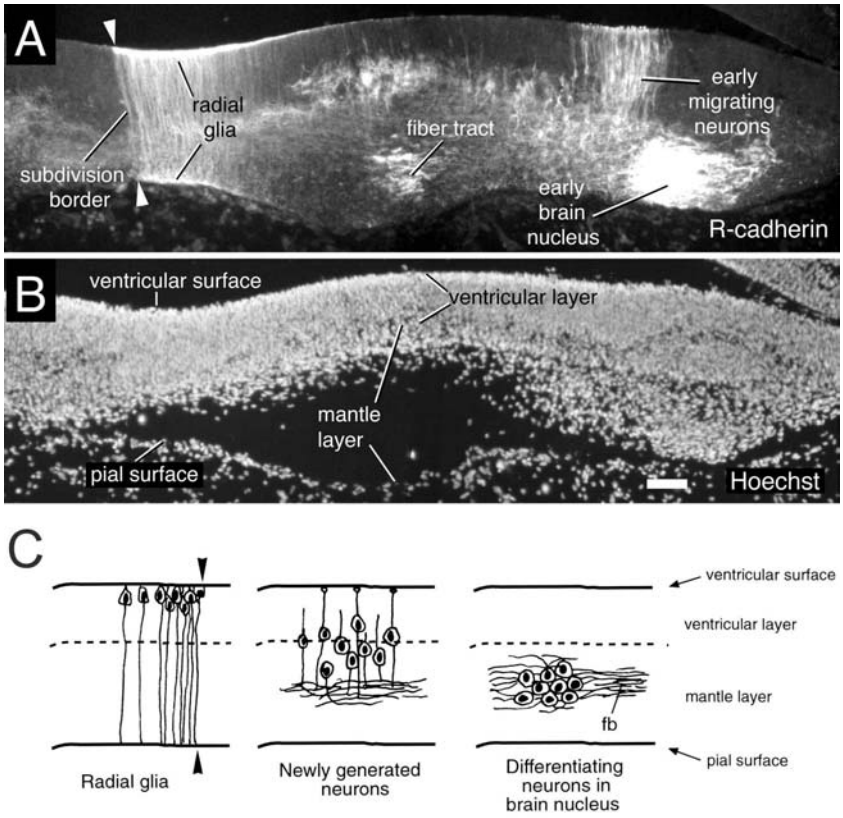

Figure 6. Examples of cell types expressing R-cadherin in the developing chicken brain. (A) Immunofluorescence staining for R-cadherin in a transverse section of the hypothalamic region in a 5-day chicken embryo. (B) Nuclear staining of the same section. (C) A schematic drawing of the various R-cadherin-expressing cell types is also shown. Scale bar = 50 μm. Figure modified and reproduced from Redies (55), Copyright 2000, with permission from Elsevier Science.

brain nuclei and cortical layers. Specific subsets of these gray matter structures become connected selectively by fibers to form neural circuits. Finally, synaptic connections are established according to precise rules and these connections are modulated later in life by processes related to nervous system plasticity. The molecular mechanisms that control these various processes have been highly conserved during vertebrate evolution.

Cadherins regulate neural development at multiple stages (55, 292). N-cadherin is a good example to demonstrate the different roles of a single cadherin at different stages of neural development. At first, the expression of N-cadherin is uniform in the neuroepithelium and plays a role in maintaining the epithelial structure (273, 274, 292, 293). In the developing mantle layer, the expression of N-cadherin becomes restricted to a subset of brain nuclei, layers and fibers, suggesting that N-cadherin is involved in the selective adhesion between particular groups of early neurons and their processes (294). In mature neural tissue, N-cadherin expression is restricted to specific neural circuits (294) and becomes localized at the synapses (109, 110), suggesting a role for this cadherin in neural circuit formation and synaptogenesis. Finally, a role for N-cadherin in synaptic plasticity in the mouse hippocampus has been suggested (295). Similarly, R-cadherin is expressed in various neural cell types, suggesting its versatile functions during neural development (Figure 6).

As was noted earlier (see section 4.4.1), the primary function of cadherins is in cell-cell adhesion. The cadherin-mediated adhesion is relatively strong due to linkage to the actin-based cytoskeleton. The coupling of strong adhesion to a preferentially homotypic binding mechanism is the basis for adhesive specificity and allows cadherins to regulate aggregation and sorting of cells. These processes, in turn, contribute to regionalization and functional specification in neural development. The large diversity of cadherins expressed in neural tissue may correlate with the complexity of the nervous system. Therefore, cadherins have been proposed to serve as a molecular "adhesive code" for the specification of nervous system divisions and neural connectivity patterns (54). This idea of an "adhesive code" is now widely accepted as one of the bases for brain regionalization and neural circuit formation (296-299).

Despite the undisputed role of cadherins in cell-cell adhesion, we should not overlook other possible cadherin functions, which are less obvious. It should be noted that signal transduction through cadherin-based adhesion may be equally important, even though it has not been studied as extensively in the CNS (see 300). As noted

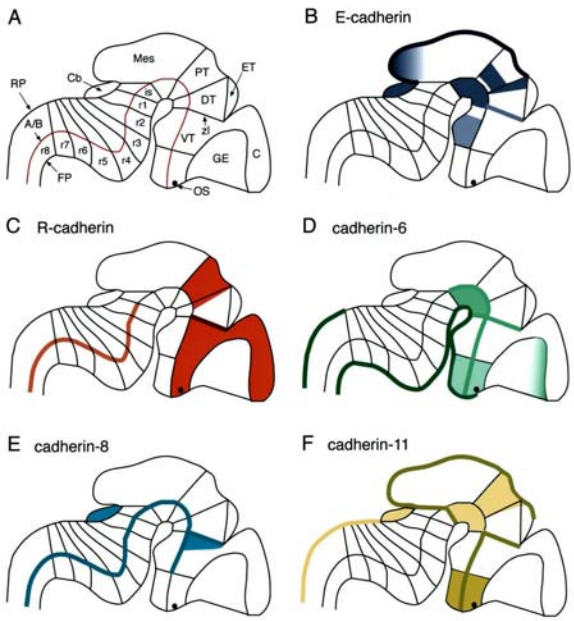

Figure 7. Expression of cadherins in embryonic brain divisions. Schematic expression maps for 5 cadherins in the E12.5 mouse brain are shown (B-F). A schematic diagram of the embryonic divisions and their boundaries is shown in "A". The colored areas indicate expression by the ventricular layer. Each cadherin is expressed in specific embryonic divisions or boundary regions. Reproduced from Redies and Takeichi (54), Copyright 1996, with permission from Elsevier Science. A/B, alar/basal plate boundary; C, cerebral cortex; Cb, cerebellar anlage; DT, dorsal thalamus; ET, epithalamus; FP, floor plate; GE, ganglionic eminence; is, isthmic region; Mes, mesencephalon; OS, optic stalk; PT, pretectal area; r1-r8, rhombomeres 1-8; RP, roof plate; VT, ventral thalamus; and zl, zona limitans intrathalamica.

in the previous sections, cadherins have the potential of interacting with many other molecules and systems. At present, it is still unclear how many of these interactions with other systems influence neural development. Therefore, in order to discuss the roles of cadherins in neural development, we need to keep in mind both the obvious functions and other, more obscure, functions of these molecules.

4.5.2. Neurulation and neuroepithelium

Neurulation is initiated when the axial mesoderm (notochord) induces the overlying ectoderm to form the presumptive neural plate region. During neurulation, E-cadherin disappears from the neural plate, whereas N-cadherin begins to be expressed in the neural plate that invaginates to form the neural groove. The prospective neural tissue then detaches completely from the ectodermal surface to form the neural tube (14). The neuroepithelium of the neural tube represents the primodium of the central nervous system. The relation between class switching of cadherin expression and the inductive signal for neural plate formation is not known. Surprisingly, in N-cadherin-deficient mutant mice, neurulation seems to proceed normally (268). However, it is reported that convergent movement of neuroectodermal cells is severely affected during neurulation (283). A similar switching of expression from E-cadherin to N-cadherin occurs in various other places where a cell layer detaches from the remaining layer, such as during the formation of the lens and the Müllerian duct (3, 267). Another example is gastrulation, when mesodermal cells emerge from the ectoderm by an epithelial-mesenchymal transition. During this transition, cadherin expression switches from E-cadherin to N-cadherin in the newly generated mesoderm (14). A similar class-switching occurs also during gastrulation in *Drosophila* under the control of twist and snail (248). It has been speculated that, in this case, the class switching of cadherins makes it possible for the mesodermal cells to dissociate from the ectoderm. Mesodermal derivatives such as the notochord and the somites continue to express N-cadherin (267). In passing, we may note that, in Hensen's node and in the primitive streak, N-cadherin is distributed asymmetrically, as left-right asymmetry is established in the early embryo (301).

The neural tube is a hollow epithelial structure, whose wall consists of the neuroepithelium. N-cadherin is uniformly expressed in the entire neuroepithelium in the early embryo, with especially high concentrations of the protein in the ventricular lining where AJ's are formed (302, 303). It has been speculated that N-cadherin plays a role in forming and maintaining the tubular and epithelial structure of the neural tube. The developing neural retina provides a good example of the importance of N-cadherin in neuroepithelial histogenesis (273). Blocking the function of N-cadherin in the early retina *in vitro* by antibodies results in a dissociation of the retinal tissue and blocking N-cadherin at a later stage results in the formation of neuroepithelium rosettes and in a disorganization of retinal layers. This result suggests that the ependymal lining is critical for maintaining epithelial structure. In a similar way, neuroepithelial histogenesis in the tectum and dorsal thalamus becomes severely disorganized following injection of anti-N-cadherin antibody into living chicken embryos (274). In N-cadherin–null mutant mice, the neural tube is undulated, but it is still formed (268). This may be due to other adhesive factors that are expressed in the neural tube. However, the N-cadherin mutants die early in development due to the failure of heart formation. The heart deficiency can be rescued by an N-cadherin or E-cadherin transgene specifically expressed in the heart tissue (304). The rescued mutants live longer than the null-mutant embryos, but show inability of the anterior neuropore to close and a collapse of the neural folds. Many dissociated cells can be observed in the lumen of the malformed neural tube. Together, these results indicate that cadherins are important for early neuroepithelial histogenesis.

4.5.3. Transverse and longitudinal embryonic divisions

The neural plate is regionalized along the anterior-posterior (A-P) and dorsal-ventral (D-V) axes (Figure 7). This regionalization is already present when neural induction occurs. In the anterior neural tube, complete transverse segments are called "neuromeres".

They are serially aligned along the A-P axis. The neuromeres are called "rhombomeres" in the hindbrain or rhombencephalon (305) and are called "prosomeres" in the forebrain or prosencephalon (291, 306, 307). The longitudinal divisions include domains such as the floor plate, basal plate, alar plate and roof plate. These primary divisions are evident at the morphological level early in development in the brain, but not in the spinal cord. Many gene regulatory factors and patterning genes, such as members of the Hox, Gbx, Wnt, Pax, Otx, Dlx, Emx, Sox, Nkx, Six and other gene families, are expressed in a region-specific manner within this framework of embryonic divisions (306, 307). The divisional borders coincide with the borders of the expression domains of many of these genes. The same holds for morphoregulatory proteins such as the cadherins (see below).

During development, the divisional organization gradually transforms into the functional architecture of the mature brain (291). In the chicken, it has been demonstrated that each embryonic division gives rise to a coherent domain of gray matter in the mature hindbrain (308-310) and forebrain (311, 312). The embryonic divisions thus act as a framework for later development and provide an important structural basis for the mature brain architecture. Moreover, the divisions can also be related to functional specializations**.** For example, it is known that the motor nerves of the hindbrain emerge in a periodic pattern from every other rhombomere (for review see ref. 313) and some divisional borders represent the preferred location for the extension of primary axon bundles in the brain (314-316). Many divisional boundaries were shown to restrict the migration of neuroepithelial cells or early neurons (317-319), although some specific cell populations also migrated across divisional boundaries (320, 321).

In this context, the regional expression of cell-adhesion molecules, such as cadherins, is of special interest. During and after the formation of the embryonic divisions various cadherins, including E-cadherin, R-cadherin, cadherin-6, cadherin-7, cadherin-8 and cadherin-11, are expressed in particular embryonic divisions throughout the brain (Figs. 6 and 7; for a review see 54). For instance, cadherin-6 is expressed in rhombomere 6 of the mouse hindbrain (258). Many other brain regions can also be characterized by their regional expression of specific cadherins in neuroepithelial cells, radial glia and/or early neurons (Figure 6). Interestingly, some cadherins are expressed more uniformly in specific divisions, whereas others are expressed only in parts of a division, often in a gradient. Strikingly, there is often a sharp border of expression at the divisional boundaries (293, 322). It is conceivable that the expression of each cadherin is controlled by a specific set of gene regulatory factors that are expressed in the same region. However, so far only very few examples of a clear-cut relationship between such expression patterns have been found (see section 4.3.11; 257).

Many of the longitudinal divisions of the neural tube are also induced by transcription factors and soluble factors, such as sonic hedgehog and dorsalin (323, 324). Some cadherins are expressed in specific longitudinal domains in response to these factors. For example, cadherin-7 is expressed in the floor plate and in the dorsal part of the basal plate in the chicken spinal cord, whereas cadherin-6B is expressed in the roof plate and in a part of the alar plate (55, 325).

In some cases, the boundary regions between two adjacent divisions themselves are composed of cells that differ in their cadherin expression from the adjacent divisions. For example, the intrathalamic zona limitans expresses several cadherins that are not expressed by the adjacent tissue of the ventral and dorsal thalamic divisions (54, 326, 327). Likewise, the floor plate and the roof plate of the hindbrain and spinal cord contain specialized midline glial cells with a unique and regional cadherin expression pattern that differs from that of the remaining gray matter (294, 328).

One of the functions of the differential cadherin expression in the embryonic brain divisions may be to stabilize the divisional frame-work by decreasing cell mixing across the divisional borders (62, 329). As outlined above (section 4.2.2), cadherins are adhesion molecules that preferentially bind homophilically (see Figure 4). Due to the differential expression of cadherins across the divisional borders, the neuroblasts in each division have adhesive properties that differ from the cells in the adjacent divisions. As a consequence, the binding affinity of a given cell is probably higher to other cells in the same division than to cells in adjacent divisions. In fact, cells isolated from different brain regions, which express different cadherins, segregate *in vitro* (322, 330). The divisional adhesive specificity may be related, in part, to the regional expression of cadherins, e.g., by radial glial processes that form dense palisades at some of the borders or within boundary regions (for review, see ref. 55). In the Pax6-deficient mutant *small eye*, the adhesive specificity of cortical and striatal cells is lost along with a corresponding change in R-cadherin expression at the border between two major telencephalic divisions, the neocortex and the striatum. In addition, the radial glial fascicle at the border defasciculates (257).

There are 2 possibilities for the emergence of sharp borders of cadherin expression at divisional boundaries. One possibility is that cells are sorted according to which cadherin they are expressing (for review, see 3). In this case, each cell would be predetermined to express a particular cadherin. Another possibility is a switch of cadherin expression at the single-cell level at the boundaries. Boundary sharpening would then be a phenomenon that is secondary to local gene regulatory processes (for review, see 331-333). Which of these two possibilities is realized in the case of cadherin expression in the developing brain remains to be determined.

Also, the importance of cadherins for the maintenance of embryonic brain subdivisions has been shown in various experimental studies. First, F-cadherin expression in a longitudinal domain at the sulcus limitans

of the spinal cord was shown to localize F-cadherin-positive neurons at this specific dorsoventral position (334). Second, the ectopic expression of cadherin-6 and R-cadherin in cells induces preferential sorting into the compartment that expresses the same cadherin (335). The null mutation of cadherin-6 shows no obvious abnormalities in telencephlic compartmentalization; however, the tendency of sorting of ectopic cadherin-6-expressing cells is abolished in the mutant mice. Third, functionally blocking antibodies against N-cadherin disrupt the epithelial structure of specific embryonic divisions in the chicken brain expressing N-cadherin, but not in those divisions expressing R-cadherin (274). Fourth, it has been shown that the forced expression of R-cadherin in neuroepithelial progenitor cells can facilitate their integration into R-cadherin-positive forebrain divisions in the mouse (336). It has also been speculated (258, 294, 337) that cadherins play a role in guiding axon growth at some of the boundary regions, such as the floor and roof plate, which serve as a selective barrier for growing axons (338).

4.5.4. Secondary embryonic subdivisions

Brain regionalization does not stop after the primary transverse and longitudinal divisions have been established. Rather, the primary divisions become further divided into secondary subdivisions, as is evident by their differential expression of cadherins. In the chicken forebrain, each primary division gives rise to multiple secondary subdivisions that differentially express cadherin-6B, cadherin-7 and R-cadherin (311, 312, 327). Like the primary divisions, the secondary divisions persist as coherent domains of gray matter in the mature brain. They give rise to various sets of brain nuclei, cortical layers and regions, or other types of gray matter architecture (see next section). Multiple secondary subdivisions are also observed in the cerebellar cortex, where discrete parasagittal segments of Purkinje cells differentially express various cadherins (339-344) and many other molecules (for review see ref. 345). The parasagittal divisions of the cerebellum have been linked to connectivity patterns. Functional subdivisions of the mammalian cerebral cortex can also be distinguished on the basis of their cadherin expression (342, 346-348).

4.5.5. Neural Cell Migration

Migration of neural cells is an important process in the transformation of the 2-dimensional neuroepithelium into the 3-dimensional architecture of the mature brain. There are several ways that migration can occur (349). First, neuroepithelial cells can migrate and disperse in the ventricular layer. This migration is usually (but not always) restricted at the major divisional boundaries (see section 4.5.3). Second, in most brain regions the early postmitotic neurons migrate radially from the ventricular zone into the developing mantle layer, e.g., in the development of the cortex. This migration is guided by processes of radial glial cells. Third, specific subpopulations of neurons migrate in the mantle layer also tangential to the brain surface. This tangential migration is often observed immediately below the pial surface and it sometimes crosses established divisional borders in the brain, e.g., at the corticostriatal boundary (320, 321).

Cadherins are proposed to be involved in multiple aspects of neural migration, but experimental proof for some of the proposed roles is still lacking. First, a role for cadherins in the restriction of cell mixing between major embryonic brain divisions has been demonstrated experimentally (see section 4.5.3; 62, 257). Second, the radial migration to the mantle layer involves a detachment of neuroblasts from the ventricular zone and inhibition of N-cadherin by functionally blocking antibodies accelerates the departure of neuroblasts from the ventricular zone in the adult canary forebrain (350). Third, the radial migration of neuroblasts itself does not depend on N-cadherin, but radial glial processes express different cadherins on a regional basis (see Figure 6; 293, 327). The role of other cadherins in radial migration has not yet been studied. In the presence of N-cadherin-blocking antibody, neuroblast migration seems to take place (274). However, a study of p35-mutant mice suggests that p35 controls the migratory pattern of neurons in mouse cortex by regulating N-cadherin-mediated adhesion (210). Fourth, it has been reported that cadherin-11 expression delineates the tangential route of migration of neurons from the basal ganglia to the neocortex in the rat (351).

During the development of the peripheral nervous system, neural crest cells detach from the neural tube and emerge at the neural fold region after having undergone an epithelial-to-mesenchymal transition. With this transition, a class switching of cadherin expression takes place. N-cadherin and cadherin-6B disappear from the emerging neural crest cells, while cadherin-7 expression is observed instead and persists during neural crest cell migration (67). If this class switching is perturbed, neural crest emigration from the neural tube is blocked (325). Similarly, overexpression of cadherin-11 in neural crest cells prevents migration and influences neural crest differentiation (352). Thus, the precise regulation of cadherins seems to be required for the proper migration of neural crest cells.

4.5.6. Gray matter regionalization and the formation of brain nuclei

Early post-mitotic neurons migrate in a radial direction from the ventricular layer, where they are born, toward the outer (pial) surface of the CNS, where they form the mantle layer. Here, the early neurons aggregate into various brain nuclei and the layers of cortical structures. From the beginning of mantle layer formation, the early neurons differentially express cadherins (Figure 6; 293, 327, 341, 351). Many cadherins are differentially expressed during the formation of brain (pro-) nuclei, and their expression persists until a late stage of gray matter differentiation (55, 293, 327). As brain nuclei become morphologically more distinct during gray matter differentiation, the expression of cadherins likewise becomes more clearly associated with specific brain nuclei (311, 327, 339). Because cadherins mediate the sorting of cells that express different cadherin subtypes *in vitro*, it has been proposed that they are involved in the formation of brain nuclei and layers from early neurons (294).

Moreover, at later stages of gray matter development, cadherins are differentially distributed in

some brain regions, which show rather homogeneous cytoarchitecture at the morphological level. Examples are the cerebellum (343, 344), the nucleus rotundus of the chicken thalamus (311) and the motor column of the chicken spinal cord (353). Because all these gray matter regions comprise areas with different connections to other parts of the brain, it has been hypothesized that cadherins play a role in determining functional properties within these regions (55, 311, 343).

There is no clear relation between cadherin expression by neuroepithelial cells in a given region of the ventricular layer and the neurons that are born in that region. Clearly, not all postmitotic neurons express the same cadherin as the neuroepithelial cells in the region where they were born. The mantle layer is formed by several waves of migration of early neurons, and cadherin expression in the different cohorts of cells may be subject to changes over time. In most gray matter domains that are derived from embryonic divisions of the brain, various (pro-)nuclei differentially express several cadherin subtypes. In the forebrain of the chicken, the borders of the embryonic divisions are gradually replaced by the borders of cadherin-expressing brain nuclei that fill the division (311, 327). Most forebrain nuclei assume their final position in the embryonic division where they are born; i.e., they are of unisegmental origin. In contrast, in the hindbrain, many brain nuclei are of multisegmental origin (308, 309, 354). Here, adjacent nuclear regions derived from several rhombomeres often fuse, perhaps because mantle layer formation in the hindbrain is more stereotyped than in the forebrain. As a consequence, populations of early neurons with similar molecular determinants (such as cadherins) may come to lie at similar levels of radial stratification in a metameric pattern. It is conceivable that cadherins have a function in the fusion of brain nuclei across rhombomere borders under these conditions (291).

In conclusion, the positional information set up in the neural tube by patterning molecules is translated into an elaborate framework of adhesive cues. Further adhesive patterning occurs in the mantle layer as it increases in thickness, finally leading to the formation of mature gray matter structures that can be characterized by their differential expression of cadherins. These gray matter structures then become connected to form parts of the functional circuitry of the brain (see below).

Until now, there has been only little experimental evidence from studies in the brain to suggest that cadherins are involved in the formation of brain nuclei. Indirect evidence for a role of cadherins in neural morphogenesis comes from studies in *Xenopus*. When N-cadherin is overexpressed in the neural tube, the N-cadherin-positive neural cells make a clump of neural tissue (58, 59). In addition, ectopic expression of N-cadherin in the ectoderm results in the fusion of the ectoderm to the neural tube. As already mentioned above (section 4.5.3), it has also been shown that cadherins are involved in positioning neural cells to specific locations in the neural tube, thus maintaining tissue compartments (334, 335). Finally, in the spinal cord of the chicken embryo, the forced expression of MN-cadherin was shown to play a role in the sorting of motor neuron pools (353). Together, these results suggest that cell sorting in differentiating gray matter is mediated, at least in part, by regional differences in cadherin expression.

4.5.7. Formation of laminar gray matter structures

In some embryonic divisions, the early neurons aggregate not in brain nuclei, but also in layers (laminae) of the mantle layer. This type of gray matter organization is seen, for example, in the cerebral and cerebellar cortices, hippocampus, retina and tectum. In the cerebral cortex the layers are formed in an inside-out manner, i.e., the early born neurons form the inner (deep) layers and the later born ones, from the outer (superficial) layers. In contrast, other laminated structures, e.g., the tectum, show an outside-in pattern of neurogenesis.

Layered gray matter structures often also show a layered expression of cadherins. For example, several cadherins are expressed in a layer-related manner in the tectum, the retina and the cerebral cortex (73, 302, 342, 355-359). In the mouse parietal cortex, cadherin-6 is mainly expressed in layers III and IV, whereas cadherin-8 is expressed in layers V and VI (342, 341).

The role of cadherins in the lamination of the gray matter is not well understood. One possibility, which remains to be tested experimentally, is that cadherins mediate the sorting and selective aggregation of neurons in specific layers in a manner similar to that proposed for brain nucleus formation, especially at the early stages of development. Another possibility is that cadherins play a role in the establishment of functional connections within the cortical laminae (see later section; 55, 360, 361). For example, in the tectum N-cadherin is expressed in the layers that receive retinal input. If N-cadherin function is blocked, the ingrowing retinal fibers do not terminate in these layers alone, but show a more diffuse termination in other layers that do not normally receive retinal input (360).

In many laminated structures, some layers contain dispersed, mixed populations of neurons that express various cadherins, e.g., in the retina and in the tectum of the chicken embryo. It has been speculated that the expression of cadherins by these neurons plays a role in the formation of neural circuits, such as in axonal pathfinding, target recognition or the formation of intrinsic neural circuitry. For example, in the chicken optic tectum 4 cadherins are differentially expressed by subsets of projection neurons. Each of these subsets gives rise to a specific neural projection pathway to other gray matter structures in the brain (73, 294). By *in ovo* electroporation, it has been shown that cadherins are not only markers for these pathways, but provide instructive cues that tell each projection neuron to which neural circuit it belongs (see section 4.5.9; 362). Another example is the inverted ganglion cells in the chicken retina, which also form specific projections to a set of retinorecipient nuclei, some of which are functionally connected to the accessory visual system (358).

4.5.8. Formation of repetitive, small-scale gray matter architecture

Besides brain nuclei and cortical layers, another type of gray matter organization has been linked to cadherin expression. This type is represented by multiple, repetitive changes in cadherin expression within a given region and is found mostly in large neuronal aggregates of the telencephalon.

In the mammalian striatum and in the avian pallium, multiple clusters (patches) of neurons are found embedded in a matrix of gray matter in some brain regions (363), e.g., in the mammalian striatum, a subpallial region. Here the patch and matrix compartments differ in their cytoarchitecture, birth dates, biochemical characteristics and functional connections. At the gene expression level, these two compartments express different cadherins (364, 363). A similar differential expression of cadherins has been observed in the avian pallium, where a correspondence to birth dating patterns has also been reported (365, 363). The fact that the cadherin-defined compartments differ in their birth dates suggests that the cells in each compartment are determined to express specific cadherins before their sorting (365, 366). In the cortex of the chicken embryo, multiple stripes of cadherin-7 expression were found. Their overall pattern is reminiscent of some animal fur patterns and ocular dominance columns in the mammalian visual cortex (367).

4.5.9. Neurite outgrowth

Neurite outgrowth is the first step required for the formation of functional connections between neurons that are at a distance from one another. Cadherins are often expressed during active axon elongation (see, for example ref. 289). It was reported that some growth cones express N-cadherin (368) and other classic cadherins (362). Many cadherins are down-regulated along the neurite bundles when neurites are no longer growing actively (294). These observations point to a possible role for cadherins in neurite outgrowth and growth cone guidance.

N-cadherin has been shown to regulate neurite outgrowth *in vitro*. Purified N-cadherin is a good substrate for neurite outgrowth (369). In addition, neurite outgrowth of retinal ganglion cells is induced by N-cadherin-transfected cells that are presented as a substrate (370). N-cadherin expressed by astrocytes also induces neurite outgrowth (371). The role of N-cadherin in neurite outgrowth has been confirmed *in vivo* in *Xenopus* (372). This study demonstrated that the juxtamembrane region, but not the C-terminal catenin-binding site of N-cadherin, is required for the induction of neurite outgrowth. Moreover, the study shows that neurite outgrowth of non-retinal ganglion cells from the inner nuclear layer and the mesencephalon is not significantly affected by the loss of N-cadherin function. The only other cadherin that has been shown to induce neurite outgrowth to date is R-cadherin (289). In contrast to N-cadherin and R-cadherin, T-cadherin inhibits the outgrowth of T-cadherin-positive neurites (see section 5.1; 373).

N-cadherin-mediated neurite outgrowth seems to require activation of second messenger cascades (142, 143, 374). Neurite outgrowth stimulated by N-cadherin is partly dependent on the tyrosine kinase activity of the FGF receptor by the *cis* association of the FGF receptor with N-cadherin and the activation of tyrosine kinase-phospholipase Cg (PLCg; 375). Intracellular downstream events of this association are a Ca^{2+} influx, release of GAP-43 and activation of calmodulin kinase (CaM kinase), which result in F-actin assembly (143). Interestingly, this cascade can be triggered by a soluble form of N-cadherin (374). However, it should be noted that this mechanism has only been demonstrated for N-cadherin-expressing neuritis, but not for neurites expressing other cadherins. On the other hand, growth cone motility is also regulated by an Abl signaling cascade (for a review see 376). It was reported that δ-catenin is a possible substrate of Abl and that it can interact with Abl in the growth cone (103). In addition, there is some evidence that cadherin-induced neurite outgrowth may be mediated by the association of cadherins with integrins (194, 222). Finally, PTP1B is also reported to regulate N-cadherin-dependent neurite outgrowth (223).

4.5.10. Neuron-glial interaction and myelination

Glial cells are vital for the proper function of the nervous system, including neural development, regulation of neural homeostasis and neural transmission. For glial cells other than the embryonic radial glia, no regional cadherin expression has been observed. This is in contrast to the striking, spatially restricted expression of cadherins by radial glia, neurons and their precursors.

Some radial glia cell populations express specific cadherins, and this expression has been shown to play a role in neural development in some cases. For example, in the retina Müller glial cells express B-cadherin, N-cadherin and R-cadherin (16, 358). B-cadherin is not expressed by any retinal neurons, suggesting that B-cadherin expression might play a specific role in the retina, e.g., in the formation of the ependymal lining by the Müller glial end feet (358). In the developing optic nerve and its head, different populations of glial cells express R-cadherin, cadherin-7 and B-cadherin (377, 378). R-cadherin can induce neurite outgrowth from N-cadherin-positive retinal ganglion cells (377). It has been shown that the different cadherin-expressing populations of glial cells in the optic nerve head play specific roles in axonal guidance, although it is not clear whether the cadherins themselves are important or not (378). N-cadherin on brain astrocytes also induces neurite outgrowth (371). In addition, cadherins seem to be involved in glial-glial interactions. For example, N-cadherin inhibits Schwann cell and oligodendrocyte migration on astrocytes *in vitro* (277, 379).

Myelination of axons is important for the propagation of action potentials in the nervous system, and cadherins have been shown to play a role in the formation of myelin sheaths. For example, N-cadherin mediates the adhesion between oligodendrocyte precursors and axons in the CNS (288, 380) and is important for their initial contact (381). It is also involved in the adhesion of Schwann cells and unmyelinated axons in the peripheral nervous system (PNS; 382). N-cadherin is up-regulated during the

regeneration of peripheral nerves and may possibly play a role in myelination (383). Furthermore, it is localized at the nodes of Ranvier, whereas E-cadherin is localized at autotypic junctions and between the myelin sheaths of Schwann cells (108, 384).

4.5.11. Fasciculation

Fasciculation is the process by which individual nerve fibers adhere to each other to form nerve fiber bundles. Fasciculation can occur between the first (pioneer) axons, as well as between axons that follow pre-existing nerve fibers (axonal "tracking"). Whether fasciculation occurs or not may be determined by whether or not individual growth cones adhere to pre-existing nerve fibers along their path of migration. In at least some cases, fasciculation may thus be related to axonal guidance (see section below). Supporting this notion, N-cadherin was shown to play a role in fasciculation and guidance of sensory neurites in the chicken hindlimb (385). In *Drosophila*, the loss of DN-cadherin function results in defective fasciculation and pathfinding errors (386). A similar function for a molecule resembling DN-cadherin has been demonstrated in *C. elegans* (387).

Fasciculation seems to be regulated by the relative strength of adhesion between the growing axons and their surrounding cells or substrate. For example, *in vitro*, fasciculation can be observed between specific types of N-cadherin-positive neurites, and this fasciculation can be blocked by antibodies against N-cadherin (289, 388). If the same neurites grow on substrate cells that express N-cadherin strongly, these axons tend to defasciculate. Similarly, the relative strength of neurite-neurite and neurite-substrate adhesion may regulate fasciculation and defasciculation also *in vivo*.

Fasciculation of axons may follow the rule of selective adhesiveness. Many large fiber tracts contain subpopulations of neurites that segregate according to the type of cadherin they are expressing. For example, N-cadherin and R-cadherin are expressed by different fiber populations in the vagus nerve of the chicken hindbrain (289, 294). The visceral fibers express R-cadherin, whereas the somatosensory fibers express N-cadherin. These fiber systems have a different course within the hindbrain. A similar segregation can be seen in the dorsal root of the spinal cord, where small fascicles of unmyelinated axons selectively express E-cadherin (389, 390). Many other examples of specific fiber populations that selectively express a given cadherin have been described in the literature (73, 294, 329, 339, 343, 356, 364, 391). For experimental support for the role for cadherins in axon fasciculation, see the section below.

4.5.12. Growth cone navigation and pathfinding

Axonal pathfinding and target recognition are critical steps in the formation of neural circuits (392). At the tips of the growing axons, the growth cones act as sensors to decide the direction of axonal navigation. It is generally established that the growth cone has receptors that read out environmental guidance cues. Many guidance mechanisms have been proposed, including contact-dependent *versus* diffusible mechanisms, attractive *versus* repellant cues and guidepost cells *versus* gradients of guidance molecules (392). Except for T-cadherin, which acts as a repellent molecule, cadherins seem to provide a contact-dependent adhesive mechanism. It has been reported that several classic cadherins are expressed on growth cones (362, 368).

In the course of growth cone navigation, cadherins are expressed in various restricted places and by different types of cell, such as by radial glia cells, neuroepithelial cells in embryonic subdivisions, pre-existing fiber fascicles and target brain nuclei and cortical layers (see sections above). It has been demonstrated experimentally that N- and R-cadherin are permissive substrates for growth cone navigation (289, 368, 371, 377).

The differential expression of cadherins along fiber pathways during the period of active axon outgrowth (see section 4.5.11) strongly suggests a role for cadherins in growth cone navigation and pathfinding. *In vitro* it has been shown that an antibody against N-cadherin can cause a reduction in the number of axonal branches and aberrations of target projections in co-culture experiments using chicken retina and tectum (360). In the *Xenopus* visual system, antibodies to N-cadherin and β1-integrin cause pathfinding errors in retinotectal projections (393). Interestingly, each antibody alone was not sufficient to cause this effect. Also in a *Drosophila* mutant of DN-cadherin subsets of axons show defective fasciculation and pathfinding errors (386).

There is also evidence from *in vivo* experiments that the differential expression of multiple cadherins directs axons along specific fiber pathways by a homotypic guidance mechanism (362). Several projection pathways leave the avian optic tectum in a thick fiber bundle, the brachium of the superior colliculus. In the chicken embryo, this fiber bundle contains subfascicles that differentially express cadherins and project to different targets in the brain (294, 358). When a relatively small number of tectal projection neurons are induced to ectopically express 1 of 4 different classic cadherins, their axons prefer to grow along the pathway that expresses the same cadherin (326). This result shows that cadherins provide instructive cues that tell neurons to which neural circuit they belong. It also supports the notion that cadherins play a role in selective fasciculation (see section 4.5.11).

4.5.13. Target recognition and functional systems

For the precise establishment of neural circuitry it is necessary that growing axons recognize their partner neurons in the appropriate target areas. As already formulated by R. Sperry in his chemoaffinity hypothesis (394), the selective growth of axons along specific pathways (see section 4.5.12), as well as the establishment of functional connections in the target, is likely to be based on molecular recognition mechanisms.

Considering that cadherins are adhesion molecules with homotypic binding specificities (“adhesive code”), it has been hypothesized that target recognition is achieved, at least in part, by the binding of the same cadherin subtype present on the growth cone and on the

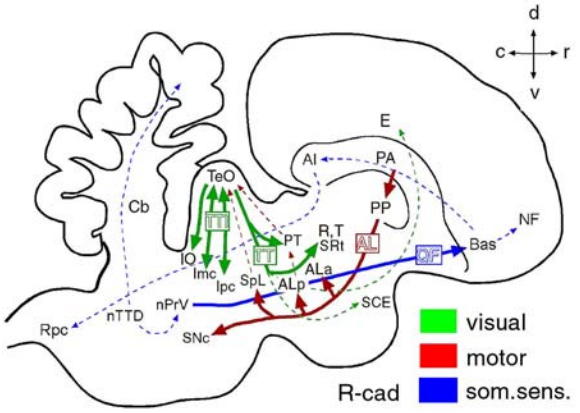

Figure 8. Expression of R-cadherin by specific neural circuits in the embryonic chicken brain. Thick arrows represent R-cadherin-positive fiber tracts of the visual system (TTI, tectoisthmic tract; TT, tectothalamic tract; in green), of the efferent motor system (AL, ansa lenticularis; in red) and of the somatosensory system (QF, quintofrontal tract; in blue). The dashed lines represent connections that could not be visualized as R-cadherin-positive but are known from the neuroanatomical literature. All the fiber tracts shown connect gray matter structures, which also express R-cadherin (abbreviations in black letters). Together, these structures form neural circuits in the different functional systems. For abbreviations of gray matter structures, see the study by Arndt and Redies (339). Data are from the same study. Figure reproduced from Redies (55), Copyright 2000, with permission from Elsevier Science.

target cells (54, 55, 294, 296, 395). This hypothesis is based on extensive studies on expression patterns of classic cadherins and some protocadherins.

Results from descriptive studies have demonstrated that the targets of a particular fiber projection often express the same type of cadherins as the neurons that send out the projections. Entire neuronal projection pathways and circuits can be characterized by the expression of a specific cadherin. Such a correlation of cadherin expression with functional connectivity patterns was first described for N-cadherin and R-cadherin in the tectofugal projection pathways of the chicken embryo (294). Various other functional systems have also been shown to be composed of neural circuits that differentially express specific cadherin subtypes. Examples are the subcircuits of the auditory and limbic systems that express differentially cadherin-6, cadherin-8, cadherin-11, N-cadherin, R-cadherin and OL-protocadherin in the mouse (342, 356, 391, 396; see section 5.2.7, and Figure 9 for OL-protocadherin) or the subcircuits of the cerebellar and retinofugal systems that express differentially N-cadherin, R-cadherin, cadherin-6B, cadherin-7 and cadherin-10 in the chicken (73, 339, 340, 343, 358, 377) and cadherin-6, cadherin-8, cadherin-11 and OL-protocadherin in the mouse (342, 364, 391, 397). In turn, a complete survey of the expression of R-cadherin in the embryonic chicken brain has shown that this molecule is present on subcircuits of several functional systems, such as the visual, somatosensory, auditory and motor systems (Figure 8; 339). Similar results have been obtained for other classic cadherins in several species (same references as above; for a review see 55) and for OL-protocadherin in the mouse (397). Secondary subdivisions within larger brain structures (brain nuclei and cortical regions) often also show differential expression of cadherins, which likely relate to functional connectivity patterns. For example, the cerebral cortex of mouse is divided into several regions that can be characterized by their expression of cadherin-6, cadherin-8 and cadherin-11 (342, 347, 348, 356, 357). Each region is connected to thalamic nuclei that express the same cadherin subtype. A similar correlation is observed between the parasagittal functional domains of the cerebellar cortex of chicken and mouse and the brain nuclei that have functional connections with the cerebellar cortex (e.g., the deep cerebellar nuclei and the inferior olive; 341-343, 364). In summary, the expression of cadherins in functional systems and in their neural subcircuits is likely to be involved in the formation or maintenance of neural connectivity.

It should be pointed out that there is co-expression of different types of cadherins both at the regional and cellular level (for a review, see 55). The adhesive code, which is mediated by cadherin expression, is thus a combinatorial one and allows for a large degree of complexity of cellular interactions during neural circuit formation (73).

Experimental evidence for a role of N-cadherin in target recognition comes from experiments in the retinotectal system of the chicken embryo (360). During normal development, N-cadherin becomes concentrated at laminae b-e of the tectum as the retinotectal synapses are forming. If N-cadherin is blocked by antibodies, retinal axons grow through these target laminae *in vitro* and *in vivo*. In addition, if one eye is removed, N-cadherin remains diffusely distributed in the tectum. Thus, it has been hypothesized that N-cadherin participates in the formation or stabilization of synapses once axons reach their target (361). Another example is the *Drosophila* visual system, in which N-cadherin seems to regulate target specificity (398). Mosaic analysis in this system shows that R7 axons, which lack N-cadherin, mistarget to the R8 recipient layer.

Other results do not seem to support a role for cadherins in target recognition. For example, major fiber projections have been reported to be normal in cadherin-11 null-mutant mice (399). In this case, it is perhaps possible that other cadherins and/or other adhesion molecules compensate for the loss of cadherin-11 function, due to a redundancy in the expression of adhesive factors. It is also possible that cadherin-11 plays a role in the fine-tuning of target specificities and thus minor misrouting may be difficult to detect. Moreover, it is clear that not all target areas express the same cadherin as the neurons that project into these areas. For example, the target layer of the E-cadherin-positive sensory neurons in the spinal cord does not express E-cadherin (389). Heterophilic interactions may mediate target recognition in these cases. Clearly, further experimental evidence is required to clarify the

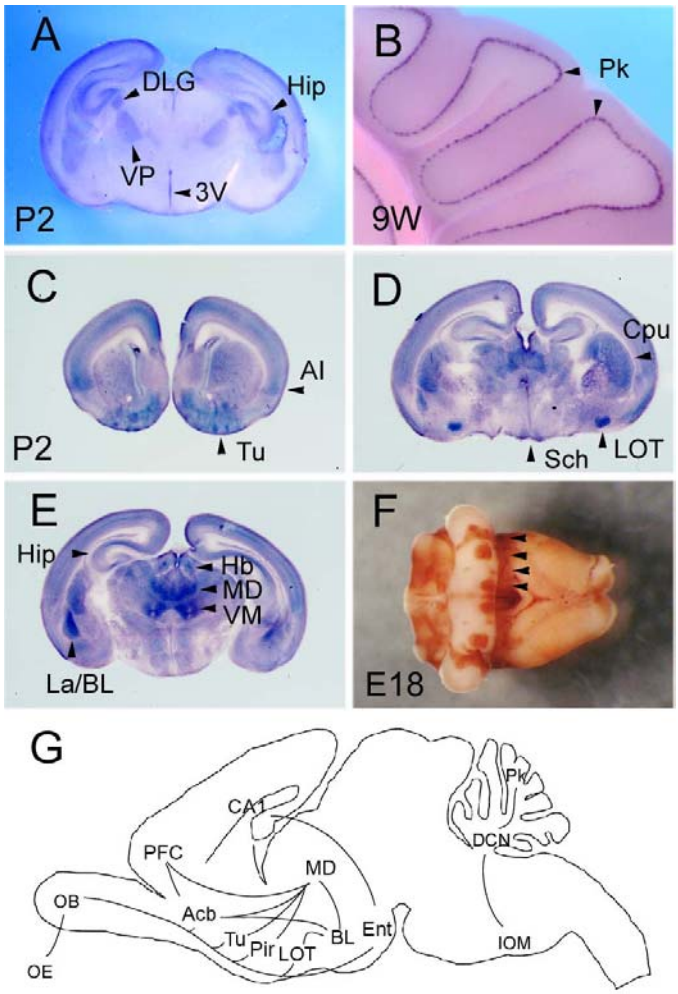

Figure 9. Expression of protocadherin 2 and OL-protocadherin in the developing brain. (A) Expression of protocadherin 2 in the P2 mouse brain. Some brain regions such as DLG, VP, 3V and hippocampus specifically express the mRNA of this protocadherin. (B) Expression of protocadherin 2A in Purkinje cells in the adult cerebellum. (C-E) mRNA of OL-protocadherin was visualized by *in situ* hybridization of coronal slices from a postnatal mouse brain. Various brain regions and brain nuclei in the olfactory system and the limbic system specifically express OL-protocadherin. (F) Distribution of OL-protocadherin protein in the cerebellar cortex of an E18 mouse embryo. Note that the protein is distributed in parasagittal stripes (arrowheads) in a manner similar to that of classical cadherins. (G) Schematic diagram of the possible OL-protocadherin-mediated neural network. All the brain nuclei listed express OL-protocadherin. However, neural connections represented by lines have not confirmed for OL-protocadherin localization yet. (A) and (B) were reproduced from Hirano *et al.* (445), Copyright 2002, with permission from Elsevier Science. Abbreviations: Acb, Accumbens nucleus; AI, agranular insular cortex; BL, basolateral amygdaloid nucleus; CA1, CA1 region of Ammon's horn; Cg, cingulate cortex; Cpu, caudate-putamen; DCN, deep cerebellar nucleus; DLG, dorsal lateral geniculate nucleus; Ent, entorhinal cortex; Hb, habenular nucleus; Hip, hippocampus; IOM, medial nucleus of the inferior olive; La, lateral amygdaloid nuclei; LOT, nucleus of the lateral olfactory tract; MD, mediodorsal thalamic nucleus; OB, olfactory bulb; OE, olfactory epithelium; PFC, prefrontal cortex; Pir, piriform cortex; Pk, Purkinje cells; Sch, suprachiasmatic nucleus; Tu, olfactory tubercle; VM, ventromedial thalamic nucleus; VP, ventral posterior thalamic nucleus; 3V; third ventricle.

specific role, if any, of cadherins in target recognition.

4.5.14. Synapse formation and plasticity

The synapse is a specialized adhesion site between neurons where signals are transmitted from the presynaptic neuron to the postsynaptic neuron (Figure 5E). Ultrastructurally, synapses are related to the adherens junction, although synapses usually have an asymmetric structure (400). So far, N-cadherin, E-cadherin, R-cadherin, cadherin-7 and cadherin-11, as well as the non-classic cadherin CNR1, have been found at the synapse of particular neurons (109, 110, 343, 399, 401, 402). Interestingly, at least N-cadherin, R-cadherin and cadherin-7 are localized at the region adjacent to the active, transmitter-releasing zone of the synapse (109, 110, 343). N-cadherin has been reported to be a component of the NMDA receptor multiprotein complex (403). It has been suggested that N-cadherin is involved both in the formation and in the maintenance of synapses (109,404). In *Drosophila*, DN-cadherin has been shown to be required

for the maturation of the synapse (405). Based on the evidence available to date, it is assumed that cadherins provide a mechanism by which adhesive specificities are conferred to synapses (406-409).

Synapses are formed by the transformation of growth cones or axonal surface membranes when they come into contacts with their target. Cadherin expression and localization are actively regulated during the formation of the synapse. For example, N-cadherin becomes concentrated at synapses at the time when the barrel structures of the thalamic projections to the somatosensory cortex are formed (410). After the establishment of this connection, N-cadherin is downregulated, although catenin expression persists. This suggests that another cadherin, such as R-cadherin, replaces N-cadherin at those synapses (356). In addition, the N-cadherin expression pattern is changed after an experimental alteration of the barrel pattern (409). Moreover, it has been reported that N-cadherin is localized at all synapses in the early phase of hippocampal development, but becomes gradually restricted to excitatory synapses *in vitro* later in development (411).

It is known that the morphology of synapses actively changes during excitation (412-414) and that the efficiency of synaptic transmission is modified in an activity-dependent manner. This modification is known as synaptic plasticity and synaptic plasticity is thought to be a major basis for memory and learning. Long-term potentiation (LTP) is an experimental model of synaptic plasticity. During the early phase of LTP (E-LTP), synapses are modified based on pre-existing synaptic mechanisms, whereas the late phase of LTP (L-LTP) involves more fundamental cellular changes such as modulations of gene transcription and protein synthesis and a remodeling of the synaptic connection. Because cell-adhesion molecules, such as members of the Ig and cadherin superfamilies and integrins, are localized at mature synapses, it has been speculated that adhesive mechanisms are involved not only in the formation of synapses but also in their plasticity. Evidence to support this notion is gradually accumulating (300, 400, 409, 415, 416).

In the case of cadherins, it has been reported that function-blocking antibodies and a blocking peptide for N-cadherin or E-cadherin reduce E-LTP in hippocampal slices (295), although questions regarding the specificity of the probes have been raised (417). It is notable that basal synaptic properties are not affected by the antibodies, as is also often the case for other cell-adhesion molecules (400). Microscopic observation showed that the morphology of synapses and the synaptic localization of cadherins actively changed during stimulation (418). These observations suggest that cadherins are involved in the induction of E-LTP.

However, the molecular mechanism of cadherin-induced synaptic plasticity remains largely unknown. One possible mechanism is that a reduction in the Ca^{2+} concentration in the synaptic cleft during stimulation leads to destabilization of cadherin-based adhesion and thereby induces synaptic plasticity (415). This hypothesis is supported by the observation that an elevation of Ca^{2+} prevents the inhibitory effect of the peptides and antibodies on plasticity (295). On the other hand, it has been reported that depolarizaton of neurons induces N-cadherin dimerization and protease resistance, leading to a strengthening of synaptic adhesion (418). Another possibility is that the width of the synaptic cleft decreases as the extracellular domains of cadherins interact in the *trans* configuration (44, 296). The distance between pre- and postsynaptic membranes derived from this model matches well the observed width of the synaptic cleft. Alternatively, cadherin binding may generate intracellular signals, which modify indirectly synaptic strength by other mechanisms. Finally, cadherin function itself may be regulated by intracellular signaling events through the cytoplasmic domain, as is known to be the case in E-cadherin function, which is regulated by the muscarinic acetylcholine receptor in lung carcinoma (172). In this context, it is of interest that N-cadherin is a component of the NMDA receptor multiprotein complex (403).

Cadherins also seem to be involved in L-LTP. At least in part, L-LTP is based on the formation of new synapses. Thus, the role of cadherins in L-LTP is thought to be similar to that in *de novo* formation of synapses (419). In fact, it has been reported that N-cadherin is synthesized and recruited to newly generated synapses during the formation of L-LTP and that the cAMP-dependent protein kinase (PKA) signaling pathway seems to be involved in this process (419). Last but not least, the cadherin-mediated remodelling of dendritic spines, as well as the observed shift in the distribution of intracellular β-catenin between dendritic spines and shafts upon depolarization have been implicated in synapse plasticity (300, 416).

In contrast to most synapses in the central nervous system, the synaptic cleft of the neuromuscular junction contains a basement membrane (420). Thus, the attachment of the presynaptic membrane to the muscle cell resembles more closely cell-substrate adhesion than cell-cell adhesion. However, N-cadherin seems to be involved in stabilization of mature neuromusculuar junctions, because N-cadherin accumulates only after the first synaptic contacts have been established (384). N-cadherin is present in the basal lamina, where it associates with collagen fibers, suggesting that N-cadherin may be processed in an unusual way. How N-cadherin is involved in the formation of the neuromuscular junction is not clear at present.

5. NONCLASSIC CADHERINS

Nonclassic cadherins comprise a variety of molecules (Figure 2 and Table 1). Major types are desmosomal cadherins, Fat-type cadherins, Ret, protocadherins, flamingo and calsyntenin. This classification is based on sequence similarities of their cytoplasmic domain and the overall structure of all domains (23, 25, 421). Basically, the cytoplasmic domains of nonclassic cadherins are completely different from those of the classic cadherins. In addition, there are striking differences in the overall organization of the extracellular domain. Thus, it is reasonable to assume that different

nonclassic cadherins have different functions and roles, including different signaling pathways.

5.1. T-cadherin (cadherin-13 / V-cadherin / H-cadherin)

T-cadherin is a unique cadherin that lacks a cytoplasmic domain and is linked to the cell-surface membrane by a glycosyl phosphatidylinositol (GPI) anchor (Figure 2; 422, 423). A splice variant with a slightly different amino acid sequence at its C-terminal region has also been reported (424). Sequence similarities between their extracellular domains suggest that T-cadherin is closely related to and may have evolved from classic cadherins (23). However, because the overall structure is quite different from that of typical classic cadherins, T-cadherin is usually classified separately. Note that cadherin-8 and cadherin-11 also have an alternatively spliced variant that lacks a transmembrane region (see section 4.1; 38).

T-cadherin is expressed in various neural tissues (425-427). Of particular interest is that T-cadherin delineates the developing motor axon-hindlimb projection pathway. Initially, T-cadherin is uniformly expressed by all motor neuron axons, but later in development it becomes restricted to a particular subset of axons. T-cadherin is expressed by parts of the mesenchyme, but growing motor axons avoid this tissue. Thus the mesenchymal expression of T-cadherin and the growth route of the motor axons are complementary, suggesting that T-cadherin is a repellent factor for motor axon growth. In agreement with this notion the extension of motor axons can be inhibited by T-cadherin *in vitro* (426). Moreover, T-cadherin is selectively excluded from the neuromuscular junction that is demarcated by the expression of N-cadherin (428). In addition, T-cadherin acts as a negative regulator of neural cell growth in response to EGF in a transfectant cell line (373). However, the mechanisms underlying the repulsive effect of T-cadherin and the associated signal transduction pathways remain to be elucidated.

T-cadherin is also known as V-cadherin, named after its discovery in (vascular) endothelial cells. It has been reported that low-density lipoprotein (LDL) binds to T-cadherin and can influence the homophilic interaction of T-cadherin in aortic smooth muscle (429, 430).

5.2. Protocadherins

First of all, it should be noted that the term "protocadherin" has been used in various different ways (431). It is often used in the more general sense to denote all "proto"-types of cadherins, which share tandemly arranged EC2-like cadherin domains. By this definition, molecules such as Fat, protocadherin 15 and flamingo can also be classified as protocadherins. This classification is supported further by the fact that most of these "protocadherins" have few introns, in contrast to the classic cadherins, which have many introns (27). However, in the present review, we will use the word "protocadherins" in a narrower sense in order to categorize the members of the cadherin superfamily more distinctly, by excluding large cadherins such as flamingo, etc. (see below). Therefore, the definition of protocadherin is narrowed to cadherin-like molecules, which have 6 or 7 consecutive cadherin domains and show no homology to classic cadherins.

Protocadherins represent one of the major subfamilies of the nonclassic cadherin family (23). All protocadherins contain EC2-like cadherin domains, but protocadherins are divided into two subtypes with 6 cadherin domains or 7 cadherin domains (Figure 2). Moreover, the cytoplasmic region is totally different from that of the classic cadherins (431). Differences in the cytoplasmic regions have been used to classify protocadherins into several subgroups. Because there is only a limited sequence conservation among protocadherins, it can be speculated that each subgroup has a distinct signaling pathway or a different type of cytoskeletal interaction and, consequently, a distinct function (432). Therefore, we will discuss each protocadherin subgroup independently in the following sections.

Interestingly, protocadherins are found only in vertebrate species and many protocadherins are specifically expressed in the nervous system (23). Thus protocadherins may have evolved rapidly in vertebrates to assume specific, as yet unidentified functions, which likely are specific to the nervous system. There are at least 3 distinct gene clusters comprising a total of about 50 protocadherins (the protocadherin 2 or protocadherin γ cluster, the protocadherin 3 or protocadherin β cluster and the CNR or protocadherin α cluster; 28). Interestingly, members of the protocadherin 2 and CNR subfamilies each share 1 common C-terminal exon (Figure 3). Other protocadherins, such as protocadherin-1 and OL-protocadherin, are not found within a cluster of related genes.

5.2.1. Protocadherin 1 (protocadherin 42, Axial protocadherin)

Protocadherin 1 (protocadherin42) was the first to be identified in humans (20). In rats, expression seems to be restricted to the nervous system and begins during later embryogenesis in the rat (20). It increases as the brain matures. On the other hand, Axial protocadherin, a *Xenopus* homologue, is expressed in the axial mesoderm in the neurula stage, but it is expressed in various tissues in the tailbud stage (433). In transfectant cell lines, protocadherin 1 is localized at cell-cell junctions and mediates weak cell adhesion (20). However, it was shown that Axial protocadherin mediated prenotochord cell sorting in *Xenopus* (433).

5.2.2. NF-protocadherin (NFPC) and BH-protocadherin

NF-protocadherin (NFPC) shares a high degree of sequence homology with protocadherin 1 in its cytoplasmic domain (434). It has been identified in *Xenopus* and is expressed in the deep sensorial layer of the embryonic ectoderm and in a restricted group of cells in the neural folds. Ectopically expressed NFPC mediates strong adhesion and inhibits cell mixing *in vivo*. If NFPC is blocked by a dominant-negative molecule, blistering is observed (434). There may be 2 possible explanations for these results: (1) NFPC mediates strong adhesion by interacting directly with the cytoskeleton and (2) NFPC

mediates strong adhesion indirectly by affecting other adhesion systems through signal transduction.

NFPC provides a good example of the functional differences between protocadherins and classic cadherins. The dominant-negative effect of NFPC on epithelial adhesion cannot be rescued by N-cadherin and E-cadherin and only partially by C-cadherin (434). This result indicates that adhesion alone is not enough to rescue the function of NFPC. Therefore, NFPC-mediated adhesion is qualitatively different from adhesion mediated by classic cadherins. Most likely, this difference is due to different signal transduction pathways induced by NFPC and classic cadherins.

BH-protocadherin has been identified in both humans and mice, and it has sequence similarity with protocadherin 1 and NFPC in its cytoplasmic domain (435, 436). BH-protocadherin seems to be an ortholog of *Xenopus* NF-protocadherin. In the human genome, BH-protocadherin is located at a locus different from that of protocadherin-1. BH-protocadherin has 3 isoforms (a, b and c type), which differ in their cytoplasmic domain, and is expressed predominantly in the cerebral cortex (437). It binds to protein phosphatase 1α isoforms PP1α and PP1α2, the former of which seems to be involved in synaptic plasticity and long-term potentiation (438, 439). BH-protocadherin can inhibit PP1α enzymatic activity in a substrate-specific manner (437). Although the biological function of BH-protocadherin is not known, similar to other cadherins**,** it may play a role in synaptic modulation.

5.2.3. Protocadherin-X's (PCDHX and PCDHY)

Protocadherin-X (PCDHX) is a novel protocadherin that maps at the human XY homology region in Xq21.3 of the X chromosome (440, 441). There are two isoforms of PCDHX with different cytosplasmic tails (440). As expected from the conservation of the regions between the sex chromosomes, the homologous locus (PCDHY) was found at Yp11.2 on the Y chromosome (441). PCDHX and PCDHY share 98.3% amino acid identity and have an identical gene structure comprising 6 exons (441). It is interesting that these protocadherins have a slight sexual dimorphism in their structures, which may cause functional differences. These genes are expressed predominantly in the brain and, surprisingly**,** the PCDHX and PCDHY genes seem to be regulated differentially (441). Therefore, it is possible that these protocadherins contribute to sexual dimorphism in neural development.

5.2.4. The protocadherin-2 (protocadherin γ, protocadherin 43) subfamily

The protocadherin-2 (protocadherin γ) subfamily has 22 members in mice and humans (Figure 3; 442). The genes for these protocadherins are clustered on one chromosome. Surprisingly, all members share 1 common C-terminal exon. Although each member seems to have its own promoter, the regulation of protocadherin expression and the splicing mechanisms involved in generating the individual mRNAs remain to be elucidated (442). There seem to be 2 or 3 splice-variants for each member (20).

Protocadherin-2A (originally named protocadherin43/protocadherin-2; 20) shows weak homophilic adhesion activity in a transfectant cell line, where it is localized at the cell-cell junctions (20). In contrast to classic cadherins, it is easily solubilized with non-ionic detergents, suggesting a weak linkage to the cytoskeleton (443). If the cytoplasmic domain of protocadherin-2A is replaced by that of E-cadherin, the chimeric molecule shows strong adhesion activity (443). Thus, the extracellular domain of protocadherin-2A may have a function in protein-protein interaction similar to that of a classic cadherin.

Members of the protocadherin-2 family seem to be differentially expressed in the mouse brain (444). Protocadherin-2A is expressed strongly in adult Purkinje cells of the cerebellum (443, 445). In the developing brain it is expressed in some specific nuclei of the brain, such as the dorsal lateral geniculate nucleus (Figure 9A; 445). In addition, prominent expression can be seen in some ependymal cells and Purkinje cells (Figure 9A and B; 445). Although details of the expression patterns still remain to be examined, protocadherin-2A, protocadherin-4 (2B) and protocadherin-5 (2D) are differentially expressed in thalamic nuclei, the hippocampus and Purkinje cells (444). Protocadherin-2C is expressed in a pattern that is quite similar to, but also distinct from that of OL-protocadherin (396). Members of the protocadherin 2 subfamily are also expressed dynamically during odonogenesis (446).

5.2.5. The protocadherin-3 (protocadherin β) subfamily

In humans the protocadherin-3 (protocadherin β) subfamily has 19 members, including pseudogenes (28). Interestingly, there are 22 members in the mouse. Unlike the protocadherin-2 and the CNR subfamilies this family is unique in that its members do not have a common C-terminal exon. Thus it has been speculated that the common exon was lost during gene evolution. Like the genes of the protocadherin-1 and protocadherin-2 subfamilies, the protocadherin-3 genes are located in 1 large cluster in the human genome.

The protein of one member of this subfamily in the rat (named "protocadherin-3") is localized at cell-cell junctions in transfectant cells, where it seems to associate with two other proteins (170 kDa and 50 kDa; 447). In contrast to classic cadherins, protocadherin-3 protein is sensitive to trypsin digestion even in the presence of Ca^{2+}. Protocadherin-3 is expressed in various areas of the rat brain.

5.2.6. CNR subfamily (cadherin-like neural receptors, protocadherin α subfamily)

The CNR subfamily of protocadherins consists of 17 members in mice and 16 members in humans**.** These genes are arranged in a single large gene cluster (28, 32). The extracellular domains of CNR's are highly conserved and there is an RGD motif in the EC1 domain (402), which is missing in 2 distant members of the CNR family (448). CNR's have 3 isoforms with variations in their C-terminal region (449). It has been shown that during brain development somatic mutations accumulate in CNR

transcripts, especially in the EC1 domain (450). It is possible that these somatic mutations give rise a diversity of binding specificity of CNR cadherins.

CNR-1 is specifically expressed in the brain and spinal cord (402, 451) and is localized at synapses (402). In addition, individual neurons in the olfactory bulb of the mouse seem to express different sets of CNR's, suggesting that CNR may contribute to the specificity of synaptic connections (402).

CNR-1 has been identified as a binding partner of Fyn, a Src family protein kinase. This interaction is probably mediated by the PXXP motifs in the cytoplasmic region of Fyn (402). In the nervous system Fyn is localized in growth cones and synapses (452) and is involved in various functions, such as N-CAM-dependent neurite growth and NMDA-dependent long-term potentiation (453, 454). Fyn-deficient mice show abnormalities in various important behavioral activities, including suckling and spatial learning (454, 455). In adult mice, many members of the CNR subfamily are reported to be expressed in the same set of brain regions, including the olfactory bulb, hippocampus and cerebellum. The synaptic localization of CNR-1 suggests that it may interact with other synaptic molecules, such as the NMDA-receptor. Taken together, these data indicate that CNR's are likely to be involved, at least in part, in Fyn-related neural processes in the nervous system.

CNR's have been proposed to be receptors for reelin (451). It has been speculated that, in the developing brain, these molecules are involved in corticogenesis in the developing brain as part of the reelin cascade (451). In a hypothetical model reelin from Cajal-Retzius cells binds to the EC1 domain of CNR expressed by migratory neurons, resulting in the activation of Fyn kinase. Fyn phosphorylates a tyrosine residue of mDab1 (the mouse homologue of Disabled 1) in the VLDR/ApoER2 lipoprotein receptor complex and phosphorylated mDab1, in turn, activates further downstream signaling. It is possible that CNRs form a receptor complex with these lipoprotein receptors. Based on all data currently available, it is thought that the reelin/CNR cascade provides a stop signal for neuroblast migration and also has an instructive role in the differentiation of cortical neuroblasts and their detachment from radial glial processes. The expression of reelin and CNR's in various other brain regions, such as the olfactory bulb, hippocampus, external granule layer of the cerebellum and spinal cord, suggests that the postulated reelin/CNR system may also have other roles in neural development (402, 456, 446).

5.2.7. OL-protocadherin

OL-protocadherin has 6 cadherin repeats in its extracellular domain, with a glycine-rich region inserted in EC2 of its extracellular domain (397). There is a splice variant with a different C-terminal region. The amino acid sequences of the cytoplasmic domains are rather unique. In a transfectant cell line, OL-protocadherin exhibits a Ca^{2+}-dependent adhesive activity that is weak and homophilic (397).

Expression of OL-protocadherin is largely restricted to the nervous system, where it is first expressed at the embryonic stage and persists in the adult (397). In the embryo, OL-protocadherin is expressed in various brain regions such as the habenular region, superior colliculus and parts of the cerebellar cortex. Postnatally, it is expressed in parts of the olfactory system and the limbic system, such as the olfactory epithelium, olfactory bulb, piriform cortex, olfactory tubercle, nucleus of lateral olfactory tract, amygdala, hippocampus and some thalamic nuclei (Figure 9C-E). The relation of the expression pattern with specific parts of functional systems is reminiscent of the expression of classic cadherins and indicates that OL-protocadherin may be involved in the formation of particular neural circuits in these systems (Figure 9G; 397). OL-protocadherin protein has been observed along some local fibers and tracts such as stria terminalis, stria medulalis, fasciculus retroflexus and inferior thalamic radiation during development (Aoki *et al.* unpublished observation). Because their cytoplasmic domains differ substantially, the molecular processes regulated by OL-protocadherin seem to be different from those regulated by classic cadherins. OL-protocadherin protein is abundant in the glomeruli of the olfactory bulb, where olfactory neurons and mitral cells make synapses. Like many other cadherins, it may thus be involved in the establishment or stabilization of synaptic contacts (397).

OL-protocadherin is expressed in parasagittal stripes of developing Purkinje cells of the cerebellar cortex of postnatal mice, both at early and later stages of cerebellar development (Figure 9F). The expression pattern has been related to similar, stripe-like expression patterns of other molecules in the cerebellum, such as several "early onset" cerebellar markers including engrailed and classic cadherins and a "late onset" marker, zebrin II (344). These markers, in turn, have been related to the mature functional organization of the cerebellar cortex. Based on these results, it has been speculated that the embryonic cerebellar compartments are delineated by early onset genes and persist into mature functional stages of development.

5.2.8. Paraxial protocadherin (PAPC)

Paraxial protocadherin (PAPC) has homophilic adhesion activity and can mediate cell sorting *in vitro*. In *Xenopus* during gastrulation it plays an important role in convergence and extension movements of mesodermal cells (457, 458). *In vitro* experiments using the animal cap assay demonstrate that exogenous PAPC can promote changes in cell morphology. These results indicate that PAPC signaling can influence the rearrangement of the cytoskeleton. PAPC is a downstream target of *spaidetail,* which is known to be involved in the convergent movement of the lateral mesoderm (458).

In *Xenopus*, PAPC is also expressed transiently in the anterior part of the developing somites, where its expression is controlled by the Thylacine1 and Notch pathway (457, 459). A study on the effects of a dominant-negative molecule of PAPC shows this protocadherin to be

involved in the establishment of segmental somite boundaries (459).

In mice PAPC is expressed in the primitive streak and paraxial mesoderm (460). At later stages it is also expressed in various parts of the brain, including the cerebral cortex, olfactory bulb, inferior colliculus and in longitudinal, stripe-like domains of the hindbrain. However, PAPC-null mutant mice show no obvious defect in these structures, perhaps due to a redundancy of PAPC function, which could be provided other protocadherins.

5.2.9. Arcadlin

Since arcadlin-transfectant cells attach specifically to culture dishes coated with arcadlin, it appears to be a homophilic adhesion molecule (461). The expression of arcardlin is brain specific and it is expressed in various parts of the brain, including the auditory system (inferior colliculus), the visual system (superior colliculus, suprachiasmatic nucleus, ventrolateral geniculate nucleus) and the limbic system (anterior limbic thalamic nuclei, hippocampus, amygdala, habenula). Arcadlin has also been localized at synapses in primary cultures of hippocampal neurons (461).

Interestingly, the expression of arcadlin in the hippocampus is increased after hippocampal stimulation. In addition, when arcadlin function is inhibited by antibodies, basal synaptic transmission is attenuated and LTP is completely inhibited (461). This result differs from that obtained by antibody blockage of N-cadherin or E-cadherin, which affects LTP without changing basal synaptic properties (295). Currently it is unclear whether the molecular mechanisms underlying arcadlin-mediated LTP enhancement is related to the general adhesive properties of arcadlin or to the induction of specific signal transduction.

5.2.10. Other protocadherins (Protocadherin 18 and PrCAD)

Protocadherin 18 has a large intracellular domain. It is expressed in a variety of tissues in the embryo, but it is restricted to the lungs and kidneys in the adult (462). Although it does not have a known Dab1-binding sequence in its cytoplasmic region, protocadherin 18 interacts with Dab-1, a component of the Reelin signaling pathway (462). Therefore, it may play a role in brain development as a component of the Reelin signaling pathway.

PrCAD is a novel retinal-photoreceptor-specific protocadherin (463). PrCAD knock-out mice show disorganization of the outer segements of the retina, but phototransduction of photoreceptor cells is rather normal (463). Thus, this molecule is essential for outer segment integrity.

5.3. Large cadherins

Here, we will describe large cadherins, which, like the protocadherins, consist of tandemly-arranged EC2-like cadherin repeats, but in which these repeats are present in much greater numbers. Using a wider definition, these large cadherins can be also categorized as protocadherins.

5.3.1 Fat and Dachsous

Fat was identified first as a tumor-suppressor gene in *Drosophila* (464). The extracellular domain contains 34 cadherin repeats, 4 EGF motifs and 2 laminin A globular domain-like motifs (Figure 2; 19). Fat is involved in cell proliferation and in the maintenance of epithelial structure and differentiation potential (464). In vertebrates, *fat* expression starts at an early pre-implantation stage and persists to the adult stages at a reduced level (465). Expression can be seen in various tissues including many epithelial cells, some endothelial cells and smooth muscle cells (466). Developing limb buds, branchial arches and forming somites also show prominent expression (465). In the brain, expression can be seen in the proliferating ventricular layer, being down-regulated as cells cease division (465). The dentate gyrus in the hippocampus and the granule cell layer in the cerebellum continue to express *fat* into adulthood (467).

Dachsous is another large cadherin, which contains containing 27 cadherin repeats. In *Drosophila*, it is expressed in the embryonic ectoderm, imaginal discs and specific regions of the larval brain (468). The mutant phenotype shows that Dachsous is involved in cell proliferation and morphogenesis. Genetic evidence has led to the hypothesis that Fat and Dachsous interact directly in both a homophilic and heterotypic manner (468). Dachsous is also involved in the establishment of tissue polarity of wing bristles through Frizzled signaling (469). In addition, Fat and Dachsous regulate Frizzled to control planar polarity signaling in the compound eye (470). Both of these large cadherins have a cytoplasmic domain with low sequence similarity to the β-catenin-binding domain of the classic cadherins, but it is not clear whether binding to β-catenin occurs under physiological conditions (468).

5.3.2. Cadherin-23 (otocadherin)

Cadherin-23 (otocadherin) is a recently discovered molecule, which in a mutated form is responsible for a genetic form of hearing loss. Its gene is mutated in the *Waltzer* mutation in the mouse and in the Usher syndrome type 1D in humans (471-474). Cadherin-23 has 27 cadherin repeats in its extracellular domain, but it does not have any sequences in its cytoplasmic domain that is known to be conserved in other molecules. Interestingly, cadherin 23 protein is encoded by 69 exons, which are many more exons than found in other "protocadherin"-type cadherins (475, 27). Expression is seen in various tissues, with high expression in testis, skeletal muscle, heart, eye, thymus and moderate expression in the brain (471). The role of cadherin-23 in the inner ear is in hair bundle formation. The locus *deafwaddler*, genetically interacting with the waltzer allele, encodes a Ca^{2+}-ATPase, suggesting that cadherin-23 function may depend on Ca^{2+} homeostasis (471).

5.3.3. Protocadherin 15

Protocadherin 15 has been identified as the product of the aberrant gene that causes hearing loss in the mouse mutant *Ames Waltzer* and human Usher syndrome type 1F (476-478). This molecule has 11 cadherin motifs in its extracellular domain and its cytoplasmic domain

shows no similarity with any known molecules (476). Protocadherin 15 is expressed in the inner ear, retina, brain and various epithelia of the developing embryo (476-479). When homozygous one mutant allele causes inner ear defects with abnormalities in hair-cell stereocilia at P10 and the degeneration of sensory cells in older mice (476). Thus, it has been speculated that protocadherin 15 is involved in the development or maintenance of the stereocilia bundles on hair cells.

5.4. Flamingo

Flamingo-like cadherins are large cadherins that are characterized by a 7-pass transmembrane domain (Figure 2; 480). The molecule originally named Flamingo is conserved between *Drosophila* and vertebrates. In vertebrates, 2 additional flamingo-like cadherins have been identified (Celsr1 and MEGF2). In *Drosophila*, the gene of Flamingo serves as a segment polarity gene and controls the planar polarity of cells under the control of Frizzled (480-482). Flamingo is localized in an asymmetric manner and controls actin and microtubule cytoskeletons (482). Although Flamingo has cell-cell adhesion activity *in vitro*, the function of Flamingo in planar polarity seems to be independent of cell adhesion. Flamingo is also involved in the patterning of dendrites (483). Interestingly, Flamingo-dependent dendritic outgrowth is independent of Frizzled (484). In *Drosophila* Flamingo is involved in the formation of CNS tracts (480). In mice mCelsr 1 expression starts at the primitive streak stage (485). Expression can be seen in various parts of the CNS during development. There is prominent expression in a segmented pattern in the hindbrain and some stripes of expression are observed in the spinal cord (485). At later stages of embryogenesis, expression can also be seen outside the CNS, such as in the kidney, testis and the facial primordium. Celsr 2 and Celsr 3 also show distinct patterns of expression in the central nervous system and other organs (486-488). The role of the Flamingo-like cadherins in vertebrates has not been established experimentally.

5.5. Desmosomal cadherins

Desmosomes are highly specialized intercellular junctions that are associated with intermediate filaments and play an important role in cell-cell adhesion of various epithelia in vertebrates. Molecular components of the desmosome include the desmogleins and desmocollins (Figure 2, Figure 5D). These proteins are members of the cadherin superfamily and are responsible for adhesion and anchorage to the cytoskeleton (489, 490). The cytoplasmic tails of the desmosomal cadherins have some similarity with those of classic cadherins, suggesting them to have been derived from a common ancestor (23). There are 3 types of desmogleins and 3 types of desmocollins, which have additional splice variants (489). The molecular architecture of the desmosome is complex (489, 490). There seem to be several ways by which the desmosomal cadherins can become linked to the intermediate filaments. Desmosomes are rarely found in the nervous system and thus more attention has been paid to epithelial desmosomes. However, it has been reported that desmosome-like structures do exist in neural tissue (491-493). In addition, desmoglein has been detected in the NMDA receptor multi-protein complex (403), suggesting that desmoglein is localized at synapses. Further studies are needed to clarify the role of desmosomal cadherins in the nervous system.

5.6. LI-cadherin (HPT-1) and Ksp-cadherin

LI-cadherin (HPT-1) is a cadherin that has 7 cadherin repeats in its extracellular domain, but 2 of these repeats have diverged from the EC2 repeats that are present in typical protocadherins (Figure 2; 494, 495). LI-cadherin was named after its expression in the liver and intestine in the rat. However, it is exclusively expressed in the intestine in humans and mice, where it is localized at the basolateral membrane. The extracellular domain of LI-cadherin is sufficient to induce adhesion (495). LI-cadherin may be involved in the control of the width of the lateral intercellular space during fluid absorption (496). LI-cadherin is identical with HPT-1, which was identified in association with the activity of a peptide transporter (494).

Ksp-cadherin has been identified in rabbits and is similar in sequence and structure to LI-cadherin. It is specifically expressed in the kidney, where it is localized at the basolateral membrane of renal tubular epithelial cells (496). Interestingly, this molecule has been proposed to be a structural component of the renal basolateral Na^+/HCO_3 cotransporter or of an associated protein (497). However, the function of Ksp-cadherin has not yet been established. Neither LI-cadherin nor Ksp-cadherin appears to be expressed in the nervous system.

5.7. Ret

Ret was discovered as an oncogene product that has a receptor tyrosine kinase in its cytoplasmic domain and 4 cadherin motifs in its extracellular domain (Figure 2; 498-501). The overall structure of the extracellular region of Ret is close to that of the classic cadherins (501). At present, there is no evidence that Ret functions as an adhesion molecule. Instead, it functions as a part of the receptor complex for glial-cell-line-derived neurotrophic factor ligands (GFLs), which include the glial cell line-derived neurotrophic factor (GDNF), neurturin, artemin and persephin (502). It is thought that Ret-mediated signaling activates several second messenger systems including the Ras/MAPK, phosphatidylinositol-3 kinase (PI3K), PLC, Rac 1 and JNK pathways (502, 503). In addition, NGF utilizes c-Ret via a GFL-independent, inter-RTK signaling mechanism (504). Ret is expressed in the PNS, the CNS and the urinary system (505) and has been reported to be involved in mesoderm induction during *Xenopus* development (506). In the nervous system Ret signaling is important for migration and axon outgrowth in neuroblasts and promotes the growth and survival of some populations of CNS and PNS neurons (507-509). Ret-deficient mice lack enteric neurons and the superior cervical ganglion (SCG; 510, 502). Ret has 2 isoforms, which have different functions *in vivo* (511). In humans Ret is involved in genetic diseases such as Hirschsprung's disease and familial endocrine neoplasia syndromes (500). These diseases all affect neural crest derivatives. It has been suggested that Ret is involved in the differentiation of enteric neurons, rather than in their survival or proliferation

(500). Thus, the role of Ret seems to be quite different from that of the classic cadherins.

5.8 Calsyntenins

Calsyntenins (CDH-11 in *C. elegans*) have 2 cadherin motifs in their extracellular domain and they are the only known example of cadherins that are highly conserved throughout their entire sequence among invertebrates and vertebrates (Figure 2; 25). This suggests that they are involved in a very basic common function throughout the animal kingdom (25, 512). There are 3 calsyntenins in humans, with calsyntenin-1 being identified as a protein fragment released from synapses by proteolytic cleavage (512). It is expressed in most neurons and it is localized at the postsynaptic membrane (512). The transmembrane stump is internalized by endocytosis after cleavage. Because its cytoplasmic domain binds Ca^{2+}, calsynthenin-1 may function as a modulator of Ca^{2+} signaling in postsynaptic neurons.

5.9 Other cadherins

There are many other types of cadherins, but most of them have not been properly characterized and investigated. For example, μ-protocadherin is a novel cadherin that has 4 cadherin repeats and several mucin-like domains (513). Its cadherin repeats have somewhat diverged from the typical cadherin motifs found in the other cadherins described above. There is also a short isoform of μ-protocadherin that lacks the mucin-like domain. μ-Protocadherin is expressed in the kidneys and lungs, and it has been suggested to be involved in branching morphogenesis of the kidney. In addition, many other cadherin-like molecules in *C. elegans* (25) cannot be classified according to the subfamilies described in this review. The expression pattern and the functions of these unclassified cadherins remain to be characterized.

6. PERSPECTIVE

In this paper, various aspects of cadherins have been reviewed. First, there are interactions of classic cadherins with cytoskeletal elements and with signaling pathways. Second, classic cadherins seem to play important roles in many processes regulating neural development. Third, different members of the cadherin superfamily seem to have divergent functions. The overview leads to the speculation that cadherins have a potential to link cellular recognition, adhesion and signaling. This linkage must be a key that makes it possible for cadherins to be interwoven in the coordinate cellular behavior and responses in various processes such as neural differentiation, neurite outgrowth, pathfinding, target recognition and synaptogenesis. Considering the great diversity of the cadherin superfamily and complexity of signaling systems it is likely that molecules in the cadherin superfamily are involved in diverse neural cell-cell interactions during development.

Although the field of cadherin research has been rapidly expanding in recent years, many questions remain to be answered. For example, what is the role of the different types of cadherins in neural circuit formation? Do cadherins confer adhesive specificity to axonal pathways and synaptic connections? How much redundancy of cadherin function is there in neural development? What is the molecular mechanism by which cadherins modulate synaptic transmission? What is the role of vertebrate-specific cadherins, such as protocadherins, in the evolution of the vertebrate nervous system? And the list of questions goes on.

Despite the vast complexity of cadherin-related molecular systems, cadherin expression is precisely orchestrated in neural cells during the formation of sophisticated neural circuits. Now that the complete genome has been sequenced in some species, our ultimate aim is to understand the entire pattern of cadherin participation in the complex regulatory network of various cellular processes, such as cell adhesion, differentiation, proliferation during neural development.

7. ACKNOWLEDGMENTS

We apologize for any omissions of references due to space limitations and the wide scope of the subjects covered. The authors are grateful to Dr. Masatoshi Takeichi for his encouragement to write this review and to Dr. Akira Nagafuchi for critical reading of the manuscript. We also thank Drs. Tadashi Uemura, Brent Thomson and Takao Ono for their expertise. The authors acknowledge Dr. Eiko Aoki and Ms. Reiko Kimura for general support of this work. We also thank Ms. Sumiko Aoba and Ms.Yuko Mutou for collecting references and Ms. Yukiko Kawamura, Ms. Yuki Nishio and Mr. Toyofumi Tamoto for help in preparing the manuscript. Work in the authors' laboratories was supported by grants from the Ministry of Education and Culture of Japan and the German Research Council (Re 616/4-3).

8. REFERENCES

1. Steinberg M. S.: Adhesion in development: an historical overview. *Dev Biol* 180, 377-388 (1996)

2. Edelman G. M.: Cell adhesion molecules in the regulation of animal form and tissue pattern. *Annu Rev Cell Biol* 2, 81-116 (1986)

3. Takeichi M.: The cadherins: cell-cell adhesion molecules controlling animal morphogenesis. *Development* 102, 639-655 (1988)

4. Grunwald G. B.: The structural and functional analysis of cadherin calcium-dependent cell adhesion molecules. *Curr Opin Cell Biol* 5, 797-805 (1993)

5. Gallin W. J., G. M. Edelman & B. A. Cunningham: Characterization of L-CAM, a major cell adhesion molecule from embryonic liver cells. *Proc Natl Acad Sci U S A* 80, 1038-1042 (1983)

6. Peyrieras N., F. Hyafil, D. Louvard, H. L. Ploegh & F. Jacob: Uvomorulin: a nonintegral membrane protein of early mouse embryo. *Proc Natl Acad Sci U S A* 80, 6274-6277 (1983)

7. Behrens J., W. Birchmeier, S. L. Goodman & B. A. Imhof: Dissociation of Madin-Darby canine kidney

epithelial cells by the monoclonal antibody anti-arc-1: mechanistic aspects and identification of the antigen as a component related to uvomorulin. *J Cell Biol* 101, 1307-1315 (1985)

8. Grunwald G. B., R. S. Pratt & J. Lilien: Enzymic dissection of embryonic cell adhesive mechanisms. III. Immunological identification of a component of the calcium-dependent adhesive system of embryonic chick neural retina cells. *J Cell Sci* 55, 69-83 (1982)

9. Damsky C. H., J. Richa, D. Solter, K. Knudsen & C. A. Buck: Identification and purification of a cell surface glycoprotein mediating intercellular adhesion in embryonic and adult tissue. *Cell* 34, 455-466 (1983)

10. Volk T. & B. Geiger: A 135-kd membrane protein of intercellular adherens junctions. *EMBO J* 3, 2249-2260. (1984)

11. Takeichi M.: Functional correlation between cell adhesive properties and some cell surface proteins. *J Cell Biol* 75, 464-474 (1977)

12. Takeichi M., T. Atsumi, C. Yoshida, K. Uno & T. S. Okada: Selective adhesion of embryonal carcinoma cells and differentiated cells by Ca2+-dependent sites. *Dev Biol* 87, 340-350 (1981)

13. Yoshida C. & M. Takeichi: Teratocarcinoma cell adhesion: identification of a cell-surface protein involved in calcium-dependent cell aggregation. *Cell* 28, 217-224 (1982)

14. Hatta K. & M. Takeichi: Expression of N-cadherin adhesion molecules associated with early morphogenetic events in chick development. *Nature* 320, 447-449 (1986)

15. Nose A. & M. Takeichi: A novel cadherin cell adhesion molecule: its expression patterns associated with implantation and organogenesis of mouse embryos. *J Cell Biol* 103, 2649-2658 (1986)

16. Inuzuka H., S. Miyatani & M. Takeichi: R-cadherin: a novel Ca(2+)-dependent cell-cell adhesion molecule expressed in the retina. *Neuron* 7, 69-79 (1991)

17. Suzuki S., K. Sano & H. Tanihara: Diversity of the cadherin family: evidence for eight new cadherins in nervous tissue. *Cell Regul* 2, 261-270 (1991)

18. Koch P. J., M. J. Walsh, M. Schmelz, M. D. Goldschmidt, R. Zimbelmann & W. W. Franke: Identification of desmoglein, a constitutive desmosomal glycoprotein, as a member of the cadherin family of cell adhesion molecules. *Eur J Cell Biol* 53, 1-12 (1990)

19. Mahoney P. A., U. Weber, P. Onofrechuk, H. Biessmann, P. J. Bryant & C. S. Goodman: The fat tumor suppressor gene in Drosophila encodes a novel member of the cadherin gene superfamily. *Cell* 67, 853-868 (1991)

20. Sano K., H. Tanihara, R. L. Heimark, S. Obata, M. Davidson, T. St John, S. Taketani & S. Suzuki: Protocadherins: a large family of cadherin-related molecules in central nervous system. *EMBO J* 12, 2249-2256 (1993)

21. Pouliot Y.: Phylogenetic analysis of the cadherin superfamily. *Bioessays* 14, 743-748 (1992)

22. Gallin W. J.: Evolution of the "classical" cadherin family of cell adhesion molecules in vertebrates. *Mol Biol Evol* 15, 1099-1107 (1998)

23. Nollet F., P. Kools & F. van Roy: Phylogenetic analysis of the cadherin superfamily allows identification of six major subfamilies besides several solitary members. *J Mol Biol* 299, 551-572 (2000)

24. Tepass U., K. Truong, D. Godt, M. Ikura & M. Peifer: Cadherins in embryonic and neural morphogenesis. *Nat Rev Mol Cell Biol* 1, 91-100 (2000)

25. Hill E., I. D. Broadbent, C. Chothia & J. Pettitt: Cadherin superfamily proteins in Caenorhabditis elegans and Drosophila melanogaster. *J Mol Biol* 305, 1011-1024 (2001)

26. Hatta M., S. Miyatani, N. G. Copeland, D. J. Gilbert, N. A. Jenkins & M. Takeichi: Genomic organization and chromosomal mapping of the mouse P-cadherin gene. *Nucleic Acids Res* 19, 4437-4441 (1991)

27. Wu Q. & T. Maniatis: Large exons encoding multiple ectodomains are a characteristic feature of protocadherin genes. *Proc Natl Acad Sci U S A* 97, 3124-3129 (2000)

28. Wu Q. & T. Maniatis: A striking organization of a large family of human neural cadherin-like cell adhesion genes. *Cell* 97, 779-790 (1999)

29. Wong E. F., S. K. Brar, H. Sesaki, C. Yang & C. H. Siu: Molecular cloning and characterization of DdCAD-1, a Ca2+-dependent cell-cell adhesion molecule, in Dictyostelium discoideum. *J Biol Chem* 271, 16399-16408 (1996)

30. Grimson M. J., J. C. Coates, J. P. Reynolds, M. Shipman, R. L. Blanton & A. J. Harwood: Adherens junctions and beta-catenin-mediated cell signalling in a non- metazoan organism. *Nature* 408, 727-731 (2000)

31. Hynes R. O. & Q. Zhao: The evolution of cell adhesion. *J Cell Biol* 150, F89-96 (2000)

32. Sugino H., S. Hamada, R. Yasuda, A. Tuji, Y. Matsuda, M. Fujita & T. Yagi: Genomic organization of the family of CNR cadherin genes in mice and humans. *Genomics* 63, 75-87 (2000)

33. Hatta K., A. Nose, A. Nagafuchi & M. Takeichi: Cloning and expression of cDNA encoding a neural calcium-dependent cell adhesion molecule: its identity in the cadherin gene family. *J Cell Biol* 106, 873-881 (1988)

34. Hirano S., N. Kimoto, Y. Shimoyama, S. Hirohashi & M. Takeichi: Identification of a neural alpha-catenin as a

key regulator of cadherin function and multicellular organization. *Cell* 70, 293-301 (1992)

35. Nose A., A. Nagafuchi & M. Takeichi: Expressed recombinant cadherins mediate cell sorting in model systems. Cell 54, 993-1001. (1988)

36. Kim J. B., S. Islam, Y. J. Kim, R. S. Prudoff, K. M. Sass, M. J. Wheelock & K. R. Johnson: N-Cadherin extracellular repeat 4 mediates epithelial to mesenchymal transition and increased motility. *J Cell Biol* 151, 1193-1206 (2000)

37. Dufour S., A. Beauvais-Jouneau, A. Delouvee & J. P. Thiery: Differential function of N-cadherin and cadherin-7 in the control of embryonic cell motility. *J Cell Biol* 146, 501-516 (1999)

38. Kido M., S. Obata, H. Tanihara, J. M. Rochelle, M. F. Seldin, S. Taketani & S. T. Suzuki: Molecular properties and chromosomal location of cadherin-8. *Genomics* 48, 186-194 (1998)

39. Kawaguchi J., S. Takeshita, T. Kashima, T. Imai, R. Machinami & A. Kudo: Expression and function of the splice variant of the human cadherin-11 gene in subordination to intact cadherin-11. *J Bone Miner Res* 14, 764-775 (1999)

40. Overduin M., T. S. Harvey, S. Bagby, K. I. Tong, P. Yau, M. Takeichi & M. Ikura: Solution structure of the epithelial cadherin domain responsible for selective cell adhesion. *Science* 267, 386-389 (1995)

41. Shapiro L., A. M. Fannon, P. D. Kwong, A. Thompson, M. S. Lehmann, G. Grubel, J. F. Legrand, J. Als-Nielsen, D. R. Colman & W. A. Hendrickson: Structural basis of cell-cell adhesion by cadherins. *Nature* 374, 327-337 (1995)

42. Nagar B., M. Overduin, M. Ikura & J. M. Rini: Structural basis of calcium-induced E-cadherin rigidification and dimerization. *Nature* 380, 360-364 (1996)

43. Pertz O., D. Bozic, A. W. Koch, C. Fauser, A. Brancaccio & J. Engel: A new crystal structure, Ca2+ dependence and mutational analysis reveal molecular details of E-cadherin homoassociation. *EMBO J* 18, 1738-1747 (1999)

44. Tomschy A., C. Fauser, R. Landwehr & J. Engel: Homophilic adhesion of E-cadherin occurs by a co-operative two-step interaction of N-terminal domains. *EMBO J* 15, 3507-3514 (1996)

45. Tamura K., W. S. Shan, W. A. Hendrickson, D. R. Colman & L. Shapiro: Structure-function analysis of cell adhesion by neural (N-) cadherin. *Neuron* 20, 1153-1163 (1998)

46. Boggon T. J., J. Murray, S. Chappuis-Flament, E. Wong, B. M. Gumbiner & L. Shapiro: C-cadherin ectodomain structure and implications for cell adhesion mechanisms. *Science* 296, 1308-1313 (2002)

47. Sivasankar S., W. Brieher, N. Lavrik, B. Gumbiner & D. Leckband: Direct molecular force measurements of multiple adhesive interactions between cadherin ectodomains. *Proc Natl Acad Sci U S A* 96, 11820-11824 (1999)

48. Chappuis-Flament S., E. Wong, L. D. Hicks, C. M. Kay & B. M. Gumbiner: Multiple cadherin extracellular repeats mediate homophilic binding and adhesion. *J Cell Biol* 154, 231-243 (2001)

49. Yap A. S., C. M. Niessen & B. M. Gumbiner: The juxtamembrane region of the cadherin cytoplasmic tail supports lateral clustering, adhesive strengthening and interaction with p120ctn. *J Cell Biol* 141, 779-789 (1998)

50. Huber O., R. Kemler & D. Langosch: Mutations affecting transmembrane segment interactions impair adhesiveness of E-cadherin. *J Cell Sci* 112, 4415-4423 (1999)

51. Troyanovsky S. M.: Mechanism of cell-cell adhesion complex assembly. *Curr Opin Cell Biol* 11, 561-566 (1999)

52. Murase S., S. Hirano, X. Wang, M. Kitagawa, M. Natori, S. Taketani & S. T. Suzuki: Lateral clustering of cadherin-4 without homophilic interaction: possible involvement in the concentration process at cell-cell adhesion sites as well as in the cell adhesion activity. *Biochem Biophys Res Commun* 276, 1191-1198 (2000)

53. Leckband D. & S. Sivasankar: Mechanism of homophilic cadherin adhesion. *Curr Opin Cell Biol* 12, 587-592 (2000)

54. Redies C. & M. Takeichi: Cadherins in the developing central nervous system: an adhesive code for segmental and functional subdivisions. *Dev Biol* 180, 413-423 (1996)

55. Redies C.: Cadherins in the central nervous system. *Prog Neurobiol* 61, 611-648 (2000)

56. Steinberg M. S. & M. Takeichi: Experimental specification of cell sorting, tissue spreading and specific spatial patterning by quantitative differences in cadherin expression. *Proc Natl Acad Sci U S A* 91, 206-209 (1994)

57. Godt D. & U. Tepass: Drosophila oocyte localization is mediated by differential cadherin- based adhesion. *Nature* 395, 387-391 (1998)

58. Detrick R. J., D. Dickey & C. R. Kintner: The effects of N-cadherin misexpression on morphogenesis in Xenopus embryos. *Neuron* 4, 493-506 (1990)

59. Fujimori T., S. Miyatani & M. Takeichi: Ectopic expression of N-cadherin perturbs histogenesis in Xenopus embryos. *Development* 110, 97-104 (1990)

60. Kintner C.: Regulation of embryonic cell adhesion by the cadherin cytoplasmic domain. *Cell* 69, 225-236 (1992)

61. Dufour S., J. P. Saint-Jeannet, F. Broders, D. Wedlich & J. P. Thiery: Differential perturbations in the morphogenesis of anterior structures induced by overexpression of truncated XB- and N-cadherins in Xenopus embryos. *J Cell Biol* 127, 521-535 (1994)

62. Delarue M., F. J. Saez, J. C. Boucaut, J. P. Thiery & F. Broders: Medial cell mixing during axial morphogenesis of the amphibian embryo requires cadherin function. *Dev Dyn* 213, 248-260 (1998)

63. Kostetskii I., R. Moore, R. Kemler & G. L. Radice: Differential adhesion leads to segregation and exclusion of N-cadherin- deficient cells in chimeric embryos. *Dev Biol* 234, 72-79 (2001)

64. Niessen C. M. & B. M. Gumbiner: Cadherin-mediated cell sorting not determined by binding or adhesion specificity. *J Cell Biol* 156, 389-399 (2002)

65. Volk T., O. Cohen & B. Geiger: Formation of heterotypic adherens-type junctions between L-CAM-containing liver cells and A-CAM-containing lens cells. *Cell* 50, 987-994 (1987)

66. Hirano S., A. Nose, K. Hatta, A. Kawakami & M. Takeichi: Calcium-dependent cell-cell adhesion molecules (cadherins): subclass specificities and possible involvement of actin bundles. *J Cell Biol* 105, 2501-2510 (1987)

67. Nakagawa S. & M. Takeichi: Neural crest cell-cell adhesion controlled by sequential and subpopulation-specific expression of novel cadherins. *Development* 121, 1321-1332 (1995)

68. Murphy-Erdosh C., C. K. Yoshida, N. Paradies & L. F. Reichardt: The cadherin-binding specificities of B-cadherin and LCAM. *J Cell Biol* 129, 1379-1390 (1995)

69. Shimoyama Y., G. Tsujimoto, M. Kitajima & M. Natori: Identification of three human type-II classic cadherins and frequent heterophilic interactions between different subclasses of type-II classic cadherins. *Biochem J* 349, 159-167 (2000)

70. Shimoyama Y., H. Takeda, S. Yoshihara, M. Kitajima & S. Hirohashi: Biochemical characterization and functional analysis of two type II classic cadherins, cadherin-6 and -14 and comparison with E-cadherin. *J Biol Chem* 274, 11987-11994 (1999)

71. Shan W. S., H. Tanaka, G. R. Phillips, K. Arndt, M. Yoshida, D. R. Colman & L. Shapiro: Functional cis-heterodimers of N- and R-cadherins. *J Cell Biol* 148, 579-590 (2000)

72. Takeichi M.: Cadherins: a molecular family important in selective cell-cell adhesion. *Annu Rev Biochem* 59, 237-252 (1990)

73. Wohrn J. C., S. Nakagawa, M. Ast, M. Takeichi & C. Redies: Combinatorial expression of cadherins in the tectum and the sorting of neurites in the tectofugal pathways of the chicken embryo. *Neuroscience* 90, 985-1000 (1999)

74. Cepek K. L., S. K. Shaw, C. M. Parker, G. J. Russell, J. S. Morrow, D. L. Rimm & M. B. Brenner: Adhesion between epithelial cells and T lymphocytes mediated by E-cadherin and the alpha E beta 7 integrin. *Nature* 372, 190-193 (1994)

75. Karecla P. I., S. J. Green, S. J. Bowden, J. Coadwell & P. J. Kilshaw: Identification of a binding site for integrin alphaEbeta7 in the N- terminal domain of E-cadherin. *J Biol Chem* 271, 30909-30915. (1996)

76. Martinez J., A. Ferber, T. L. Bach & C. H. Yaen: Interaction of fibrin with VE-cadherin. *Ann N Y Acad Sci* 936, 386-405 (2001)

77. Nagafuchi A.: Molecular architecture of adherens junctions. *Curr Opin Cell Biol* 13, 600-603 (2001)

78. Lilien J., J. Balsamo, C. Arregui & G. Xu: Turn-off, drop-out: Functional state switching of cadherins. *Dev Dyn* 224, 18-29 (2002)

79. Steinberg M. S. & P. M. McNutt: Cadherins and their connections: adhesion junctions have broader functions. *Curr Opin Cell Biol* 11, 554-560 (1999)

80. Provost E. & D. L. Rimm: Controversies at the cytoplasmic face of the cadherin-based adhesion complex. *Curr Opin Cell Biol* 11, 567-572 (1999)

81. Sirotkin H., H. O'Donnell, R. DasGupta, S. Halford, B. St Jore, A. Puech, S. Parimoo, B. Morrow, A. Skoultchi, S. M. Weissman, P. Scambler & R. Kucherlapati: Identification of a new human catenin gene family member (ARVCF) from the region deleted in velo-cardio-facial syndrome. *Genomics* 41, 75-83 (1997)

82. Hatzfeld M.: The armadillo family of structural proteins. *Int Rev Cytol* 186, 179-224 (1999)

83. Butz S. & R. Kemler: Distinct cadherin-catenin complexes in Ca(2+)-dependent cell-cell adhesion. *FEBS Lett* 355, 195-200 (1994)

84. Zhurinsky J., M. Shtutman & A. Ben-Ze'ev: Plakoglobin and beta-catenin: protein interactions, regulation and biological roles. *J Cell Sci* 113, 3127-3139 (2000)

85. Huber A. H. & W. I. Weis: The structure of the beta-catenin/E-cadherin complex and the molecular basis of diverse ligand recognition by beta-catenin. *Cell* 105, 391-402 (2001)

86. Meigs T. E., T. A. Fields, D. D. McKee & P. J. Casey: Interaction of Galpha 12 and Galpha 13 with the cytoplasmic domain of cadherin provides a mechanism for beta -catenin release. *Proc Natl Acad Sci U S A* 98, 519-524 (2001)

87. Kaplan D. D., T. E. Meigs & P. J. Casey: Distinct regions of the cadherin cytoplasmic domain are essential

for functional interaction with Galpha 12 and beta-catenin. *J Biol Chem* 276, 44037-44043 (2001)

88. Meigs T. E., M. Fedor-Chaiken, D. D. Kaplan, R. Brackenbury & P. J. Casey: Galpha 12 and Galpha 13 negatively regulate the adhesive functions of cadherin. *J Biol Chem* 277, 24594-24600 (2002)

89. Watabe M., A. Nagafuchi, S. Tsukita & M. Takeichi: Induction of polarized cell-cell association and retardation of growth by activation of the E-cadherin-catenin adhesion system in a dispersed carcinoma line. *J Cell Biol* 127, 247-256 (1994)

90. Vasioukhin V., C. Bauer, M. Yin & E. Fuchs: Directed actin polymerization is the driving force for epithelial cell-cell adhesion. *Cell* 100, 209-219 (2000)

91. Uchida N., K. Shimamura, S. Miyatani, N. G. Copeland, D. J. Gilbert, N. A. Jenkins & M. Takeichi: Mouse alpha N-catenin: two isoforms, specific expression in the nervous system and chromosomal localization of the gene. *Dev Biol* 163, 75-85 (1994)

92. Janssens B., S. Goossens, K. Staes, B. Gilbert, J. van Hengel, C. Colpaert, E. Bruyneel, M. Mareel & F. van Roy: alphaT-catenin: a novel tissue-specific beta-catenin-binding protein mediating strong cell-cell adhesion. *J Cell Sci* 114, 3177-3188 (2001)

93. Anastasiadis P. Z. & A. B. Reynolds: The p120 catenin family: complex roles in adhesion, signaling and cancer. *J Cell Sci* 113, 1319-1334 (2000)

94. Lu Q., M. Paredes, M. Medina, J. Zhou, R. Cavallo, M. Peifer, L. Orecchio & K. S. Kosik: delta-catenin, an adhesive junction-associated protein which promotes cell scattering. *J Cell Biol* 144, 519-532 (1999)

95. Mariner D. J., J. Wang & A. B. Reynolds: ARVCF localizes to the nucleus and adherens junction and is mutually exclusive with p120(ctn) in E-cadherin complexes. *J Cell Sci* 113, 1481-1490 (2000)

96. Ozawa M. & R. Kemler: The membrane-proximal region of the E-cadherin cytoplasmic domain prevents dimerization and negatively regulates adhesion activity. *J Cell Biol* 142, 1605-1613 (1998)

97. Aono S., S. Nakagawa, A. B. Reynolds & M. Takeichi: p120(ctn) acts as an inhibitory regulator of cadherin function in colon carcinoma cells. *J Cell Biol* 145, 551-562 (1999)

98. Anastasiadis P. Z., S. Y. Moon, M. A. Thoreson, D. J. Mariner, H. C. Crawford, Y. Zheng & A. B. Reynolds: Inhibition of RhoA by p120 catenin. *Nat Cell Biol* 2, 637-644 (2000)

99. Noren N. K., B. P. Liu, K. Burridge & B. Kreft: p120 catenin regulates the actin cytoskeleton via Rho family GTPases. *J Cell Biol* 150, 567-580 (2000)

100. Grosheva I., M. Shtutman, M. Elbaum & A. D. Bershadsky: p120 catenin affects cell motility via modulation of activity of Rho-family GTPases: a link between cell-cell contact formation and regulation of cell locomotion. *J Cell Sci* 114, 695-707 (2001)

101. Ho C., J. Zhou, M. Medina, T. Goto, M. Jacobson, P. G. Bhide & K. S. Kosik: delta-catenin is a nervous system-specific adherens junction protein which undergoes dynamic relocalization during development. *J Comp Neurol* 420, 261-276 (2000)

102. Kim K., A. Sirota, Y. H. Chen Yh, S. B. Jones, R. Dudek, G. W. Lanford, C. Thakore & Q. Lu: Dendrite-like process formation and cytoskeletal remodeling regulated by delta-catenin expression. *Exp Cell Res* 275, 171-184 (2002)

103. Lu Q., N. K. Mukhopadhyay, J. D. Griffin, M. Paredes, M. Medina & K. S. Kosik: Brain armadillo protein delta-catenin interacts with Abl tyrosine kinase and modulates cellular morphogenesis in response to growth factors. *J Neurosci Res* 67, 618-624 (2002)

104. Izawa I., M. Nishizawa, K. Ohtakara & M. Inagaki: Densin-180 interacts with delta-catenin/neural plakophilin-related armadillo repeat protein at synapses. *J Biol Chem* 277, 5345-5350 (2002)

105. Laura R. P., A. S. Witt, H. A. Held, R. Gerstner, K. Deshayes, M. F. Koehler, K. S. Kosik, S. S. Sidhu & L. A. Lasky: The Erbin PDZ domain binds with high affinity and specificity to the carboxyl termini of delta-catenin and ARVCF. *J Biol Chem* 277, 12906-12914 (2002)

106. Deguchi M., T. Iizuka, Y. Hata, W. Nishimura, K. Hirao, I. Yao, H. Kawabe & Y. Takai: PAPIN. A novel multiple PSD-95/Dlg-A/ZO-1 protein interacting with neural plakophilin-related armadillo repeat protein/delta-catenin and p0071. *J Biol Chem* 275, 29875-29880 (2000)

107. Sako Y., A. Nagafuchi, S. Tsukita, M. Takeichi & A. Kusumi: Cytoplasmic regulation of the movement of E-cadherin on the free cell surface as studied by optical tweezers and single particle tracking: corralling and tethering by the membrane skeleton. *J Cell Biol* 140, 1227-1240 (1998)

108. Fannon A. M., D. L. Sherman, G. Ilyina-Gragerova, P. J. Brophy, V. L. Friedrich, Jr. & D. R. Colman: Novel E-cadherin-mediated adhesion in peripheral nerve: Schwann cell architecture is stabilized by autotypic adherens junctions. *J Cell Biol* 129, 189-202 (1995)

109. Fannon A. M. & D. R. Colman: A model for central synaptic junctional complex formation based on the differential adhesive specificities of the cadherins. *Neuron* 17, 423-434 (1996)

110. Uchida N., Y. Honjo, K. R. Johnson, M. J. Wheelock & M. Takeichi: The catenin/cadherin adhesion system is localized in synaptic junctions bordering transmitter release zones. *J Cell Biol* 135, 767-779 (1996)

111. Rose O., C. Grund, S. Reinhardt, A. Starzinski-Powitz & W. W. Franke: Contactus adherens, a special type of plaque-bearing adhering junction containing M-cadherin, in the granule cell layer of the cerebellar glomerulus. *Proc Natl Acad Sci USA* 92, 6022-6026 (1995)

112. Bahjaoui-Bouhaddi M., F. Padilla, M. Nicolet, C. Cifuentes-Diaz, D. Fellmann & R. M. Mege: Localized deposition of M-cadherin in the glomeruli of the granular layer during the postnatal development of mouse cerebellum. *J Comp Neurol* 378, 180-195 (1997)

113. Tsukita S.: Isolation of cell-to-cell adherens junctions from rat liver. *J Cell Biol* 108, 31-41 (1989)

114. Nelson W. J., E. M. Shore, A. Z. Wang & R. W. Hammerton: Identification of a membrane-cytoskeletal complex containing the cell adhesion molecule uvomorulin (E-cadherin), ankyrin and fodrin in Madin- Darby canine kidney epithelial cells. *J Cell Biol* 110, 349-357 (1990)

115. Geiger B. & D. Ginsberg: The cytoplasmic domain of adherens-type junctions. *Cell Motil Cytoskeleton* 20, 1-6 (1991)

116. Tsukita S., A. Nagafuchi & S. Yonemura: Molecular linkage between cadherins and actin filaments in cell-cell adherens junctions. *Curr Opin Cell Biol* 4, 834-839 (1992)

117. Yap A. S., W. M. Brieher & B. M. Gumbiner: Molecular and functional analysis of cadherin-based adherens junctions. *Annu Rev Cell Dev Biol* 13, 119-146 (1997)

118. Jo K., R. Derin, M. Li & D. S. Bredt: Characterization of MALS/Velis-1, -2 and -3: a family of mammalian LIN-7 homologs enriched at brain synapses in association with the postsynaptic density-95/NMDA receptor postsynaptic complex. *J Neurosci* 19, 4189-4199 (1999)

119. Perego C., C. Vanoni, S. Massari, R. Longhi & G. Pietrini: Mammalian LIN-7 PDZ proteins associate with beta-catenin at the cell-cell junctions of epithelia and neurons. *EMBO J* 19, 3978-3989 (2000)

120. Coussen F., E. Normand, C. Marchal, P. Costet, D. Choquet, M. Lambert, R. M. Mege & C. Mulle: Recruitment of the kainate receptor subunit glutamate receptor 6 by cadherin/catenin complexes. *J Neurosci* 22, 6426-6436 (2002)

121. Dobrosotskaya I. Y. & G. L. James: MAGI-1 interacts with beta-catenin and is associated with cell-cell adhesion structures. *Biochem Biophys Res Commun* 270, 903-909 (2000)

122. Nishimura W., I. Yao, J. Iida, N. Tanaka & Y. Hata: Interaction of synaptic scaffolding molecule and Beta -catenin. *J Neurosci* 22, 757-765 (2002)

123. Tsukita S., K. Oishi, T. Akiyama, Y. Yamanashi & T. Yamamoto: Specific proto-oncogenic tyrosine kinases of src family are enriched in cell-to-cell adherens junctions where the level of tyrosine phosphorylation is elevated. *J Cell Biol* 113, 867-879 (1991)

124. Klebes A. & E. Knust: A conserved motif in Crumbs is required for E-cadherin localisation and zonula adherens formation in Drosophila. *Curr Biol* 10, 76-85 (2000)

125. Knox A. L. & N. H. Brown: Rap1 GTPase regulation of adherens junction positioning and cell adhesion. *Science* 295, 1285-1288 (2002)

126. Lu B., F. Roegiers, L. Y. Jan & Y. N. Jan: Adherens junctions inhibit asymmetric division in the Drosophila epithelium. *Nature* 409, 522-525 (2001)

127. Mandai K., H. Nakanishi, A. Satoh, H. Obaishi, M. Wada, H. Nishioka, M. Itoh, A. Mizoguchi, T. Aoki, T. Fujimoto, Y. Matsuda, S. Tsukita & Y. Takai: Afadin: A novel actin filament-binding protein with one PDZ domain localized at cadherin-based cell-to-cell adherens junction. *J Cell Biol* 139, 517-528 (1997)

128. Takahashi K., H. Nakanishi, M. Miyahara, K. Mandai, K. Satoh, A. Satoh, H. Nishioka, J. Aoki, A. Nomoto, A. Mizoguchi & Y. Takai: Nectin/PRR: an immunoglobulin-like cell adhesion molecule recruited to cadherin-based adherens junctions through interaction with Afadin, a PDZ domain-containing protein. *J Cell Biol* 145, 539-549 (1999)

129. Mandai K., H. Nakanishi, A. Satoh, K. Takahashi, K. Satoh, H. Nishioka, A. Mizoguchi & Y. Takai: Ponsin/SH3P12: an l-afadin- and vinculin-binding protein localized at cell-cell and cell-matrix adherens junctions. *J Cell Biol* 144, 1001-1017 (1999)

130. Tachibana K., H. Nakanishi, K. Mandai, K. Ozaki, W. Ikeda, Y. Yamamoto, A. Nagafuchi, S. Tsukita & Y. Takai: Two cell adhesion molecules, nectin and cadherin, interact through their cytoplasmic domain-associated proteins. *J Cell Biol* 150, 1161-1176 (2000)

131. Satoh-Horikawa K., H. Nakanishi, K. Takahashi, M. Miyahara, M. Nishimura, K. Tachibana, A. Mizoguchi & Y. Takai: Nectin-3, a new member of immunoglobulin-like cell adhesion molecules that shows homophilic and heterophilic cell-cell adhesion activities. *J Biol Chem* 275, 10291-10299 (2000)

132. Buchert M., S. Schneider, V. Meskenaite, M. T. Adams, E. Canaani, T. Baechi, K. Moelling & C. M. Hovens: The junction-associated protein AF-6 interacts and clusters with specific Eph receptor tyrosine kinases at specialized sites of cell- cell contact in the brain. *J Cell Biol* 144, 361-371 (1999)

133. Ikeda W., H. Nakanishi, J. Miyoshi, K. Mandai, H. Ishizaki, M. Tanaka, A. Togawa, K. Takahashi, H. Nishioka, H. Yoshida, A. Mizoguchi, S. Nishikawa & Y. Takai: Afadin: A key molecule essential for structural organization of cell- cell junctions of polarized epithelia during embryogenesis. *J Cell Biol* 146, 1117-1132 (1999)

134. Kussel-Andermann P., A. El-Amraoui, S. Safieddine, S. Nouaille, I. Perfettini, M. Lecuit, P. Cossart, U. Wolfrum

& C. Petit: Vezatin, a novel transmembrane protein, bridges myosin VIIA to the cadherin-catenins complex. *EMBO J* 19, 6020-6029 (2000)

135. Litvinov S. V., M. Balzar, M. J. Winter, H. A. Bakker, I. H. Briaire-de Bruijn, F. Prins, G. J. Fleuren & S. O. Warnaar: Epithelial cell adhesion molecule (Ep-CAM) modulates cell-cell interactions mediated by classic cadherins. *J Cell Biol* 139, 1337-1348 (1997)

136. Tomita K., A. van Bokhoven, C. F. Jansen, M. J. Bussemakers & J. A. Schalken: Coordinate recruitment of E-cadherin and ALCAM to cell-cell contacts by alpha-catenin. *Biochem Biophys Res Commun* 267, 870-844 (2000)

137. Huan Y. & J. van Adelsberg: Polycystin-1, the PKD1 gene product, is in a complex containing E-cadherin and the catenins. *J Clin Invest* 104, 1459-1468 (1999)

138. Adams C. L., W. J. Nelson & S. J. Smith: Quantitative analysis of cadherin-catenin-actin reorganization during development of cell-cell adhesion. *J Cell Biol* 135, 1899-1911 (1996)

139. Knudsen K. A., C. Frankowski, K. R. Johnson & M. J. Wheelock: A role for cadherins in cellular signaling and differentiation. *J Cell Biochem* Suppl 31, 168-176 (1998)

140. Vleminckx K. & R. Kemler: Cadherins and tissue formation: integrating adhesion and signaling. *Bioessays* 21, 211-220 (1999)

141. Carmeliet P., M. G. Lampugnani, L. Moons, F. Breviario, V. Compernolle, F. Bono, G. Balconi, R. Spagnuolo, B. Oostuyse, M. Dewerchin, A. Zanetti, A. Angellilo, V. Mattot, D. Nuyens, E. Lutgens, F. Clotman, M. C. de Ruiter, A. Gittenberger-de Groot, R. Poelmann, F. Lupu, J. M. Herbert, D. Collen & E. Dejana: Targeted deficiency or cytosolic truncation of the VE-cadherin gene in mice impairs VEGF-mediated endothelial survival and angiogenesis. *Cell* 98, 147-157 (1999)

142. Walsh F. S., K. Meiri & P. Doherty: Cell signalling and CAM-mediated neurite outgrowth. *Soc Gen Physiol* Ser 52, 221-226 (1997)

143. Doherty P., G. Williams & E. J. Williams: CAMs and axonal growth: a critical evaluation of the role of calcium and the MAPK cascade. *Mol Cell Neurosci* 16, 283-295 (2000)

144. Kinch M. S., L. Petch, C. Zhong & K. Burridge: E-cadherin engagement stimulates tyrosine phosphorylation. *Cell Adhes Commun* 4, 425-437 (1997)

145. Daniel J. M. & A. B. Reynolds: Tyrosine phosphorylation and cadherin/catenin function. *Bioessays* 19, 883-891 (1997)

146. Hoschuetzky H., H. Aberle & R. Kemler: Beta-catenin mediates the interaction of the cadherin-catenin complex with epidermal growth factor receptor. *J Cell Biol* 127, 1375-1380 (1994)

147. Pece S., M. Chiariello, C. Murga & J. S. Gutkind: Activation of the protein kinase Akt/PKB by the formation of E-cadherin-mediated cell-cell junctions. Evidence for the association of phosphatidylinositol 3-kinase with the E-cadherin adhesion complex. *J Biol Chem* 274, 19347-19351 (1999)

148. Brady-Kalnay S. M., T. Mourton, J. P. Nixon, G. E. Pietz, M. Kinch, H. Chen, R. Brackenbury, D. L. Rimm, R. L. Del Vecchio & N. K. Tonks: Dynamic interaction of PTPmu with multiple cadherins *in vivo*. *J Cell Biol* 141, 287-296 (1998)

149. Zondag G. C., A. B. Reynolds & W. H. Moolenaar: Receptor protein-tyrosine phosphatase RPTPmu binds to and dephosphorylates the catenin p120(ctn). *J Biol Chem* 275, 11264-11269 (2000)

150. Fuchs M., T. Muller, M. M. Lerch & A. Ullrich: Association of human protein-tyrosine phosphatase kappa with members of the armadillo family. *J Biol Chem* 271, 16712-16719 (1996)

151. Cheng J., K. Wu, M. Armanini, N. O'Rourke, D. Dowbenko & L. A. Lasky: A novel protein-tyrosine phosphatase related to the homotypically adhering kappa and mu receptors. *J Biol Chem* 272, 7264-7277 (1997)

152. Balsamo J., T. Leung, H. Ernst, M. K. Zanin, S. Hoffman & J. Lilien: Regulated binding of PTP1B-like phosphatase to N-cadherin: control of cadherin-mediated adhesion by dephosphorylation of beta-catenin. *J Cell Biol* 134, 801-813 (1996)

153. Balsamo J., C. Arregui, T. Leung & J. Lilien: The nonreceptor protein tyrosine phosphatase PTP1B binds to the cytoplasmic domain of N-cadherin and regulates the cadherin-actin linkage. *J Cell Biol* 143, 523-532 (1998)

154. Keilhack H., U. Hellman, J. van Hengel, F. van Roy, J. Godovac-Zimmermann & F. D. Bohmer: The protein-tyrosine phosphatase SHP-1 binds to and dephosphorylates p120 catenin. *J Biol Chem* 275, 26376-26384 (2000)

155. Ukropec J. A., M. K. Hollinger, S. M. Salva & M. J. Woolkalis: SHP2 association with VE-cadherin complexes in human endothelial cells is regulated by thrombin. *J Biol Chem* 275, 5983-5986 (2000)

156. Hiscox S. & W. G. Jiang: Association of the HGF/SF receptor, c-met, with the cell-surface adhesion molecule, E-cadherin and catenins in human tumor cells. *Biochem Biophys Res Commun* 261, 406-411 (1999)

157. Kypta R. M., H. Su & L. F. Reichardt: Association between a transmembrane protein tyrosine phosphatase and the cadherin-catenin complex. *J Cell Biol* 134, 1519-1529 (1996)

158. Mourton T., C. B. Hellberg, S. M. Burden-Gulley, J. Hinman, A. Rhee & S. M. Brady-Kalnay: The PTPmu protein-tyrosine phosphatase binds and recruits the scaffolding protein RACK1 to cell-cell contacts. *J Biol Chem* 276, 14896-14901 (2001)

159. Kinch M. S., G. J. Clark, C. J. Der & K. Burridge: Tyrosine phosphorylation regulates the adhesions of ras-transformed breast epithelia. *J Cell Biol* 130, 461-471 (1995)

160. Roura S., S. Miravet, J. Piedra, A. Garcia de Herreros & M. Dunach: Regulation of E-cadherin/Catenin association by tyrosine phosphorylation. *J Biol Chem* 274, 36734-36740 (1999)

161. Ozawa M. & T. Ohkubo: Tyrosine phosphorylation of p120(ctn) in v-Src transfected L cells depends on its association with E-cadherin and reduces adhesion activity. *J Cell Sci* 114, 503-512 (2001)

162. Calautti E., M. Grossi, C. Mammucari, Y. Aoyama, M. Pirro, Y. Ono, J. Li & G. P. Dotto: Fyn tyrosine kinase is a downstream mediator of Rho/PRK2 function in keratinocyte cell-cell adhesion. *J Cell Biol* 156, 137-148 (2002)

163. Potempa S. & A. J. Ridley: Activation of both MAP kinase and phosphatidylinositide 3-kinase by Ras is required for hepatocyte growth factor/scatter factor-induced adherens junction disassembly. *Mol Biol Cell* 9, 2185-2200 (1998)

164. Dumstrei K., F. Wang, D. Shy, U. Tepass & V. Hartenstein: Interaction between EGFR signaling and DE-cadherin during nervous system morphogenesis. *Development* 129, 3983-3994 (2002)

165. Zondag G. C. & W. H. Moolenaar: Receptor protein tyrosine phosphatases: involvement in cell-cell interaction and signaling. *Biochimie* 79, 477-483 (1997)

166. Muller T., A. Choidas, E. Reichmann & A. Ullrich: Phosphorylation and free pool of beta-catenin are regulated by tyrosine kinases and tyrosine phosphatases during epithelial cell migration. *J Biol Chem* 274, 10173-10183 (1999)

167. Meng K., A. Rodriguez-Pena, T. Dimitrov, W. Chen, M. Yamin, M. Noda & T. F. Deuel: Pleiotrophin signals increased tyrosine phosphorylation of beta beta-catenin through inactivation of the intrinsic catalytic activity of the receptor-type protein tyrosine phosphatase beta/zeta. *Proc Natl Acad Sci USA* 97, 2603-2608 (2000)

168. Rhee J., J. Lilien & J. Balsamo: Essential tyrosine residues for interaction of the non-receptor protein-tyrosine phosphatase PTP1B with N-cadherin. *J Biol Chem* 276, 6640-6644 (2001)

169. Xu Y. & G. Carpenter: Identification of cadherin tyrosine residues that are phosphorylated and mediate Shc association. *J Cell Biochem* 75, 264-271 (1999)

170. Lewis J. E., P. J. Jensen, K. R. Johnson & M. J. Wheelock: E-cadherin mediates adherens junction organization through protein kinase C. *J Cell Sci* 107, 3615-3621 (1994)

171. Ratcliffe M. J., L. L. Rubin & J. M. Staddon: Dephosphorylation of the cadherin-associated p100/p120 proteins in response to activation of protein kinase C in epithelial cells. *J Biol Chem* 272, 31894-31901 (1997)

172. Williams C. L., V. Y. Hayes, A. M. Hummel, J. E. Tarara & T. J. Halsey: Regulation of E-cadherin-mediated adhesion by muscarinic acetylcholine receptors in small cell lung carcinoma. *J Cell Biol* 121, 643-654 (1993)

173. Shafer S. H., H. L. Puhl, S. H. Phelps & C. L. Williams: Activation of transfected M1 or M3 muscarinic acetylcholine receptors induces cell-cell adhesion of Chinese hamster ovary cells expressing endogenous cadherins. *Exp Cell Res* 248, 148-159 (1999)

174. Aberle H., A. Bauer, J. Stappert, A. Kispert & R. Kemler: beta-catenin is a target for the ubiquitin-proteasome pathway. *EMBO J* 16, 3797-3804 (1997)

175. Serres M., O. Filhol, H. Lickert, C. Grangeasse, E. M. Chambaz, J. Stappert, C. Vincent & D. Schmitt: The disruption of adherens junctions is associated with a decrease of E- cadherin phosphorylation by protein kinase CK2. *Exp Cell Res* 257, 255-264 (2000)

176. Sheibani N., C. M. Sorenson & W. A. Frazier: Differential modulation of cadherin-mediated cell-cell adhesion by platelet endothelial cell adhesion molecule-1 isoforms through activation of extracellular regulated kinases. *Mol Biol Cell* 11, 2793-2802 (2000)

177. Lickert H., A. Bauer, R. Kemler & J. Stappert: Casein kinase II phosphorylation of E-cadherin increases E-cadherin/beta-catenin interaction and strengthens cell-cell adhesion. *J Biol Chem* 275, 5090-5095 (2000)

178. Kovacs E. M., R. G. Ali, A. J. McCormack & A. S. Yap: E-cadherin homophilic ligation directly signals through Rac and phosphatidylinositol 3-kinase to regulate adhesive contacts. *J Biol Chem* 277, 6708-6718 (2002)

179. Laprise P., P. Chailler, M. Houde, J. F. Beaulieu, M. J. Boucher & N. Rivard: Phosphatidylinositol 3-kinase controls human intestinal epithelial cell differentiation by promoting adherens junction assembly and p38 MAPK activation. *J Biol Chem* 277, 8226-8234 (2002)

180. Tran N. L., D. G. Adams, R. L. Vaillancourt & R. L. Heimark: Signaling from N-cadherin increases Bcl-2: regulation of the phosphatidylinositol 3-Kinase/Akt pathway by homophilic adhesion and actin cytoskeletal organization. *J Biol Chem* 277, 32905-32914 (2002)

181. Shinohara M., A. Kodama, T. Matozaki, A. Fukuhara, K. Tachibana, H. Nakanishi & Y. Takai: Roles of cell-cell

adhesion-dependent tyrosine phosphorylation of Gab-1. *J Biol Chem* 276, 18941-18946 (2001)

182. Hall A. & C. D. Nobes: Rho GTPases: molecular switches that control the organization and dynamics of the actin cytoskeleton. *Philos Trans R Soc Lond B Biol Sci* 355, 965-970 (2000)

183. Takai Y., T. Sasaki & T. Matozaki: Small GTP-binding proteins. *Physiol Rev* 81, 153-208 (2001)

184. Fukata M. & K. Kaibuchi: Rho-family GTPases in cadherin-mediated cell-cell adhesion. *Nat Rev Mol Cell Biol* 2, 887-897 (2001)

185. Skaper S. D., S. E. Moore & F. S. Walsh: Cell signalling cascades regulating neuronal growth-promoting and inhibitory cues. *Prog Neurobiol* 65, 593-608 (2001)

186. Braga V. M., L. M. Machesky, A. Hall & N. A. Hotchin: The small GTPases Rho and Rac are required for the establishment of cadherin-dependent cell-cell contacts. *J Cell Biol* 137, 1421-1431 (1997)

187. Lee S. & P. A. Kolodziej: The plakin Short Stop and the RhoA GTPase are required for E-cadherin-dependent apical surface remodeling during tracheal tube fusion. *Development* 129, 1509-1520 (2002)

188. Braga V. M., A. Del Maschio, L. Machesky & E. Dejana: Regulation of cadherin function by Rho and Rac: modulation by junction maturation and cellular context. *Mol Biol Cell* 10, 9-22 (1999)

189. Braga V. M., M. Betson, X. Li & N. Lamarche-Vane: Activation of the small GTPase Rac is sufficient to disrupt cadherin- dependent cell-cell adhesion in normal human keratinocytes. *Mol Biol Cell* 11, 3703-3721 (2000)

190. Magie C. R., D. Pinto-Santini & S. M. Parkhurst: Rho1 interacts with p120(ctn) and alpha-catenin and regulates cadherin-based adherens junction components in Drosophila. *Development* 129, 3771-3782 (2002)

191. Kuroda S., M. Fukata, M. Nakagawa, K. Fujii, T. Nakamura, T. Ookubo, I. Izawa, T. Nagase, N. Nomura, H. Tani, I. Shoji, Y. Matsuura, S. Yonehara & K. Kaibuchi: Role of IQGAP1, a target of the small GTPases Cdc42 and Rac1, in regulation of E-cadherin- mediated cell-cell adhesion. *Science* 281, 832-835 (1998)

192. Fukata M., M. Nakagawa, N. Itoh, A. Kawajiri, M. Yamaga, S. Kuroda & K. Kaibuchi: Involvement of IQGAP1, an effector of Rac1 and Cdc42 GTPases, in cell-cell dissociation during cell scattering. *Mol Cell Biol* 21, 2165-2183 (2001)

193. Li Z., S. H. Kim, J. M. Higgins, M. B. Brenner & D. B. Sacks: IQGAP1 and calmodulin modulate E-cadherin function. *J Biol Chem* 274, 37885-37892 (1999)

194. Li S., Q. Wang, A. Chakladar, R. T. Bronson & A. Bernards: Gastric hyperplasia in mice lacking the putative Cdc42 effector IQGAP1. *Mol Cell Biol* 20, 697-701 (2000)

195. Noren N. K., C. M. Niessen, B. M. Gumbiner & K. Burridge: Cadherin engagement regulates Rho family GTPases. *J Biol Chem* 276, 33305-3338 (2001)

196. Nakagawa M., M. Fukata, M. Yamaga, N. Itoh & K. Kaibuchi: Recruitment and activation of Rac1 by the formation of E-cadherin-mediated cell-cell adhesion sites. *J Cell Sci* 114, 1829-1838 (2001)

197. Espada J., M. Perez-Moreno, V. M. Braga, P. Rodriguez-Viciana & A. Cano: H-Ras activation promotes cytoplasmic accumulation and phosphoinositide 3-OH kinase association of beta-catenin in epidermal keratinocytes. *J Cell Biol* 146, 967-980 (1999)

198. Patapoutian A. & L. F. Reichardt: Roles of Wnt proteins in neural development and maintenance. *Curr Opin Neurobiol* 10, 392-399 (2000)

199. Huelsken J. & W. Birchmeier: New aspects of Wnt signaling pathways in higher vertebrates. *Curr Opin Genet Dev* 11, 547-553 (2001)

200. Ben-Ze'ev A. & B. Geiger: Differential molecular interactions of beta-catenin and plakoglobin in adhesion, signaling and cancer. *Curr Opin Cell Biol* 10, 629-639 (1998)

201. Shimamura K., S. Hirano, A. P. McMahon & M. Takeichi: Wnt-1-dependent regulation of local E-cadherin and alpha N-catenin expression in the embryonic mouse brain. *Development* 120, 2225-2234 (1994)

202. Hinck L., W. J. Nelson & J. Papkoff: Wnt-1 modulates cell-cell adhesion in mammalian cells by stabilizing beta-catenin binding to the cell adhesion protein cadherin. *J Cell Biol* 124, 729-741 (1994)

203. Sehgal R. N., B. M. Gumbiner & L. F. Reichardt: Antagonism of cell adhesion by an alpha-catenin mutant and of the Wnt- signaling pathway by alpha-catenin in Xenopus embryos. *J Cell Biol* 139, 1033-1046 (1997)

204. Bienz M. & H. Clevers: Linking colorectal cancer to Wnt signaling. *Cell* 103, 311-320 (2000)

205. Marambaud P., J. Shioi, G. Serban, A. Georgakopoulos, S. Sarner, V. Nagy, L. Baki, P. Wen, S. Efthimiopoulos, Z. Shao, T. Wisniewski & N. K. Robakis: A presenilin-1/gamma-secretase cleavage releases the E-cadherin intracellular domain and regulates disassembly of adherens junctions. *EMBO J* 21, 1948-1956 (2002)

206. Daniel J. M. & A. B. Reynolds: The catenin p120(ctn) interacts with Kaiso, a novel BTB/POZ domain zinc finger transcription factor. *Mol Cell Biol* 19, 3614-3623 (1999)

207. Bar I., C. Lambert de Rouvroit & A. M. Goffinet: The Reelin signaling pathway in mouse cortical development. *Eur J Morphol* 38, 321-325 (2000)

208. Rice D. S. & T. Curran: Role of the reelin signaling pathway in central nervous system development. *Annu Rev Neurosci* 24, 1005-1039 (2001)

209. Howell B. W. & J. Herz: The LDL receptor gene family: signaling functions during development. *Curr Opin Neurobiol* 11, 74-81 (2001)

210. Kwon Y. T., A. Gupta, Y. Zhou, M. Nikolic & L. H. Tsai: Regulation of N-cadherin-mediated adhesion by the p35-Cdk5 kinase. *Curr Biol* 10, 363-372 (2000)

211. Homayouni R. & T. Curran: Cortical development: Cdk5 gets into sticky situations. *Curr Biol* 10, R331-334 (2000)

212. Georgakopoulos A., P. Marambaud, S. Efthimiopoulos, J. Shioi, W. Cui, H. C. Li, M. Schutte, R. Gordon, G. R. Holstein, G. Martinelli, P. Mehta, V. L. Friedrich, Jr. & N. K. Robakis: Presenilin-1 forms complexes with the cadherin/catenin cell-cell adhesion system and is recruited to intercellular and synaptic contacts. *Mol Cell* 4, 893-902 (1999)

213. Baki L., P. Marambaud, S. Efthimiopoulos, A. Georgakopoulos, P. Wen, W. Cui, J. Shioi, E. Koo, M. Ozawa, V. L. Friedrich, Jr. & N. K. Robakis: Presenilin-1 binds cytoplasmic epithelial cadherin, inhibits cadherin/p120 association and regulates stability and function of the cadherin/catenin adhesion complex. *Proc Natl Acad Sci USA* 98, 2381-2386 (2001)

214. De Strooper B., W. Annaert, P. Cupers, P. Saftig, K. Craessaerts, J. S. Mumm, E. H. Schroeter, V. Schrijvers, M. S. Wolfe, W. J. Ray, A. Goate & R. Kopan: A presenilin-1-dependent gamma-secretase-like protease mediates release of Notch intracellular domain. *Nature* 398, 518-522 (1999)

215. O'Leary D. D. & D. G. Wilkinson: Eph receptors and ephrins in neural development. *Curr Opin Neurobiol* 9, 65-73 (1999)

216. Schmucker D. & S. L. Zipursky: Signaling downstream of Eph receptors and ephrin ligands. *Cell* 105, 701-704 (2001)

217. Zantek N. D., M. Azimi, M. Fedor-Chaiken, B. Wang, R. Brackenbury & M. S. Kinch: E-cadherin regulates the function of the EphA2 receptor tyrosine kinase. *Cell Growth Differ* 10, 629-638 (1999)

218. Orsulic S. & R. Kemler: Expression of Eph receptors and ephrins is differentially regulated by E-cadherin. *J Cell Sci* 113, 1793-802 (2000)

219. von Schlippe M., J. F. Marshall, P. Perry, M. Stone, A. J. Zhu & I. R. Hart: Functional interaction between E-cadherin and alphav-containing integrins in carcinoma cells. *J Cell Sci* 113, 425-437 (2000)

220. Gimond C., A. van Der Flier, S. van Delft, C. Brakebusch, I. Kuikman, J. G. Collard, R. Fassler & A. Sonnenberg: Induction of cell scattering by expression of beta1 integrins in beta1- deficient epithelial cells requires activation of members of the rho family of GTPases and downregulation of cadherin and catenin function. *J Cell Biol* 147, 1325-1340 (1999)

221. Li H., T. C. Leung, S. Hoffman, J. Balsamo & J. Lilien: Coordinate regulation of cadherin and integrin function by the chondroitin sulfate proteoglycan neurocan. *J Cell Biol* 149, 1275-1288 (2000)

222. Arregui C., P. Pathre, J. Lilien & J. Balsamo: The nonreceptor tyrosine kinase fer mediates cross-talk between N- cadherin and beta1-integrins. *J Cell Biol* 149, 1263-1274 (2000)

223. Pathre P., C. Arregui, T. Wampler, I. Kue, T. C. Leung, J. Lilien & J. Balsamo: PTP1B regulates neurite extension mediated by cell-cell and cell-matrix adhesion molecules. *J Neurosci Res* 63, 143-150 (2001)

224. Rapraeger A. C.: Syndecan-regulated receptor signaling. *J Cell Biol* 149, 995-998 (2000)

225. Vleminckx K. L., J. J. Deman, E. A. Bruyneel, G. M. Vandenbossche, A. A. Keirsebilck, M. M. Mareel & F. M. van Roy: Enlarged cell-associated proteoglycans abolish E-cadherin functionality in invasive tumor cells. *Cancer Res* 54, 873-877 (1994)

226. Hsueh Y. P. & M. Sheng: Regulated expression and subcellular localization of syndecan heparan sulfate proteoglycans and the syndecan-binding protein CASK/LIN-2 during rat brain development. *J Neurosci* 19, 7415-7425 (1999)

227. Waterman-Storer C. M., W. C. Salmon & E. D. Salmon: Feedback interactions between cell-cell adherens junctions and cytoskeletal dynamics in newt lung epithelial cells. *Mol Biol Cell* 11, 2471-2483 (2000)

228. Kaufmann U., J. Kirsch, A. Irintchev, A. Wernig & A. Starzinski-Powitz: The M-cadherin catenin complex interacts with microtubules in skeletal muscle cells: implications for the fusion of myoblasts. *J Cell Sci* 112, 55-68 (1999)

229. Ligon L. A., S. Karki, M. Tokito & E. L. Holzbaur: Dynein binds to beta-catenin and may tether microtubules at adherens junctions. *Nat Cell Biol* 3, 913-917 (2001)

230. Chausovsky A., A. D. Bershadsky & G. G. Borisy: Cadherin-mediated regulation of microtubule dynamics. *Nat Cell Biol* 2, 797-804 (2000)

231. Kee S. H. & P. M. Steinert: Microtubule disruption in keratinocytes induces cell-cell adhesion through activation of endogenous E-cadherin. *Mol Biol Cell* 12, 1983-1993 (2001)

232. Kamei T., T. Matozaki, T. Sakisaka, A. Kodama, S. Yokoyama, Y. F. Peng, K. Nakano, K. Takaishi & Y. Takai: Coendocytosis of cadherin and c-Met coupled to disruption of cell-cell adhesion in MDCK cells--regulation by Rho, Rac and Rab small G proteins. *Oncogene* 18, 6776-6784 (1999)

233. Akhtar N. & N. A. Hotchin: RAC1 regulates adherens junctions through endocytosis of E-cadherin. *Mol Biol Cell* 12, 847-862 (2001)

234. Palacios F., L. Price, J. Schweitzer, J. G. Collard & C. D'Souza-Schorey: An essential role for ARF6-regulated membrane traffic in adherens junction turnover and epithelial cell migration. *EMBO J* 20, 4973-4986 (2001)

235. Fujita Y., G. Krause, M. Scheffner, D. Zechner, H. E. Leddy, J. Behrens, T. Sommer & W. Birchmeier: Hakai, a c-Cbl-like protein, ubiquitinates and induces endocytosis of the E-cadherin complex. *Nat Cell Biol* 4, 222-231 (2002)

236. Nagafuchi A., Y. Shirayoshi, K. Okazaki, K. Yasuda & M. Takeichi: Transformation of cell adhesion properties by exogenously introduced E-cadherin cDNA. *Nature* 329, 341-343 (1987)

237. McNeill H., M. Ozawa, R. Kemler & W. J. Nelson: Novel function of the cell adhesion molecule uvomorulin as an inducer of cell surface polarity. *Cell* 62, 309-316 (1990)

238. Grindstaff K. K., C. Yeaman, N. Anandasabapathy, S. C. Hsu, E. Rodriguez-Boulan, R. H. Scheller & W. J. Nelson: Sec6/8 complex is recruited to cell-cell contacts and specifies transport vesicle delivery to the basal-lateral membrane in epithelial cells. *Cell* 93, 731-740 (1998)

239. Hazuka C. D., D. L. Foletti, S. C. Hsu, Y. Kee, F. W. Hopf & R. H. Scheller: The sec6/8 complex is located at neurite outgrowth and axonal synapse-assembly domains. *J Neurosci* 19, 1324-1334 (1999)

240. Tsukita S., M. Furuse & M. Itoh: Structural and signalling molecules come together at tight junctions. *Curr Opin Cell Biol* 11, 628-633 (1999)

241. Itoh M., A. Nagafuchi, S. Moroi & S. Tsukita: Involvement of ZO-1 in cadherin-based cell adhesion through its direct binding to alpha catenin and actin filaments. *J Cell Biol* 138, 181-192 (1997)

242. Itoh M., K. Morita & S. Tsukita: Characterization of ZO-2 as a MAGUK family member associated with tight as well as adherens junctions with a binding affinity to occludin and alpha catenin. *J Biol Chem* 274, 5981-5986 (1999)

243. Gumbiner B., B. Stevenson & A. Grimaldi: The role of the cell adhesion molecule uvomorulin in the formation and maintenance of the epithelial junctional complex. *J Cell Biol* 107, 1575-1587 (1988)

244. Mege R. M., F. Matsuzaki, W. J. Gallin, J. I. Goldberg, B. A. Cunningham & G. M. Edelman: Construction of epithelioid sheets by transfection of mouse sarcoma cells with cDNAs for chicken cell adhesion molecules. *Proc Natl Acad Sci USA* 85, 7274-7278 (1988)

245. Meyer R. A., D. W. Laird, J. P. Revel & R. G. Johnson: Inhibition of gap junction and adherens junction assembly by connexin and A-CAM antibodies. *J Cell Biol* 119, 179-189 (1992)

246. Matsuzaki F., R. M. Mege, S. H. Jaffe, D. R. Friedlander, W. J. Gallin, J. I. Goldberg, B. A. Cunningham & G. M. Edelman: cDNAs of cell adhesion molecules of different specificity induce changes in cell shape and border formation in cultured S180 cells. *J Cell Biol* 110, 1239-1252 (1990)

247. Xu X., W. E. Li, G. Y. Huang, R. Meyer, T. Chen, Y. Luo, M. P. Thomas, G. L. Radice & C. W. Lo: Modulation of mouse neural crest cell motility by N-cadherin and connexin 43 gap junctions. *J Cell Biol* 154, 217-230 (2001)

248. Oda H., S. Tsukita & M. Takeichi: Dynamic behavior of the cadherin-based cell-cell adhesion system during Drosophila gastrulation. *Dev Biol* 203, 435-450 (1998)

249. Lincecum J. M., A. Fannon, K. Song, Y. Wang & D. A. Sassoon: Msh homeobox genes regulate cadherin-mediated cell adhesion and cell- cell sorting. *J Cell Biochem* 70, 22-28 (1998)

250. Comijin J., G. Berx, P. Vermassen, K. Verschueren, L. van Grunsven, E. Bruyneel, M. Mareel, D. Huylebroeck & F. van Roy: The two-handed E box binding zinc finger protein SIP1 downregulates E-cadherin and induces invasion. *Mol Cell* 7, 1267-1278 (2001)

251. Perez-Moreno M. A., A. Locascio, I. Rodrigo, G. Dhondt, F. Portillo, M. A. Nieto & A. Cano: A new role for E12/E47 in the repression of E-cadherin expression and epithelial-mesenchymal transitions. *J Biol Chem* 276, 27424-27431 (2001)

252. Niewiadomska P., D. Godt & U. Tepass: DE-Cadherin is required for intercellular motility during Drosophila oogenesis. *J Cell Biol* 144, 533-547 (1999)

253. King M. W., M. Ndiema & A. W. Neff: Anterior structural defects by misexpression of Xgbx-2 in early Xenopus embryos are associated with altered expression of cell adhesion molecules. *Dev Dyn* 212, 563-579 (1998)

254. Liu Q., J. A. Marrs, J. C. Chuang & P. A. Raymond: Cadherin-4 expression in the zebrafish central nervous system and regulation by ventral midline signaling. *Brain Res Dev Brain Res* 131, 17-29 (2001)

255. Li B., N. E. Paradies & R. W. Brackenbury: Isolation and characterization of the promoter region of the chicken N- cadherin gene. *Gene* 191, 7-13 (1997)

256. Bishop K. M., G. Goudreau & D. D. O'Leary: Regulation of area identity in the mammalian neocortex by Emx2 and Pax6. *Science* 288, 344-349 (2000)

257. Stoykova A., M. Gotz, P. Gruss & J. Price: Pax6-dependent regulation of adhesive patterning, R-cadherin

expression and boundary formation in developing forebrain. *Development* 124, 3765-3777 (1997)

258. Inoue T., O. Chisaka, H. Matsunami & M. Takeichi: Cadherin-6 expression transiently delineates specific rhombomeres, other neural tube subdivisions and neural crest subpopulations in mouse embryos. *Dev Biol* 183, 183-194 (1997)

259. Chen G. T., S. Getsios & C. D. MacCalman: Antisteroidal compounds and steroid withdrawal down-regulate cadherin- 11 mRNA and protein expression levels in human endometrial stromal cells undergoing decidualisation *in vitro*. *Mol Reprod Dev* 53, 384-393 (1999)

260. Blaschuk O. W. & R. Farookhi: Estradiol stimulates cadherin expression in rat granulosa cells. *Dev Biol* 136, 564-567 (1989)

261. Zhou H., A. A. Welcher & E. M. Shooter: BDNF/NT4-5 receptor TrkB and cadherin participate in cell-cell adhesion. J *Neurosci* Res 49, 281-291 (1997)

262. D'Souza B. & J. Taylor-Papadimitriou: Overexpression of ERBB2 in human mammary epithelial cells signals inhibition of transcription of the E-cadherin gene. *Proc Natl Acad Sci USA* 91, 7202-7206 (1994)

263. Leppa S., K. Vleminckx, F. Van Roy & M. Jalkanen: Syndecan-1 expression in mammary epithelial tumor cells is E-cadherin- dependent. *J Cell Sci* 109, 1393-1403 (1996)

264. Holt C. E., P. Lemaire & J. B. Gurdon: Cadherin-mediated cell interactions are necessary for the activation of MyoD in Xenopus mesoderm. *Proc Natl Acad Sci USA* 91, 10844-10848 (1994)

265. Duband J. L., S. Dufour, K. Hatta, M. Takeichi, G. M. Edelman & J. P. Thiery: Adhesion molecules during somitogenesis in the avian embryo. *J Cell Biol* 104, 1361-1374 (1987)

266. Horikawa K., G. Radice, M. Takeichi & O. Chisaka: Adhesive subdivisions intrinsic to the epithelial somites. *Dev Biol* 215, 182-189 (1999)

267. Hatta K., S. Takagi, H. Fujisawa & M. Takeichi: Spatial and temporal expression pattern of N-cadherin cell adhesion molecules correlated with morphogenetic processes of chicken embryos. *Dev Biol* 120, 215-227 (1987)

268. Radice G. L., H. Rayburn, H. Matsunami, K. A. Knudsen, M. Takeichi & R. O. Hynes: Developmental defects in mouse embryos lacking N-cadherin. *Dev Biol* 181, 64-78 (1997)

269. Hirai Y., A. Nose, S. Kobayashi & M. Takeichi: Expression and role of E- and P-cadherin adhesion molecules in embryonic histogenesis. II. Skin morphogenesis. *Development* 105, 271-277 (1989)

270. Hirai Y., A. Nose, S. Kobayashi & M. Takeichi: Expression and role of E- and P-cadherin adhesion molecules in embryonic histogenesis. I. Lung epithelial morphogenesis. *Development* 105, 263-270 (1989)

271. Oberlender S. A. & R. S. Tuan: Expression and functional involvement of N-cadherin in embryonic limb chondrogenesis. *Development* 120, 177-187 (1994)

272. Bronner-Fraser M., J. J. Wolf & B. A. Murray: Effects of antibodies against N-cadherin and N-CAM on the cranial neural crest and neural tube. *Dev Biol* 153, 291-301 (1992)

273. Matsunaga M., K. Hatta & M. Takeichi: Role of N-cadherin cell adhesion molecules in the histogenesis of neural retina. *Neuron* 1, 289-295 (1988)

274. Ganzler-Odenthal S. I. & C. Redies: Blocking N-cadherin function disrupts the epithelial structure of differentiating neural tissue in the embryonic chicken brain. *J Neurosci* 18, 5415-5425 (1998)

275. Nakagawa S. & M. Takeichi: N-cadherin is crucial for heart formation in the chick embryo. *Dev Growth Differ* 39, 451-455 (1997)

276. Larue L., M. Ohsugi, J. Hirchenhain & R. Kemler: E-cadherin null mutant embryos fail to form a trophectoderm epithelium. *Proc Natl Acad Sci USA* 91, 8263-8267 (1994)

277. Schnadelbach O., O. W. Blaschuk, M. Symonds, B. J. Gour, P. Doherty & J. W. Fawcett: N-cadherin influences migration of oligodendrocytes on astrocyte monolayers. *Mol Cell Neurosci* 15, 288-302 (2000)

278. Wang X., A. A. Thant, K. Machida, Y. Hiraiwa, H. Iwata, S. Matsuda & M. Hamaguchi: Suppression of cell growth by ectopic expression of N-cadherin. *Int J Oncol* 12, 1097-1101 (1998)

279. Caveda L., I. Martin-Padura, P. Navarro, F. Breviario, M. Corada, D. Gulino, M. G. Lampugnani & E. Dejana: Inhibition of cultured cell growth by vascular endothelial cadherin (cadherin-5/VE-cadherin). *J Clin Invest* 98, 886-893 (1996)

280. Kandikonda S., D. Oda, R. Niederman & B. C. Sorkin: Cadherin-mediated adhesion is required for normal growth regulation of human gingival epithelial cells. *Cell Adhes Commun* 4, 13-24 (1996)

281. Levenberg S., A. Yarden, Z. Kam & B. Geiger: p27 is involved in N-cadherin-mediated contact inhibition of cell growth and S-phase entry. *Oncogene* 18, 869-876 (1999)

282. Radice G. L., M. C. Ferreira-Cornwell, S. D. Robinson, H. Rayburn, L. A. Chodosh, M. Takeichi & R. O. Hynes: Precocious mammary gland development in P-cadherin-deficient mice. *J Cell Biol* 139, 1025-1032 (1997)

283. Lele Z., A. Folchert, M. Concha, G. J. Rauch, R. Geisler, F. Rosa, S. W. Wilson, M. Hammerschmidt & L. Bally-Cuif: parachute/n-cadherin is required for morphogenesis and maintained integrity of the zebrafish neural tube. *Development* 129, 3281-3294 (2002)

284. Rosenberg P., F. Esni, A. Sjodin, L. Larue, L. Carlsson, D. Gullberg, M. Takeichi, R. Kemler & H. Semb: A potential role of R-cadherin in striated muscle formation. *Dev Biol* 187, 55-70 (1997)

285. Goichberg P. & B. Geiger: Direct involvement of N-cadherin-mediated signaling in muscle differentiation. *Mol Biol Cell* 9, 3119-3131 (1998)

286. Larue L., C. Antos, S. Butz, O. Huber, V. Delmas, M. Dominis & R. Kemler: A role for cadherins in tissue formation. *Development* 122, 3185-3194 (1996)

287. Gao X., W. Bian, J. Yang, K. Tang, H. Kitani, T. Atsumi & N. Jing: A role of N-cadherin in neuronal differentiation of embryonic carcinoma P19 cells. *Biochem Biophys Res Commun* 284, 1098-10103 (2001)

288. Payne H. R. & V. Lemmon: Glial cells of the O-2A lineage bind preferentially to N-cadherin and develop distinct morphologies. *Dev Biol* 159, 595-607 (1993)

289. Redies C., H. Inuzuka & M. Takeichi: Restricted expression of N- and R-cadherin on neurites of the developing chicken CNS. *J Neurosci* 12, 3525-3534 (1992)

290. Takeichi M., H. Inuzuka, K. Shimamura, T. Fujimori & A. Nagafuchi: Cadherin subclasses: differential expression and their roles in neural morphogenesis. *Cold Spring Harb Symp Quant Biol* 55, 319-325 (1990)

291. Redies C. & L. Puelles: Modularity in vertebrate brain development. Bioessays 23, 1100-1111 (2001)

292. Redies C.: Cadherin expression in the developing vertebrate CNS: from neuromeres to brain nuclei and neural circuits. *Exp Cell Res* 220, 243-256 (1995)

293. Ganzler S. I. & C. Redies: R-cadherin expression during nucleus formation in chicken forebrain neuromeres. *J Neurosci* 15, 4157-4172 (1995)

294. Redies C., K. Engelhart & M. Takeichi: Differential expression of N- and R-cadherin in functional neuronal systems and other structures of the developing chicken brain. *J Comp Neuro*l 333, 398-416 (1993)

295. Tang L., C. P. Hung & E. M. Schuman: A role for the cadherin family of cell adhesion molecules in hippocampal long-term potentiation. *Neuron* 20, 1165-1175 (1998)

296. Ranscht B.: Cadherins: molecular codes for axon guidance and synapse formation. *Int J Dev Neurosci* 18, 643-6451 (2000)

297. Serafini T.: Finding a partner in a crowd: neuronal diversity and synaptogenesis. *Cell* 98, 133-136 (1999)

298. Shapiro L. & D. R. Colman: The diversity of cadherins and implications for a synaptic adhesive code in the CNS. *Neuron* 23, 427-430 (1999)

299. Martinek S. & U. Gaul: Neural development: how cadherins zipper up neural circuits. *Curr Biol* 7, R712-715 (1997)

300. Murase S., E. Mosser & E. M. Schuman: Depolarization drives beta-catenin into neuronal spines promoting changes in synaptic structure and function. *Neuron* 35, 91-105 (2002)

301. Garcia-Castro M. I., E. Vielmetter & M. Bronner-Fraser: N-Cadherin, a cell adhesion molecule involved in establishment of embryonic left-right asymmetry. *Science* 288, 1047-1051 (2000)

302. Redies C. & M. Takeichi: Expression of N-cadherin mRNA during development of the mouse brain. *Dev Dyn* 197, 26-39 (1993)

303. Aaku-Saraste E., A. Hellwig & W. B. Huttner: Loss of occludin and functional tight junctions, but not ZO-1, during neural tube closure--remodeling of the neuroepithelium prior to neurogenesis. *Dev Biol* 180, 664-679 (1996)

304. Luo Y., M. Ferreira-Cornwell, H. Baldwin, I. Kostetskii, J. Lenox, M. Lieberman & G. Radice: Rescuing the N-cadherin knockout by cardiac-specific expression of N- or E-cadherin. *Development* 128, 459-469 (2001)

305. Lumsden A. & R. Krumlauf: Patterning the vertebrate neuraxis. *Science* 274, 1109-1115 (1996)

306. Rubenstein J. L., K. Shimamura, S. Martinez & L. Puelles: Regionalization of the prosencephalic neural plate. *Annu Rev Neurosci* 21, 445-477 (1998)

307. Puelles L. & J. L. Rubenstein: Expression patterns of homeobox and other putative regulatory genes in the embryonic mouse forebrain suggest a neuromeric organization. *Trends Neurosci* 16, 472-479 (1993)

308. Wingate R. J. & A. Lumsden: Persistence of rhombomeric organisation in the postsegmental hindbrain. *Development* 122, 2143-2152 (1996)

309. Marin F. & L. Puelles: Morphological fate of rhombomeres in quail/chick chimeras: a segmental analysis of hindbrain nuclei. *Eur J Neurosci* 7, 1714-1738 (1995)

310. Cambronero F. & L. Puelles: Rostrocaudal nuclear relationships in the avian medulla oblongata: a fate map with quail chick chimeras. *J Comp Neurol* 427, 522-545 (2000)

311. Redies C., M. Ast, S. Nakagawa, M. Takeichi, M. Martinez-de-la-Torre & L. Puelles: Morphologic fate of diencephalic prosomeres and their subdivisions revealed by mapping cadherin expression. *J Comp Neurol* 421, 481-514 (2000)

312. Redies C., L. Medina & L. Puelles: Cadherin expression by embryonic divisions and derived gray matter structures in the telencephalon of the chicken. *J Comp Neurol* 438, 253-285 (2001)

313. Lumsden A. & R. Keynes: Segmental patterns of neuronal development in the chick hindbrain. *Nature* 337, 424-428 (1989)

314. Krauss S., T. Johansen, V. Korzh & A. Fjose: Expression pattern of zebrafish pax genes suggests a role in early brain regionalization. *Nature* 353, 267-270 (1991)

315. Mastick G. S. & S. S. Easter, Jr.: Initial organization of neurons and tracts in the embryonic mouse fore- and midbrain. *Dev Biol* 173, 79-94 (1996)

316. Wilson S. W., M. Placzek & A. J. Furley: Border disputes: do boundaries play a role in growth-cone guidance? *Trends in Neurosciences* 16, 316-323 (1993)

317. Fraser S., R. Keynes & A. Lumsden: Segmentation in the chick embryo hindbrain is defined by cell lineage restrictions. *Nature* 344, 431-435 (1990)

318. Figdor M. C. & C. D. Stern: Segmental organization of embryonic diencephalon. *Nature* 363, 630-634 (1993)

319. Fishell G., C. A. Mason & M. E. Hatten: Dispersion of neural progenitors within the germinal zones of the forebrain. *Nature* 362, 636-638 (1993)

320. Anderson S. A., D. D. Eisenstat, L. Shi & J. L. Rubenstein: Interneuron migration from basal forebrain to neocortex: dependence on Dlx genes. *Science* 278, 474-476 (1997)

321. Cobos I., L. Puelles & S. Martinez: The avian telencephalic subpallium originates tangentially migrating inhibitory neurons that invade the dorsal ventricular ridge and the cortical areas. *Dev Biol* 239, 30-45 (2001)

322. Matsunami H. & M. Takeichi: Fetal brain subdivisions defined by R- and E-cadherin expressions: evidence for the role of cadherin activity in region-specific, cell- cell adhesion. *Dev Biol* 172, 466-478 (1995)

323. Basler K., T. Edlund, T. M. Jessell & T. Yamada: Control of cell pattern in the neural tube: regulation of cell differentiation by dorsalin-1, a novel TGF beta family member. *Cell* 73, 687-702 (1993)

324. Ericson J., J. Briscoe, P. Rashbass, V. van Heyningen & T. M. Jessell: Graded sonic hedgehog signaling and the specification of cell fate in the ventral neural tube. *Cold Spring Harb Symp Quant Biol* 62, 451-466 (1997)

325. Nakagawa S. & M. Takeichi: Neural crest emigration from the neural tube depends on regulated cadherin expression. *Development* 125, 2963-2971 (1998)

326. Kimura Y., H. Matsunami & M. Takeichi: Expression of cadherin-11 delineates boundaries, neuromeres and nuclei in the developing mouse brain. *Dev Dyn* 206, 455-462 (1996)

327. Yoon M. S., L. Puelles & C. Redies: Formation of cadherin-expressing brain nuclei in diencephalic alar plate divisions. *J Comp Neurol* 427, 461-480 (2000)

328. Shimamura K., D. J. Hartigan, S. Martinez, L. Puelles & J. L. Rubenstein: Longitudinal organization of the anterior neural plate and neural tube. *Development* 121, 3923-3933 (1995)

329. Redies C.: Cadherins and the formation of neural circuitry in the vertebrate CNS. *Cell Tissue Res* 290, 405-413 (1997)

330. Gotz M., A. Wizenmann, S. Reinhardt, A. Lumsden & J. Price: Selective adhesion of cells from different telencephalic regions. *Neuron* 16, 551-564 (1996)

331. Irvine K. D. & C. Rauskolb: Boundaries in development: formation and function. *Annu Rev Cell Dev Biol* 17, 189-214 (2001)

332. Dahmann C. & K. Basler: Compartment boundaries: at the edge of development. *Trends Genet* 15, 320-326 (1999)

333. Pasini A. & D. G. Wilkinson: Stabilizing the regionalisation of the developing vertebrate central nervous system. *Bioessays* 24, 427-438 (2002)

334. Espeseth A., G. Marnellos & C. Kintner: The role of F-cadherin in localizing cells during neural tube formation in Xenopus embryos. *Development* 125, 301-312 (1998)

335. Inoue T., T. Tanaka, M. Takeichi, O. Chisaka, S. Nakamura & O. Noriko: Role of cadherins in maintaining the compartment boundary between the cortex and striatum during development. *Development* 128, 561-569 (2001)

336. McCarthy M., E. Na, C. Neyt, A. Langston & G. Fishell: Calcium-dependent adhesion is necessary for the maintenance of prosomeres. *Dev Biol* 233, 80-94 (2001)

337. Ranscht B.: Cadherin cell adhesion molecules in vertebrate neural development. *Semi Neurosci* 3, 285-296 (1991)

338. Snow D. M., D. A. Steindler & J. Silver: Molecular and cellular characterization of the glial roof plate of the spinal cord and optic tectum: a possible role for a proteoglycan in the development of an axon barrier. *Dev Biol* 138, 359-376 (1990)

339. Arndt K. & C. Redies: Restricted expression of R-cadherin by brain nuclei and neural circuits of the developing chicken brain. *J Comp Neurol* 373, 373-399 (1996)

340. Fushimi D., K. Arndt, M. Takeichi & C. Redies: Cloning and expression analysis of cadherin-10 in the CNS of the chicken embryo. *Dev Dyn* 209, 269-285 (1997)

341. Korematsu K. & C. Redies: Restricted expression of cadherin-8 in segmental and functional subdivisions of the embryonic mouse brain. *Dev Dyn* 208, 178-189 (1997)

342. Suzuki S. C., T. Inoue, Y. Kimura, T. Tanaka & M. Takeichi: Neuronal circuits are subdivided by differential expression of type-II classic cadherins in postnatal mouse brains. *Mol Cell Neurosci* 9, 433-447 (1997)

343. Arndt K., S. Nakagawa, M. Takeichi & C. Redies: Cadherin-defined segments and parasagittal cell ribbons in the developing chicken cerebellum. *Mol Cell Neurosci* 10, 211-228 (1998)

344. Luckner R., K. Obst-Pernberg, S. Hirano, S. T. Suzuki & C. Redies: Granule cell raphes in the developing mouse cerebellum. *Cell Tissue Res* 303, 159-172 (2001)

345. Oberdick J., S. L. Baader & K. Schilling: From zebra stripes to postal zones: deciphering patterns of gene expression in the cerebellum. *Trends Neurosci* 21, 383-390 (1998)

346. Miyashita-Lin E. M., R. Hevner, K. M. Wassarman, S. Martinez & J. L. Rubenstein: Early neocortical regionalization in the absence of thalamic innervation. *Science* 285, 906-909 (1999)

347. Nakagawa Y., J. E. Johnson & D. D. O'Leary: Graded and areal expression patterns of regulatory genes and cadherins in embryonic neocortex independent of thalamocortical input. *J Neurosci* 19, 10877-10885 (1999)

348. Rubenstein J. L., S. Anderson, L. Shi, E. Miyashita-Lin, A. Bulfone & R. Hevner: Genetic control of cortical regionalization and connectivity. *Cereb Cortex* 9, 524-532 (1999)

349. Hatten M. E.: Central nervous system neuronal migration. *Annu Rev Neurosci* 22, 511-539 (1999)

350. Barami K., B. Kirschenbaum, V. Lemmon & S. A. Goldman: N-cadherin and Ng-CAM/8D9 are involved serially in the migration of newly generated neurons into the adult songbird brain. *Neuron* 13, 567-582 (1994)

351. Simonneau L. & J. P. Thiery: The mesenchymal cadherin-11 is expressed in restricted sites during the ontogeny of the rat brain in modes suggesting novel functions. *Cell Adhes Commun* 6, 431-450 (1998)

352. Borchers A., R. David & D. Wedlich: Xenopus cadherin-11 restrains cranial neural crest migration and influences neural crest specification. *Development* 128, 3049-3060 (2001)

353. Price S. R., N. V. De Marco Garcia, B. Ranscht & T. M. Jessell: Regulation of motor neuron pool sorting by differential expression of type II cadherins. *Cell* 109, 205-216 (2002)

354. Diaz C., L. Puelles, F. Marin & J. C. Glover: The relationship between rhombomeres and vestibular neuron populations as assessed in quail-chicken chimeras. *Dev Biol* 202, 14-28 (1998)

355. Faulkner-Jones B. E., L. N. Godinho, B. E. Reese, G. F. Pasquini, A. Ruefli & S. S. Tan: Cloning and expression of mouse Cadherin-7, a type-II cadherin isolated from the developing eye. *Mol Cell Neurosci* 14, 1-16 (1999)

356. Obst-Pernberg K., L. Medina & C. Redies: Expression of R-cadherin and N-cadherin by cell groups and fiber tracts in the developing mouse forebrain: relation to the formation of functional circuits. *Neuroscience* 106, 505-533 (2001)

357. Korematsu K. & C. Redies: Expression of cadherin-8 mRNA in the developing mouse central nervous system. *J Comp Neurol* 387, 291-306 (1997)

358. Wohrn J. C., L. Puelles, S. Nakagawa, M. Takeichi & C. Redies: Cadherin expression in the retina and retinofugal pathways of the chicken embryo. *J Comp Neurol* 396, 20-38 (1998)

359. Honjo M., H. Tanihara, S. Suzuki, T. Tanaka, Y. Honda & M. Takeichi: Differential expression of cadherin adhesion receptors in neural retina of the postnatal mouse. *Invest Ophthalmol Vis Sci* 41, 546-551 (2000)

360. Inoue A. & J. R. Sanes: Lamina-specific connectivity in the brain: regulation by N-cadherin, neurotrophins and glycoconjugates. *Science* 276, 1428-1431 (1997)

361. Sanes J. R. & M. Yamagata: Formation of lamina-specific synaptic connections. *Curr Opin Neurobio*l 9, 79-87 (1999)

362. Treubert-Zimmermann U., D. Heyer & C. Redies: Targeting axons to specific fibre tracts *in vivo* by altering cadherin expression. *J Neurosci* 22, 7617-7626 (2002)

363. Redies C., D. Kovjanic, D. Heyers, L. Medina, S. Hirano, S. T. Suzuki & L. Puelles: Patch/matrix patterns of gray matter differentiation in the telencephalon of chicken and mouse. *Brain Res Bull* 57, 489-493 (2002)

364. Korematsu K., T. Nishi, A. Okamura, S. Goto, M. Morioka, J. Hamada & Y. Ushio: Cadherin-8 protein expression in gray matter structures and nerve fibers of the neonatal and adult mouse brain. *Neuroscience* 87, 303-315 (1998)

365. Heyers D., D. Kovjanic & C. Redies: Cadherin expression coincides with birth-dating patterns in patch/matrix compartments of the developing chicken telencephalon. (submitted)

366. Krushel L. A., G. Fishell & D. van der Kooy: Pattern formation in the mammalian forebrain: striatal patch and matrix neurons intermix prior to compartment formation. *Eur J Neurosci* 7, 1210-1219 (1995)

367. Kovajanic D. & C. Redies: Small-scale pattern formation in a cortical area of the embryonic chicken telencephalon. *J Comp Neurol* (in press)

368. Letourneau P. C., T. A. Shattuck, F. K. Roche, M. Takeichi & V. Lemmon: Nerve growth cone migration onto Schwann cells involves the calcium- dependent adhesion molecule, N-cadherin. *Dev Biol* 138, 430-442 (1990)

369. Bixby J. L. & R. Zhang: Purified N-cadherin is a potent substrate for the rapid induction of neurite outgrowth. *J Cell Biol* 110, 1253-1260 (1990)

370. Matsunaga M., K. Hatta, A. Nagafuchi & M. Takeichi: Guidance of optic nerve fibres by N-cadherin adhesion molecules. *Nature* 334, 62-64 (1988)

371. Tomaselli K. J., K. M. Neugebauer, J. L. Bixby, J. Lilien & L. F. Reichardt: N-cadherin and integrins: two receptor systems that mediate neuronal process outgrowth on astrocyte surfaces. *Neuron* 1, 33-43 (1988)

372. Riehl R., K. Johnson, R. Bradley, G. B. Grunwald, E. Cornel, A. Lilienbaum & C. E. Holt: Cadherin function is required for axon outgrowth in retinal ganglion cells *in vivo*. *Neuron* 17, 837-848 (1996)

373. Fredette B. J., J. Miller & B. Ranscht: Inhibition of motor axon growth by T-cadherin substrata. *Developmen*t 122, 3163-3171 (1996)

374. Utton M. A., B. Eickholt, F. V. Howell, J. Wallis & P. Doherty: Soluble N-cadherin stimulates fibroblast growth factor receptor dependent neurite outgrowth and N-cadherin and the fibroblast growth factor receptor co-cluster in cells. *J Neurochem* 76, 1421-1430 (2001)

375. Doherty P. & F. S. Walsh: CAM-FGF Receptor Interactions: A Model for Axonal Growth. *Mol Cell Neurosci* 8, 99-111 (1996)

376. Lanier L. M. & F. B. Gertler: From Abl to actin: Abl tyrosine kinase and associated proteins in growth cone motility. *Curr Opin Neurobiol* 10, 80-87 (2000)

377. Redies C. & M. Takeichi: N- and R-cadherin expression in the optic nerve of the chicken embryo. *Glia* 8, 161-171 (1993)

378. Gerhardt H., G. Rascher, J. Schuck, U. Weigold, C. Redies & H. Wolburg: R- and B-cadherin expression defines subpopulations of glial cells involved in axonal guidance in the optic nerve head of the chicken. *Glia* 31, 131-143 (2000)

379. Wilby M. J., E. M. Muir, J. Fok-Seang, B. J. Gour, O. W. Blaschuk & J. W. Fawcett: N-Cadherin inhibits Schwann cell migration on astrocytes. *Mol Cell Neurosci* 14, 66-84 (1999)

380. Payne H. R., J. J. Hemperly & V. Lemmon: N-cadherin expression and function in cultured oligodendrocytes. *Brain Res Dev Brain Res* 97, 9-15 (1996)

381. Schnadelbach O., I. Ozen, O. W. Blaschuk, B. J. Gour, R. L. Meyer & J. W. Fawcett: N-cadherin is involved in axon-oligodendrocyte contact and myelination. *Mol Cell Neurosci* 17, 1084-1093 (2001)

382. Letourneau P. C., F. K. Roche, T. A. Shattuck, V. Lemmon & M. Takeichi: Interactions of Schwann cells with neurites and with other Schwann cells involve the calcium-dependent adhesion molecule, N-cadherin. *J Neurobio*l 22, 707-720 (1991)

383. Shibuya Y., A. Mizoguchi, M. Takeichi, K. Shimada & C. Ide: Localization of N-cadherin in the normal and regenerating nerve fibers of the chicken peripheral nervous system. *Neuroscience* 67, 253-261 (1995)

384. Cifuentes-Diaz C., M. Nicolet, D. Goudou, F. Rieger & R. M. Mege: N-cadherin expression in developing, adult and denervated chicken neuromuscular system: accumulations at both the neuromuscular junction and the node of Ranvier. *Development* 120, 1-11 (1994)

385. Honig M. G. & U. S. Rutishauser: Changes in the segmental pattern of sensory neuron projections in the chick hindlimb under conditions of altered cell adhesion molecule function. *Dev Biol* 175, 325-337 (1996)

386. Iwai Y., T. Usui, S. Hirano, R. Steward, M. Takeichi & T. Uemura: Axon patterning requires DN-cadherin, a novel neuronal adhesion receptor, in the Drosophila embryonic CNS. *Neuron* 19, 77-89 (1997)

387. Broadbent I. D. & J. Pettitt: The C. elegans hmr-1 gene can encode a neuronal classic cadherin involved in the regulation of axon fasciculation. *Curr Biol* 12, 59-63 (2002)

388. Drazba J. & V. Lemmon: The role of cell adhesion molecules in neurite outgrowth on Muller cells. *Dev Bio*l 138, 82-93 (1990)

389. Shimamura K., T. Takahashi & M. Takeichi: E-cadherin expression in a particular subset of sensory neurons. *Dev Biol* 152, 242-54 (1992)

390. Uchiyama N., M. Hasegawa, T. Yamashima, J. Yamashita, K. Shimamura & M. Takeichi: Immunoelectron microscopic localization of E-cadherin in dorsal root ganglia, dorsal root and dorsal horn of postnatal mice. *J Neurocytol* 23, 460-468 (1994)

391. Inoue T., T. Tanaka, S. C. Suzuki & M. Takeichi: Cadherin-6 in the developing mouse brain: expression along restricted connection systems and synaptic localization suggest a potential role in neuronal circuitry. *Dev Dyn* 211, 338-3351 (1998)

392. Tessier-Lavigne M. & C. S. Goodman: The molecular biology of axon guidance. *Science* 274, 1123-1133 (1996)

393. Stone K. E. & D. S. Sakaguchi: Perturbation of the developing Xenopus retinotectal projection following injections of antibodies against beta1 integrin receptors and N-cadherin. *Dev Biol* 180, 297-310 (1996)

394. Sperry R. W.: Chemoaffinity in the orderly growth of nerve fiber patterns and connections. *Proc Natl Acad Sci USA* 50, 703-710 (1963)

395. Hagler D. J., Jr. & Y. Goda: Synaptic adhesion: the building blocks of memory? *Neuron* 20, 1059-1062 (1998)

396. Hirano S., T. Ono, Q. Yan, X. Wang, S. Sonta & S. T. Suzuki: Protocadherin 2C: a new member of the protocadherin 2 subfamily expressed in a redundant manner with OL-protocadherin in the developing brain. *Biochem Biophys Res Commun* 260, 641-645 (1999)

397. Hirano S., Q. Yan & S. T. Suzuki: Expression of a novel protocadherin, OL-protocadherin, in a subset of functional systems of the developing mouse brain. *J Neurosci* 19, 995-1005 (1999)

398. Lee C. H., T. Herman, T. R. Clandinin, R. Lee & S. L. Zipursky: N-cadherin regulates target specificity in the Drosophila visual system. *Neuron* 30, 437-450 (2001)

399. Manabe T., H. Togashi, N. Uchida, S. C. Suzuki, Y. Hayakawa, M. Yamamoto, H. Yoda, T. Miyakawa, M. Takeichi & O. Chisaka: Loss of cadherin-11 adhesion receptor enhances plastic changes in hippocampal synapses and modifies behavioral responses. *Mol Cell Neurosci* 15, 534-546 (2000)

400. Benson D. L., L. M. Schnapp, L. Shapiro & G. W. Huntley: Making memories stick: cell-adhesion molecules in synaptic plasticity. *Trends Cell Biol* 10, 473-482 (2000)

401. Yamagata M., J. P. Herman & J. R. Sanes: Lamina-specific expression of adhesion molecules in developing chick optic tectum. *J Neurosci* 15, 4556-4571 (1995)

402. Kohmura N., K. Senzaki, S. Hamada, N. Kai, R. Yasuda, M. Watanabe, H. Ishii, M. Yasuda, M. Mishina & T. Yagi: Diversity revealed by a novel family of cadherins expressed in neurons at a synaptic complex. *Neuron* 20, 1137-1151 (1998)

403. Husi H., M. A. Ward, J. S. Choudhary, W. P. Blackstock & S. G. Grant: Proteomic analysis of NMDA receptor-adhesion protein signaling complexes. *Nat Neurosci* 3, 661-669 (2000)

404. Squitti R., M. E. De Stefano, D. Edgar & G. Toschi: Effects of axotomy on the expression and ultrastructural localization of N-cadherin and neural cell adhesion molecule in the quail ciliary ganglion: an *in vivo* model of neuroplasticity. *Neuroscience* 91, 707-722 (1999)

405. Iwai Y., Y. Hirota, K. Ozaki, H. Okano, M. Takeichi & T. Uemura: DN-Cadherin Is Required for Spatial Arrangement of Nerve Terminals and Ultrastructural Organization of Synapses. *Mol Cell Neurosci* 19, 375-388 (2002)

406. Bruses J. L.: Cadherin-mediated adhesion at the interneuronal synapse. *Curr Opin Cell Biol* 12, 593-597 (2000)

407. Colman D. R.: Neurites, synapses and cadherins reconciled. *Mol Cell Neurosci* 10, 1-6 (1997)

408. Obst-Pernberg K. & C. Redies: Cadherins and synaptic specificity. *J Neurosci Res* 58, 130-138 (1999)

409. Huntley G. W., O. Gil & O. Bozdagi: The cadherin family of cell adhesion molecules: multiple roles in synaptic plasticity. *Neuroscientist* 8, 221-233 (2002)

410. Huntley G. W. & D. L. Benson: Neural (N)-cadherin at developing thalamocortical synapses provides an adhesion mechanism for the formation of somatopically organized connections. *J Comp Neurol* 407, 453-471 (1999)

411. Benson D. L. & H. Tanaka: N-cadherin redistribution during synaptogenesis in hippocampal neurons. *J Neurosci* 18, 6892-6904 (1998)

412. Vrensen G. & J. N. Cardozo: Changes in size and shape of synaptic connections after visual training: an ultrastructural approach of synaptic plasticity. *Brain Res* 218, 79-97 (1981)

413. Edwards F. A.: Anatomy and electrophysiology of fast central synapses lead to a structural model for long-term potentiation. *Physiol Rev* 75, 759-787 (1995)

414. Weiler I. J., N. Hawrylak & W. T. Greenough: Morphogenesis in memory formation: synaptic and cellular mechanisms. *Behav Brain Res* 66, 1-6 (1995)

415. Murase S. & E. M. Schuman: The role of cell adhesion molecules in synaptic plasticity and memory. *Curr Opin Cell Biol* 11, 549-553 (1999)

416. Togashi H., K. Abe, A. Mizoguchi, K. Takaoka, O. Chisaka & M. Takeichi: Cadherin regulates dendritic spine morphogenesis. *Neuron* 35, 77-89 (2002)

417. Uemura T.: The cadherin superfamily at the synapse: more members, more missions. *Cell* 93, 1095-1098 (1998)

418. Tanaka H., W. Shan, G. R. Phillips, K. Arndt, O. Bozdagi, L. Shapiro, G. W. Huntley, D. L. Benson & D. R. Colman: Molecular modification of N-cadherin in response to synaptic activity. *Neuron* 25, 93-107 (2000)

419. Bozdagi O., W. Shan, H. Tanaka, D. L. Benson & G. W. Huntley: Increasing numbers of synaptic puncta during late-phase LTP: N-cadherin is synthesized, recruited to synaptic sites and required for potentiation. *Neuron* 28, 245-259 (2000)

420. Hall Z. W. & J. R. Sanes: Synaptic structure and development: the neuromuscular junction. *Cell* 72 Suppl, 99-121 (1993)

421. Suzuki S. T.: Structural and functional diversity of cadherin superfamily: are new members of cadherin superfamily involved in signal transduction pathway? *J Cell Biochem* 61, 531-542 (1996)

422. Ranscht B. & M. T. Dours-Zimmermann: T-cadherin, a novel cadherin cell adhesion molecule in the nervous system lacks the conserved cytoplasmic region. *Neuron* 7, 391-402 (1991)

423. Takeuchi T. & Y. Ohtsuki: Recent progress in T-cadherin (CDH13, H-cadherin) research. *Histol Histopathol* 16, 1287-1293 (2001)

424. Sacristan M. P., D. J. Vestal, M. T. Dours-Zimmermann & B. Ranscht: T-cadherin 2: molecular characterization, function in cell adhesion and coexpression with T-cadherin and N-cadherin. *J Neurosci Res* 34, 664-680 (1993)

425. Ranscht B. & M. Bronner-Fraser: T-cadherin expression alternates with migrating neural crest cells in the trunk of the avian embryo. *Development* 111, 15-22 (1991)

426. Fredette B. J. & B. Ranscht: T-cadherin expression delineates specific regions of the developing motor axon-hindlimb projection pathway. *J Neurosci* 14, 7331-7346 (1994)

427. Takeuchi T., A. Misaki, S. B. Liang, A. Tachibana, N. Hayashi, H. Sonobe & Y. Ohtsuki: Expression of T-cadherin (CDH13, H-Cadherin) in human brain and its characteristics as a negative growth regulator of epidermal growth factor in neuroblastoma cells. *J Neurochem* 74, 1489-1497 (2000)

428. Cifuentes-Diaz C., D. Goudou, F. Padilla, P. Facchinetti, M. Nicolet, R. M. Mege & F. Rieger: M-cadherin distribution in the mouse adult neuromuscular system suggests a role in muscle innervation. *Eur J Neurosci* 8, 1666-1676 (1996)

429. Stambolsky D. V., Y. S. Kuzmenko, M. P. Philippova, V. N. Bochkov, Z. D. Bespalova, A. A. Azmuko, N. M. Kashirina, T. N. Vlasik, V. A. Tkachuk & T. J. Resink: Identification of 130 kDa cell surface LDL-binding protein from smooth muscle cells as a partially processed T-cadherin precursor. *Biochim Biophys Acta* 1416, 155-160 (1999)

430. Resink T. J., Y. S. Kuzmenko, F. Kern, D. Stambolsky, V. N. Bochkov, V. A. Tkachuk, P. Erne & T. Niermann: LDL binds to surface-expressed human T-cadherin in transfected HEK293 cells and influences homophilic adhesive interactions. *FEBS Lett* 463, 29-34 (1999)

431. Suzuki S. T.: Recent progress in protocadherin research. *Exp Cell Res* 261, 13-18 (2000)

432. Wolverton T. & M. Lalande: Identification and characterization of three members of a novel subclass of protocadherins. *Genomics* 76, 66-72 (2001)

433. Kuroda H., M. Inui, K. Sugimoto, T. Hayata & M. Asashima: Axial protocadherin is a mediator of prenotochord cell sorting in Xenopus. *Dev Biol* 244, 267-277 (2002)

434. Bradley R. S., A. Espeseth & C. Kintner: NF-protocadherin, a novel member of the cadherin superfamily, is required for Xenopus ectodermal differentiation. *Curr Biol* 8, 325-334 (1998)

435. Yoshida K., K. Yoshitomo-Nakagawa, N. Seki, M. Sasaki & S. Sugano: Cloning, expression analysis and chromosomal localization of BH- protocadherin (PCDH7), a novel member of the cadherin superfamily. *Genomics* 49, 458-461 (1998)

436. Yoshida K., M. Hida, M. Watanabe, R. Yamaguchi, S. Tateyama & S. Sugano: cDNA cloning and chromosomal mapping of mouse BH-protocadherin. *DNA Seq* 10, 43-47 (1999)

437. Yoshida K., M. Watanabe, H. Kato, A. Dutta & S. Sugano: BH-protocadherin-c, a member of the cadherin superfamily, interacts with protein phosphatase 1 alpha through its intracellular domain. *FEBS Lett* 460, 93-98 (1999)

438. Mulkey R. M., S. Endo, S. Shenolikar & R. C. Malenka: Involvement of a calcineurin/inhibitor-1 phosphatase cascade in hippocampal long-term depression. *Nature* 369, 486-488 (1994)

439. Malenka R. C.: Synaptic plasticity in the hippocampus: LTP and LTD. *Cell* 78, 535-538 (1994)

440. Yoshida K. & S. Sugano: Identification of a novel protocadherin gene (PCDH11) on the human XY homology region in Xq21.3. *Genomics* 62, 540-543 (1999)

441. Blanco P., C. A. Sargent, C. A. Boucher, M. Mitchell & N. A. Affara: Conservation of PCDHX in mammals; expression of human X/Y genes predominantly in brain. *Mamm Genome* 11, 906-914 (2000)

442. Wu Q., T. Zhang, J. F. Cheng, Y. Kim, J. Grimwood, J. Schmutz, M. Dickson, J. P. Noonan, M. Q. Zhang, R. M. Myers & T. Maniatis: Comparative DNA sequence analysis of mouse and human protocadherin gene clusters. *Genome Res* 11, 389-404 (2001)

443. Obata S., H. Sago, N. Mori, J. M. Rochelle, M. F. Seldin, M. Davidson, T. St John, S. Taketani & S. T. Suzuki: Protocadherin Pcdh2 shows properties similar to, but distinct from, those of classical cadherins. *J Cell Sci* 108, 3765-3773 (1995)

444. Obata S., H. Sago, N. Mori, M. Davidson, T. St John & S. T. Suzuki: A common protocadherin tail: multiple protocadherins share the same sequence in their cytoplasmic domains and are expressed in different regions of brain. *Cell Adhes Commun* 6, 323-333 (1998)

445. Hirano S., X. Wang & S. T. Suzuki: Restricted expression of protocadherin 2A in the developing mouse brain. *Brain Res Mol Brain Res* 98, 119-123 (2002)

446. Heymann R., S. Kallenbach, S. Alonso, P. Carroll & T. A. Mitsiadis: Dynamic expression patterns of the new protocadherin families CNRs and Pcdh-gamma during

mouse odontogenesis: comparison with reelin expression. *Mech Dev* 106, 181-184 (2001)

447. Sago H., M. Kitagawa, S. Obata, N. Mori, S. Taketani, J. M. Rochelle, M. F. Seldin, M. Davidson, T. St John & S. T. Suzuki: Cloning, expression and chromosomal localization of a novel cadherin- related protein, protocadherin-3. *Genomics* 29, 631-640 (1995)

448. Takei Y., S. Hamada, K. Senzaki, T. Mutoh, H. Sugino & T. Yagi: Two novel CNRs from the CNR gene cluster have molecular features distinct from those of CNR1 to 8. *Genomics* 72, 321-330 (2001)

449. Yagi T. & M. Takeichi: Cadherin superfamily genes: functions, genomic organization and neurologic diversity. *Genes Dev* 14, 1169-1180 (2000)

450. Hirayama T., H. Sugino & T. Yagi: Somatic mutations of synaptic cadherin (CNR family) transcripts in the nervous system. *Genes Cells* 6, 151-164 (2001)

451. Senzaki K., M. Ogawa & T. Yagi: Proteins of the CNR family are multiple receptors for Reelin. *Cell* 99, 635-647 (1999)

452. Bixby J. L. & P. Jhabvala: Tyrosine phosphorylation in early embryonic growth cones. *J Neurosci* 13, 3421-3432 (1993)

453. Beggs H. E., P. Soriano & P. F. Maness: NCAM-dependent neurite outgrowth is inhibited in neurons from Fyn-minus mice. *J Cell Biol* 127, 825-833 (1994)

454. Grant S. G., T. J. O'Dell, K. A. Karl, P. L. Stein, P. Soriano & E. R. Kandel: Impaired long-term potentiation, spatial learning and hippocampal development in fyn mutant mice. *Science* 258, 1903-1910 (1992)

455. Yagi T., S. Aizawa, T. Tokunaga, Y. Shigetani, N. Takeda & Y. Ikawa: A role for Fyn tyrosine kinase in the suckling behaviour of neonatal mice. *Nature* 366, 742-745 (1993)

456. Carroll P., O. Gayet, C. Feuillet, S. Kallenbach, B. de Bovis, K. Dudley & S. Alonso: Juxtaposition of CNR protocadherins and reelin expression in the developing spinal cord. *Mol Cell Neurosci* 17, 611-623 (2001)

457. Kim S. H., A. Yamamoto, T. Bouwmeester, E. Agius & E. M. Robertis: The role of paraxial protocadherin in selective adhesion and cell movements of the mesoderm during Xenopus gastrulation. *Development* 125, 4681-4690 (1998)

458. Yamamoto A., S. L. Amacher, S. H. Kim, D. Geissert, C. B. Kimmel & E. M. De Robertis: Zebrafish paraxial protocadherin is a downstream target of spadetail involved in morphogenesis of gastrula mesoderm. *Development* 125, 3389-3397 (1998)

459. Kim S. H., W. C. Jen, E. M. De Robertis & C. Kintner: The protocadherin PAPC establishes segmental boundaries during somitogenesis in xenopus embryos. *Curr Biol* 10, 821-830 (2000)

460. Yamamoto A., C. Kemp, D. Bachiller, D. Geissert & E. M. De Robertis: Mouse paraxial protocadherin is expressed in trunk mesoderm and is not essential for mouse development. *Genesis* 27, 49-57 (2000)

461. Yamagata K., K. I. Andreasson, H. Sugiura, E. Maru, M. Dominique, Y. Irie, N. Miki, Y. Hayashi, M. Yoshioka, K. Kaneko, H. Kato & P. F. Worley: Arcadlin is a neural activity-regulated cadherin involved in long term potentiation. *J Biol Chem* 274, 19473-19479 (1999)

462. Homayouni R., D. S. Rice & T. Curran: Disabled-1 interacts with a novel developmentally regulated protocadherin. *Biochem Biophys Res Commun* 289, 539-547 (2001)

463. Rattner A., P. M. Smallwood, J. Williams, C. Cooke, A. Savchenko, A. Lyubarsky, E. N. Pugh & J. Nathans: A photoreceptor-specific cadherin is essential for the structural integrity of the outer segment and for photoreceptor survival. *Neuron* 32, 775-786 (2001)

464. Bryant P. J., B. Huettner, L. I. Held, Jr., J. Ryerse & J. Szidonya: Mutations at the fat locus interfere with cell proliferation control and epithelial morphogenesis in Drosophila. *Dev Biol* 129, 541-554 (1988)

465. Cox B., A. K. Hadjantonakis, J. E. Collins & A. I. Magee: Cloning and expression throughout mouse development of mfat1, a homologue of the Drosophila tumour suppressor gene fat. *Dev Dyn* 217, 233-240 (2000)

466. Dunne J., A. M. Hanby, R. Poulsom, T. A. Jones, D. Sheer, W. G. Chin, S. M. Da, Q. Zhao, P. C. Beverley & M. J. Owen: Molecular cloning and tissue expression of FAT, the human homologue of the Drosophila fat gene that is located on chromosome 4q34-q35 and encodes a putative adhesion molecule. *Genomics* 30, 207-223 (1995)

467. Ponassi M., T. S. Jacques, L. Ciani & C. ffrench Constant: Expression of the rat homologue of the Drosophila fat tumour suppressor gene. *Mech Dev* 80, 207-212 (1999)

468. Clark H. F., D. Brentrup, K. Schneitz, A. Bieber, C. Goodman & M. Noll: Dachsous encodes a member of the cadherin superfamily that controls imaginal disc morphogenesis in Drosophila. *Genes Dev* 9, 1530-1542 (1995)

469. Adler P. N., J. Charlton & J. Liu: Mutations in the cadherin superfamily member gene dachsous cause a tissue polarity phenotype by altering frizzled signaling. *Development* 125, 959-968 (1998)

470. Yang C. H., J. D. Axelrod & M. A. Simon: Regulation of Frizzled by fat-like cadherins during planar polarity

signaling in the Drosophila compound eye. *Cell* 108, 675-688 (2002)

471. Di Palma F., R. H. Holme, E. C. Bryda, I. A. Belyantseva, R. Pellegrino, B. Kachar, K. P. Steel & K. Noben-Trauth: Mutations in Cdh23, encoding a new type of cadherin, cause stereocilia disorganization in waltzer, the mouse model for Usher syndrome type 1D. *Nat Genet* 27, 103-107 (2001)

472. Bolz H., B. von Brederlow, A. Ramirez, E. C. Bryda, K. Kutsche, H. G. Nothwang, M. Seeliger, C. S. C. M. del, M. C. Vila, O. P. Molina, A. Gal & C. Kubisch: Mutation of CDH23, encoding a new member of the cadherin gene family, causes Usher syndrome type 1D. *Nat Genet* 27, 108-112 (2001)

473. Bork J. M., L. M. Peters, S. Riazuddin, S. L. Bernstein, Z. M. Ahmed, S. L. Ness, R. Polomeno, A. Ramesh, M. Schloss, C. R. Srisailpathy, S. Wayne, S. Bellman, D. Desmukh, Z. Ahmed, S. N. Khan, V. M. Kaloustian, X. C. Li, A. Lalwani, M. Bitner-Glindzicz, W. E. Nance, X. Z. Liu, G. Wistow, R. J. Smith, A. J. Griffith, E. R. Wilcox, T. B. Friedman & R. J. Morell: Usher syndrome 1D and nonsyndromic autosomal recessive deafness DFNB12 are caused by allelic mutations of the novel cadherin-like gene CDH23. *Am J Hum Genet* 68, 26-37 (2001)

474. Wada T., Y. Wakabayashi, S. Takahashi, T. Ushiki, Y. Kikkawa, H. Yonekawa & R. Kominami: A point mutation in a cadherin gene, Cdh23, causes deafness in a novel mutant, Waltzer mouse niigata. *Biochem Biophys Res Commun* 283, 113-117 (2001)

475. Di Palma F., R. Pellegrino & K. Noben-Trauth: Genomic structure, alternative splice forms and normal and mutant alleles of cadherin 23 (Cdh23). *Gene* 281, 31-41 (2001)

476. Alagramam K. N., C. L. Murcia, H. Y. Kwon, K. S. Pawlowski, C. G. Wright & R. P. Woychik: The mouse Ames waltzer hearing-loss mutant is caused by mutation of Pcdh15, a novel protocadherin gene. *Nat Genet* 27, 99-102 (2001)

477. Ahmed Z. M., S. Riazuddin, S. L. Bernstein, Z. Ahmed, S. Khan, A. J. Griffith, R. J. Morell, T. B. Friedman & E. R. Wilcox: Mutations of the protocadherin gene PCDH15 cause Usher syndrome type 1F. *Am J Hum Genet* 69, 25-34 (2001)

478. Alagramam K. N., H. Yuan, M. H. Kuehn, C. L. Murcia, S. Wayne, C. R. Srisailpathy, R. B. Lowry, R. Knaus, L. Van Laer, F. P. Bernier, S. Schwartz, C. Lee, C. C. Morton, R. F. Mullins, A. Ramesh, G. Van Camp, G. S. Hagemen, R. P. Woychik & R. J. Smith: Mutations in the novel protocadherin PCDH15 cause Usher syndrome type 1F. *Hum Mol Genet* 10, 1709-1718 (2001)

479. Murcia C. L. & R. P. Woychik: Expression of Pcdh15 in the inner ear, nervous system and various epithelia of the developing embryo. *Mech Dev* 105, 163-166 (2001)

480. Usui T., Y. Shima, Y. Shimada, S. Hirano, R. W. Burgess, T. L. Schwarz, M. Takeichi & T. Uemura: Flamingo, a seven-pass transmembrane cadherin, regulates planar cell polarity under the control of Frizzled. *Cell* 98, 585-595 (1999)

481. Chae J., M. J. Kim, J. H. Goo, S. Collier, D. Gubb, J. Charlton, P. N. Adler & W. J. Park: The Drosophila tissue polarity gene starry night encodes a member of the protocadherin family. *Development* 126, 5421-5429 (1999)

482. Lu B., T. Usui, T. Uemura, L. Jan & Y. N. Jan: Flamingo controls the planar polarity of sensory bristles and asymmetric division of sensory organ precursors in Drosophila. *Curr Biol* 9, 1247-1250 (1999)

483. Gao F. B., J. E. Brenman, L. Y. Jan & Y. N. Jan: Genes regulating dendritic outgrowth, branching and routing in Drosophila. *Genes Dev* 13, 2549-2561 (1999)

484. Gao F. B., M. Kohwi, J. E. Brenman, L. Y. Jan & Y. N. Jan: Control of dendritic field formation in Drosophila: the roles of flamingo and competition between homologous neurons. *Neuron* 28, 91-101 (2000)

485. Hadjantonakis A. K., C. J. Formstone & P. F. Little: mCelsr1 is an evolutionarily conserved seven-pass transmembrane receptor and is expressed during mouse embryonic development. *Mech Dev* 78, 91-95 (1998)

486. Formstone C. J. & P. F. Little: The flamingo-related mouse Celsr family (Celsr1-3) genes exhibit distinct patterns of expression during embryonic development. *Mech Dev* 109, 91-94 (2001)

487. Tissir F., O. De-Backer, A. M. Goffinet & C. Lambert de Rouvroit: Developmental expression profiles of Celsr (Flamingo) genes in the mouse. *Mech Dev* 112, 157-1560 (2002)

488. Shima Y., N. G. Copeland, D. J. Gilbert, N. A. Jenkins, O. Chisaka, M. Takeichi & T. Uemura: Differential expression of the seven-pass transmembrane cadherin genes Celsr1-3 and distribution of the Celsr2 protein during mouse development. *Dev Dyn* 223, 321-332 (2002)

489. Kowalczyk A. P., E. A. Bornslaeger, S. M. Norvell, H. L. Palka & K. J. Green: Desmosomes: intercellular adhesive junctions specialized for attachment of intermediate filaments. *Int Rev Cytol* 185, 237-302 (1999)

490. Troyanovsky S. M. & R. E. Leube: Molecular dissection of desmosomal assembly and intermediate filament anchorage. *Subcell Biochem* 31, 263-289 (1998)

491. Nakazawa E. & H. Ishikawa: Ultrastructural observations of astrocyte end-feet in the rat central nervous system. *J Neurocytol* 27, 431-440 (1998)

492. Altman J. & S. A. Bayer: Development of the cerebellar system: in relation to its evolution, structure and functions.CRC Press, NY (1996)

493. Haverkamp S., U. Grunert & H. Wassle: The cone pedicle, a complex synapse in the retina. *Neuron* 27, 85-95 (2000)

494. Dantzig A. H., J. A. Hoskins, L. B. Tabas, S. Bright, R. L. Shepard, I. L. Jenkins, D. C. Duckworth, J. R. Sportsman, D. Mackensen, P. R. Rosteck, Jr., & P. L. Skatrud: Association of intestinal peptide transport with a protein related to the cadherin superfamily. *Science* 264, 430-433 (1994)

495. Kreft B., D. Berndorff, A. Bottinger, S. Finnemann, D. Wedlich, M. Hortsch, R. Tauber & R. Gessner: LI-cadherin-mediated cell-cell adhesion does not require cytoplasmic interactions. *J Cell Biol* 136, 1109-1121 (1997)

496. Gessner R. & R. Tauber: Intestinal cell adhesion molecules. Liver-intestine cadherin. *Ann N Y Acad Sci* 915, 136-143 (2000)

497. Thomson R. B., P. Igarashi, D. Biemesderfer, R. Kim, A. Abu-Alfa, M. Soleimani & P. S. Aronson: Isolation and cDNA cloning of Ksp-cadherin, a novel kidney-specific member of the cadherin multigene family. *J Biol Chem* 270, 17594-17601 (1995)

498. Edery P., C. Eng, A. Munnich & S. Lyonnet: RET in human development and oncogenesis. *Bioessays* 19, 389-395 (1997)

499. van Weering D. H. & J. L. Bos: Signal transduction by the receptor tyrosine kinase Ret. *Recent Results Cancer Res* 154, 271-281 (1998)

500. Mason I.: The RET receptor tyrosine kinase: activation, signalling and significance in neural development and disease. *Pharm Acta Helv* 74, 261-264 (2000)

501. Anders J., S. Kjar & C. F. Ibanez: Molecular modeling of the extracellular domain of the RET receptor tyrosine kinase reveals multiple cadherin-like domains and a calcium- binding site. *J Biol Chem* 9, 9 (2001)

502. Manie S., M. Santoro, A. Fusco & M. Billaud: The RET receptor: function in development and dysfunction in congenital malformation. *Trends Genet* 17, 580-589 (2001)

503. Fukuda T., K. Kiuchi & M. Takahashi: Novel mechanism of regulation of Rac activity and lamellipodia formation by RET tyrosine kinase. *J Biol Chem* 277, 19114-19121 (2002)

504. Tsui-Pierchala B. A., J. Milbrandt & E. M. Johnson, Jr.: NGF utilizes c-Ret via a novel GFL-independent, inter-RTK signaling mechanism to maintain the trophic status of mature sympathetic neurons. *Neuron* 33, 261-273 (2002)

505. Pachnis V., B. Mankoo & F. Costantini: Expression of the c-ret proto-oncogene during mouse embryogenesis. *Development* 119, 1005-1017 (1993)

506. Umbhauer M., C. J. Marshall, C. S. Mason, R. W. Old & J. C. Smith: Mesoderm induction in Xenopus caused by activation of MAP kinase. *Nature* 376, 58-62 (1995)

507. Durbec P., C. V. Marcos-Gutierrez, C. Kilkenny, M. Grigoriou, K. Wartiowaara, P. Suvanto, D. Smith, B. Ponder, F. Costantini, M. Saarma, H. Sariola & V. Pachnis: GDNF signalling through the Ret receptor tyrosine kinase. *Nature* 381, 789-793 (1996)

508. Enomoto H., P. A. Crawford, A. Gorodinsky, R. O. Heuckeroth, E. M. Johnson, Jr. & J. Milbrandt: RET signaling is essential for migration, axonal growth and axon guidance of developing sympathetic neurons. *Development* 128, 3963-3974 (2001)

509. Baloh R. H., H. Enomoto, E. M. Johnson, Jr. & J. Milbrandt: The GDNF family ligands and receptors - implications for neural development. *Curr Opin Neurobiol* 10, 103-110 (2000)

510. Schuchardt A., V. D'Agati, L. Larsson-Blomberg, F. Costantini & V. Pachnis: Defects in the kidney and enteric nervous system of mice lacking the tyrosine kinase receptor Ret. *Nature* 367, 380-383 (1994)

511. de Graaff E., S. Srinivas, C. Kilkenny, V. D'Agati, B. S. Mankoo, F. Costantini & V. Pachnis: Differential activities of the RET tyrosine kinase receptor isoforms during mammalian embryogenesis. *Genes Dev* 15, 2433-2444 (2001)

512. Vogt L., S. P. Schrimpf, V. Meskenaite, R. Frischknecht, J. Kinter, D. P. Leone, U. Ziegler & P. Sonderegger: Calsyntenin-1, a proteolytically processed postsynaptic membrane protein with a cytoplasmic calcium-binding domain. *Mol Cell Neurosci* 17, 151-166 (2001)

513. Goldberg M., C. Peshkovsky, A. Shifteh & Q. Al-Awqati: mu-Protocadherin, a novel developmentally regulated protocadherin with mucin-like domains. *J Biol Chem* 275, 24622-24929 (2000)

Abbreviations:

AJ:	Adherens junction
ApoER2:	Apolipoprotein E receptor 2
CAM:	Cell adhesion molecule
CNR:	Cadherin-like neural receptor
CNS:	Central nervous system
EC:	Extracellular domain
EGF:	Epidermal growth factor
FGF	Fibroblastic growth factor
GalNAcPTase:	N-acetylgalactosaminylphosphotransferase
HGF:	Hepatocyte growth factor
Ig:	Immunoglobulin
JNK:	c-Jun N-terminal kinase
LAR:	Leukocyte antigen-related protein
LTP:	Long-term potentiation
NMDA	N-methyl-D-aspartate
PLC:	Phospholipase C
PKC:	Protein kinase C
PNS:	Peripheral nervous system
PP:	Protein phosphatase
PTP:	Protein tyrosine phosphatases
RTK:	Receptor-type protein tyrosine kinase
TJ:	Tight junction
VLDR:	Very-low-density lipoprotein receptor

Key Words: Cadherin, Cadherin Superfamily, Cell Adhesion Molecule, Protocadherin, CNR, Flamingo, Fat, Ret, Calsyntenin, Desmoglein, Desmocollin, Cell Adhesion, Cell-Cell Interaction, Neural Development, Embryonic Subdivision, Brain Nuclei, Axon Outgrowth, Synapse, Pathfinding, Target Recognition, Neural Circuit, Signal Transduction, Adherens Junction, Catenin, Phosphorylation, Rho GTPase, Wnt, Reelin, Review

Send correspondence to: Shinji Hirano, Center for Developmental Biology, Kobe RIKEN, 2-2-3 Minatojima-minamimachi, Chuou-ku, Kobe-City 650-0047, Japan, Tel: +81-78-306-3120, Fax: +81-78-306-8118, E-mail: s-hirano@cdb.riken.go.jp