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Leptin receptor signaling: pathways to leptin resistance

Joris Wauman[1,2], Jan Tavernier[1,2]

[1]Department of Medical Protein Research, Flanders Interuniversity Institute for Biotechnology (VIB), [2]Department of Biochemistry, Faculty of Medicine and Health Sciences, Ghent University, Albert Baertsoenkaai 3, B-9000 Ghent, Belgium

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1. ABSTRACT

The identification of spontaneous mutations in the leptin- and leptin receptor (ObR)-encoding *ob* and *db* gene, respectively, opened up a new field in obesity research. Leptin, an adipocyte-derived hormone, mirrors the body's fat stores and thereby informs the brain about the body's energy status. In the hypothalamus, leptin triggers specific neuronal subpopulations, like POMC and AgRP/NPY neurons, and activates several intracellular signaling events, including the JAK/STAT, MAPK, PI3K and mTOR pathway, which eventually translates into decreased food intake and increased energy expenditure. Leptin is also involved in the regulation of other physiological processes including reproduction, bone homeostasis and immune function. Here, we review the pathways that are activated upon ObR activation, how ObR expression is controlled and the molecular mechanisms leading to leptin resistance, i.e. the inability to adequately respond to elevated leptin levels and therefore a primary risk factor for obesity.

2. INTRODUCTION

During the last decade, obesity and obesity-related conditions like type 2 diabetes, heart disease and cancer represent a steadily increasing health risk worldwide. Therefore, research on the mechanisms regulating energy homeostasis, the balance between food intake and energy expenditure, has rapidly expanded in recent years. Leptin is a 16 kDa polypeptide that is mainly produced and secreted by the white adipose tissue (1). Plasma leptin levels correlate with the amount of body fat (2) and have a central effect on the regulation of food intake and energy expenditure by activating the hypothalamic leptin receptor (ObR) (3-6). Moreover, leptin also plays an important role in the regulation of energy-demanding processes such as reproduction, angiogenesis, bone homeostasis, wound healing and regulation of immune responses (7-13). Leptin also regulates glucose homeostasis and lipid metabolism independently of its central weight regulatory function, partly via direct action

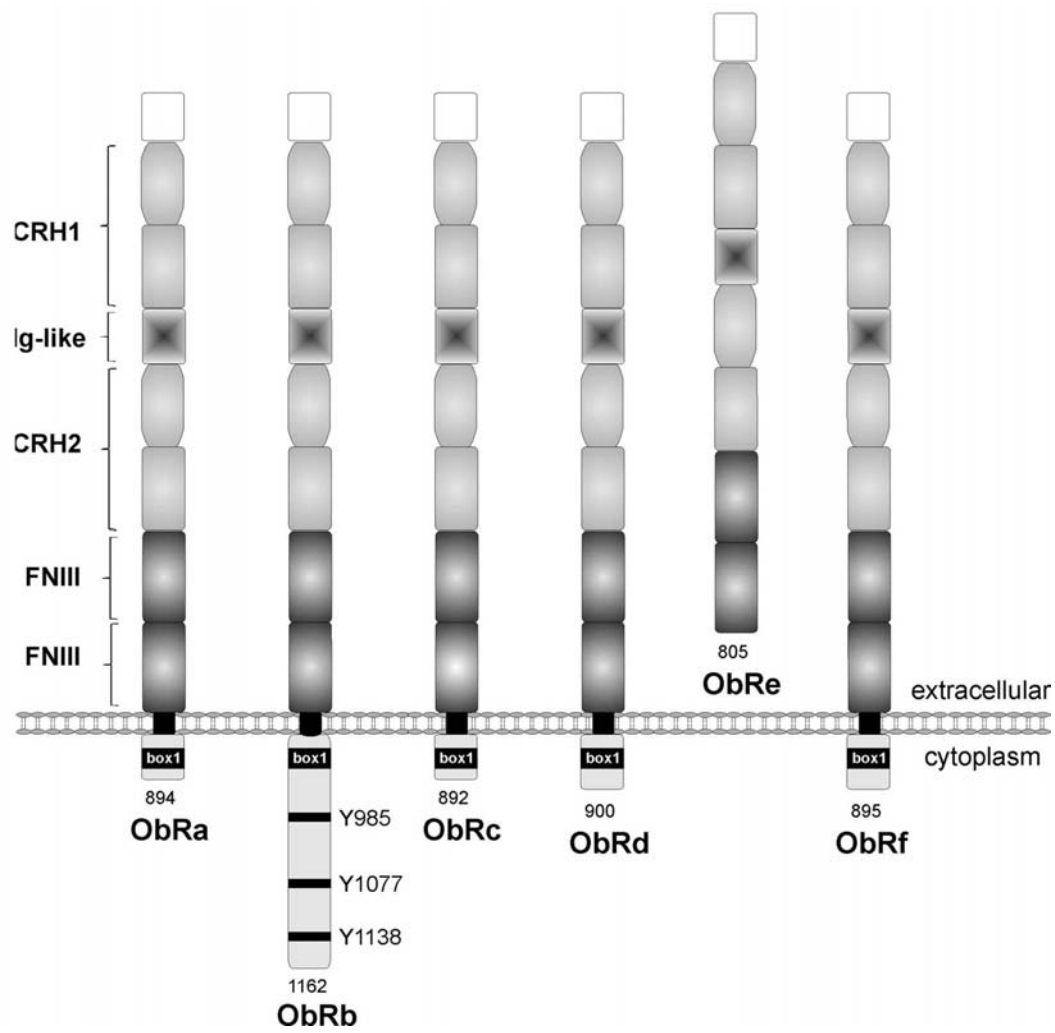

Figure 1. Schematic overview of the leptin receptor isoforms (in rat). All leptin receptor isoforms share the same ligand-binding extracellular domain consisting of two cytokine receptor homology (CRH) domains separated by an immunoglobulin (Ig)-like domain and followed by two membrane proximal fibronectin type III (FNIII) domains. Except for the secreted ObRe isoform, the ObR is anchored in the membrane via its transmembrane region. JAKs associate constitutively with a conserved box 1 motif, which is critical for JAK2 activation. A putative box 2 motif, apparently required for maximal activation of JAK2, has also been identified. Additionally, ObRb has three conserved tyrosines in its cytoplasmic domain, corresponding to positions Y985, Y1077, and Y1138 (murine numbering).

on pancreatic β-cells and hepatocytes (14-16).

Leptin resistance, a primary risk factor for the development of obesity, refers to the reduced ability of leptin to induce a suppression of appetite and weight gain. Multiple factors may underlie the molecular mechanism leading to the onset of this phenomenon, including defects in leptin transport across the blood-brain barrier (BBB), in leptin signaling (like the control of ObR expression or negative feedback regulation) and/or in the central neural circuitry that regulates energy homeostasis.

This review provides an update on leptin signal transduction, focusing on the role of individual signaling pathways and their effect on gene expression induced by leptin. How leptin signaling is negatively regulated and possible mechanisms underlying leptin resistance are also discussed.

3. THE LEPTIN RECEPTOR

The leptin receptor (ObR) is a single membrane-spanning receptor of the class 1 cytokine receptor family (17). At present, six ObR isoforms, produced by alternative splicing of the *db* gene, have been identified in rat (ObRa – ObRf) (Figure 1). In mice and human, only five (ObRa-ObRe) and four (ObRa-ObRd) alternative spliced isoforms have been described, respectively (7,17). They all share the same complex extracellular domain, consisting of two cytokine receptor homology (CRH) domains separated by an immunoglobulin (Ig)-like domain and followed by two membrane proximal fibronectin type III (FN III) domains.

The membrane proximal CRH2 domain is necessary and sufficient for leptin binding with an affinity in the nanomolar range (18). The two FN III domains have no affinity for the ligand, but nevertheless are essential for receptor activation since mutation of two conserved cysteines on positions 672 and 751 completely blocks leptin signaling (19). The Ig-like domain is also critical for receptor activation since receptors lacking this domain are properly expressed on the cell surface and bind leptin comparable to the wild type receptor, but fail to activate the associated Janus kinases (JAKs) and subsequent leptin signaling (20, 21). The role of the membrane distal CRH1 domain is still unclear. So far, most studies were based on overexpression of ObR deletion mutants. Additional studies in mouse models expressing, at physiological levels, an ObR variant lacking this domain might provide more insight. Only the long isoform (ObRb) has an extended intracellular domain of 301 amino acids with binding sites for downstream signaling molecules. The phenotype of *db/db* mice that lack the ObRb is similar to that of leptin-deficient *ob/ob* mice including morbid obesity, hypothermia, hyperglycemia, hyperlipidemia, decreased insulin sensitivity and infertility (5, 22-25). Mice with a neuron-specific disruption of ObR exhibit obesity (26), while neuron-specific restoration of ObRb expression reverses the obese phenotype in ObRb-null animals (27-29), indicating that the regulatory effect of leptin on body weight is controlled in the brain. The ObRb is present in several neural tissues, but is highly expressed in multiple hypothalamic regions including the arcuate nucleus (ARC), the ventromedial hypothalamus (VMH), the paraventricular nucleus (PVN), the dorsomedial hypothalamus (DMH), the lateral hypothalamic area (LHA) and the ventral premammillary nucleus (PMV) (30-37). Leptin action on two distinct populations of ARC neurons is well described. One population synthesizes the orexigenic (appetite-stimulating) neuropeptides neuropeptide Y (NPY) and agouti-related peptide (AgRP) (38), while the other population synthesizes the anorexigenic (appetite-depressing) neuropeptides cocaine and amphetamine-related transcript (CART) and pro-opiomelanocortin (POMC). POMC is processed further to produce alpha-melanocyte-stimulating hormone (αMSH) which signals by activating melanocortin receptors, MC3R and MC4R. Deletion of MC3R or MC4R (or both) results in leptin resistance and obesity in mice (39, 40). ObR activation of POMC neurons triggers POMC expression and stimulates αMSH secretion (41-43). Specific expression of ObRb in POMC neurons leads to a marked decrease in energy intake and a modest reduction in body weight in *db/db* mice, but remarkably completely normalized blood glucose levels and locomotor activity (44). Reciprocally, leptin inhibits NPY/AgRP neurons and suppresses the secretion of NPY and AgRP (45). AgRP is a potent antagonist of αMSH signaling and opposes the anorexigenic action of POMC (46). AgRP neurons also innervate POMC neurons and thereby inhibit POMC neuronal activity by releasing inhibitory gamma-aminobutyric acid (GABA). Leptin inhibits GABA release from AgRP neurons thereby reducing the inhibitory effect on POMC neurons (43). Remarkably, selective deletion of ObRb in POMC or AgRP neurons only results in a mild obese phenotype indicating that other, extra-arcuate neurons (in the VMH, DMH, LHA,…) are involved in the control of energy homeostatis by leptin (35, 47, 48). Moreover, POMC expressing neurons in the ARC are innerved by ObRb expressing neurons in the VMH, whereby the strength of the excitatory input from the VMH was diminished by fasting (49) and targeted deletion of the ObRb in a subpopulation of VMH neurons (SF-1 neurons) induces obesity (50). Synaptic plasticity adds another level of complexity to the regulation of leptin signaling. Leptin rapidly modifies synaptic connections between ARC neurons, inducing changes in the balance of excitatory and inhibitory synapses to both POMC and NPY-expressing neurons (51) and ARC neural projections are permanently disrupted in diet-induced obese rats (52).

In addition to the brain, the ObRb is also expressed in multiple peripheral tissues, including the pancreatic islets, adipose tissue, skeletal muscle, the liver and immune cells. In the pancreatic islets, leptin directly inhibits insulin expression and secretion (53, 54). In the liver and white adipose tissue, leptin inhibits lipogenesis and stimulates lipolysis (55, 56) and adipocyte-specific overexpression of ObRb prevents diet-induced obesity (DIO) in mice (57). Leptin directly promotes fatty acid oxidation in isolated adipocytes and skeletal muscles (55, 58, 59) and decreases lipid levels in isolated livers. Liver-specific overexpression of ObRb prevents hepatic steatosis in ObR-deficient *fa/fa* rats (60, 61). However, deletion of the ObRb in these pheripheral tissues has no effect on energy balance, body weight or glucose homeostasis in mice, indicating that these processes are mainly directed by the central effects of leptin in the brain (62).

Increasing evidence also indicates that leptin plays a pro-inflammatory role in the regulation of innate and adaptive immune responses. Leptin enhances the proliferation and maturation of T cells, macrophages, natural killer (NK) cells and dendritic cells and promotes the production of pro-inflammatory cytokines leading towards a T helper 1 (T_H1) immune response (10, 12, 63-65). Leptin also acts a negative signal for the proliferation of regulatory T cells (T_{Regs}), which express high levels of both leptin and the ObRb (66). These findings may partly explain why *ob/ob* mice show increased susceptibility to infection and resistance to T cell-mediated autoimmune disorders (67-71) and the increased risk of infection and reduced incidence of autoimmunity in individuals with low leptin levels (68, 72).

The four splicing variants ObRa, ObRc, ObRd and ObRf (the latter only in rat) share the extracellular and transmembrane region and the first 29 intracellular amino acids and diverge thereafter, comprising only 3-11 additional intracellular residues. The ObRa is the most widely expressed isoform and exhibits some signaling capacity in overexpression experiments (73, 74). Whether these short isoforms are still able to bind JAK2 and signal *in vivo* is still doubtful since none of the short isoforms mediate activation of JAK2 at physiologic levels of JAK2 (75,76). A role for ObRa in leptin internalization and subsequent degradation and leptin transport across the

blood-brain barrier has been suggested (77-79). The soluble isoform, ObRe, lacks the transmembrane and cytoplasmic parts. In humans, a soluble ObR is formed by shedding of the extracellular domain of the membrane-bound receptor isoforms by surface metalloproteases (80, 81). We recently demonstrated that Ring Finger Protein 41 (RNF41), an interaction partner of type 1 cytokine receptor complexes, sends the ObRb to subcellular compartiments where ectodomain shedding occurs by metalloproteases of the ADAM (A Disintegrin And Metalloprotease) family, ADAM10 and ADAM17 (82). These soluble receptors may prolong the half-life of leptin by regulating the amount of free and protein-bound leptin in circulation, thereby altering leptin receptor signaling and leptin clearance (83-86). Soluble leptin receptors antagonize the permeation of leptin across the mouse blood-brain barrier by reducing the binding and endocytosis of leptin and thereby may attenuate central leptin receptor signaling (87, 88).

4. LEPTIN RECEPTOR ACTIVATION

The ObRb has no intrinsic kinase activity and therefore relies on the kinase activity of the constitutively associated tyrosine kinase of the Janus kinase family, JAK2 (89). A well conserved membrane-proximal proline-rich region in the ObRb, called the box1 motif, is essential for JAK2 association, while a less well defined box2 motif (which is absent in the short isoforms) also contributes to JAK activation (75, 76).

According to the current view of the ObRb complex and activation mechanism, receptors exist as preformed dimers (or oligomers) (90-93), possibly stabilized by disulfide bridges between residues in the CRH2 domains during receptor biosynthesis (19). ObRb and ObRa were shown to homo-dimerize in the absence of ligand, while hetero-dimerisation between both isoforms was only observed in the presence of leptin (91). Recently, formation of ObRb/ObRa and ObRb/ObRc complexes at the plasma membrane was demonstrated using bioluminescence resonance energy transfer (BRET) and optimized co-immunoprecipitation. However, these complexes do not seem to alter JAK/STAT signaling by the ObRb (94). This observation can further be explained by the proposed hexameric leptin:ObR model (95). Higher-order receptor clustering may help to understand why the ObRb is able to signal in the presence of an excess ObRa as seen in many tissues.

Binding of leptin to the extracellular domain of the ObRb results in juxtaposition of the catalytic domains of the associated JAKs and induces transphosphorylation on two conserved tyrosines Y1007 and Y1008 in the activation loop of JAK2, allowing subsequent phosphorylation on additional tyrosines in JAK2 and the intracellular domain of the ObRb (96-98). At least two JAK2 molecules within the receptor complex are required for JAK transactivation (20, 89, 99). A complementation-of-signaling strategy suggests that at least three ObRb chains are needed in the leptin:ObRb complex and that higher order clustering is determined by the extracellular domains of the ObRb (20). Based on these observations our group proposed a hexameric leptin:ObRb complex whereby two leptin molecules cluster two preformed leptin receptor dimers (95).

Next to the transphosphorylation, activated JAK2 phosphorylates three conserved tyrosines residues in the intracellular domain of the ObRb (Y985, Y1077 and Y1138 in the murine ObRb or Y986, Y1079 and Y1141 in the human ObRb) (98, 100). These phosphorylated tyrosine residues in JAK2 and the ObRb then serve as specific docking sites for downstream signaling molecules with phosphotyrosine-recognizing Src homology 2 (SH2) domains whereby the specificity of the interaction is determined by the amino acids surrounding the phosphorylated tyrosine. Replacement of the three tyrosines in the ObRb with phenylalanines induces marked leptin resistance and obesity. However, the mutant mice are less obese and less hyperglycemic than *db/db* mice, indicating that the ObRb can mediate some actions independently of these tyrosines (e.g. via JAK2) (101). Recently it was also shown that mice expressing a truncated ObRb lacking all intracellular tyrosines had a similar phenotype as *db/db* animals in terms of energy homeostasis, neuroendocrine and immune function, and the regulation of the hypothalamic arcuate nucleus, but demonstrated modest improvements in glucose homeostasis (102).

Using a JAK2 deficient cell line, JAK2-independent ObR signaling was described and attributed to kinases of the Src family (103). However, compensation by other JAK family members cannot be ruled out in this experimental set-up. Moreover, since mutant mice where all three ObR tyrosines are mutated to phenylalanines, are less obese and less hyperglycemic than db/db mice, the same group demonstrated that tyrosine phosphorylation-independent leptin signaling cannot be excluded (101).

5. LEPTIN RECEPTOR SIGNALING PATHWAYS

Activation of the ObRb initiates a cascade of signal transduction pathways (Figure 2). Knock-out and knock-in phenotypes of key molecules involved in central leptin receptor signaling are summarized in Table 1. Aberrant signaling may play an important role in the etiology of leptin resistance.

5.1. The JAK/STAT pathway

The best studied pathway activated by leptin is the JAK/STAT (Janus kinase/signal transducers and activators of transcription) pathway. Tyrosine 1138 of the ObRb lies within a YXXQ motif (also called box 3), the consensus binding motif for STAT3 (104). Upon ligand binding and JAK2 activation, STAT3 transiently binds via its SH2 domain to phospho-Y1138, becomes phosphorylated by JAK2 on Y705 and translocates as dimers to the nucleus where it modulates the transcription of several target genes (see further) (22, 105, 106). Phosphorylation of STAT3 on S727 in the activation domain was shown to be necessary for the full transcriptional activity of STAT3 in several cell systems

Table 1. Knock-out and knock-in phenotypes of key proteins involved in central leptin receptor signaling

Protein	Knock-out/in pattern			**Phenotype** (not limiting)	Ref.
	Systemic	**Neuronal**	**POMC**		
leptin (*ob/ob*)	x			obesity syndrome, infertility	5
ObRb (*db/db*)	x			obesity syndrome, infertility	23-25
ObRb		x		obesity syndrome, infertility	26
ObRb			x	modest obesity	35, 47-48
ObRb (Y->F)	x			similar as db/db mice, although less obese and hyperglycemic	101
ObRb (truncated)	x			similar as db/db mice, although less hyperglycemic	102
$ObRb^{S1138}$ or $STAT3^{-/-}$ in ObRb expressing cells	x			obesity syndrome, although less hyperglycemic and still fertile	115, 118 130
ObRb (*l/l*)	x			neuroendocrinologically normal, fertile, enhanced leptin sensitivity, decreased feeding	146
STAT3		x		leptin resistance, obesity syndrome, infertilty	116, 117
STAT3			x	modest obesity	121
STAT5		x		leptin resistance, obesity	136
MC3R & MC4R	x			leptin resisitance, obesity syndrome	39, 40
PRMT2	x			hypophagic, lean, more resistant to DIO	113
SHP2 (DN)		x		leptin resistance, obesity	141
SHP2			x	elevated adiposity, decreased leptin sensitivity and energy expenditure	142
SH2B1	x	x		leptin resistance, obesity syndrome	156, 157
SH2B1 (OE)		x		resistance to DIO	157
FoxO1 (CA)		x		leptin insensitivity	158, 159
FoxO1		x		increased leptin sensitivity, decreased body weight	158, 159
IRS2	x			obesity syndrome	165, 166
IRS2		x		obesity syndrome	167, 168
IRS2			x	no apparent body weight phenotype	169, 170
PTEN		x		increased leptin sensitivity, decreased adiposity	177
PTEN			x	leptin resistance, obesity	178
PDK1			x	modest obesity	179
Insulin receptor		x		leptin resistance, obesity	183
APMK (DN)		x		reduced food intake and body weight	189
AMPK (CA)		x		attenuation of leptin's anorexigenic effects	189
AMPKα2			x	prevention of glucose sensing	186
CaMKK2	x			protection from hig-fat DIO and glucose intolerance	191
Crtc1	x			obesity, infertility	192
RSK	x			decreased leptin sensitivity	150
RSK (DN)		x		decreased leptin sensitivity	194
RSK (CA)		x		enhanced leptin sensitivity	194
TSC1			x	leptin resistance, obesity	197
BBS	x			leptin resistance, obesity	204, 205
Ob-RGRP		x		enhanced leptin sensitivity	206
SOCS3		x		enhanced leptin sensitivity	212
SOCS3			x	enhanced leptin sensitivity	214
SOCS3 (OE)			x	leptin resistance, obesity, glucose intolerance	215
PTP1B	x			enhanced leptin sensitivity and protection from DIO	219, 221
PTP1B		x		enhanced leptin sensitivity and protection from DIO	220, 222
PTP1B			x	enhanced leptin sensitivity and protection from DIO	142
IKKβ		x		protection from high-fat DIO	237
TLR4 (DN)	x			protection from high-fat DIO	241
MyD88		x		protection from high-fat DIO	242

Obesity syndrome includes hypothermia, hyperphagia, hyperglycemia and hyperlipidemia, CA: constitutively active; DN: dominant-negative; OE: overexpression; DIO: diet-induced obesity

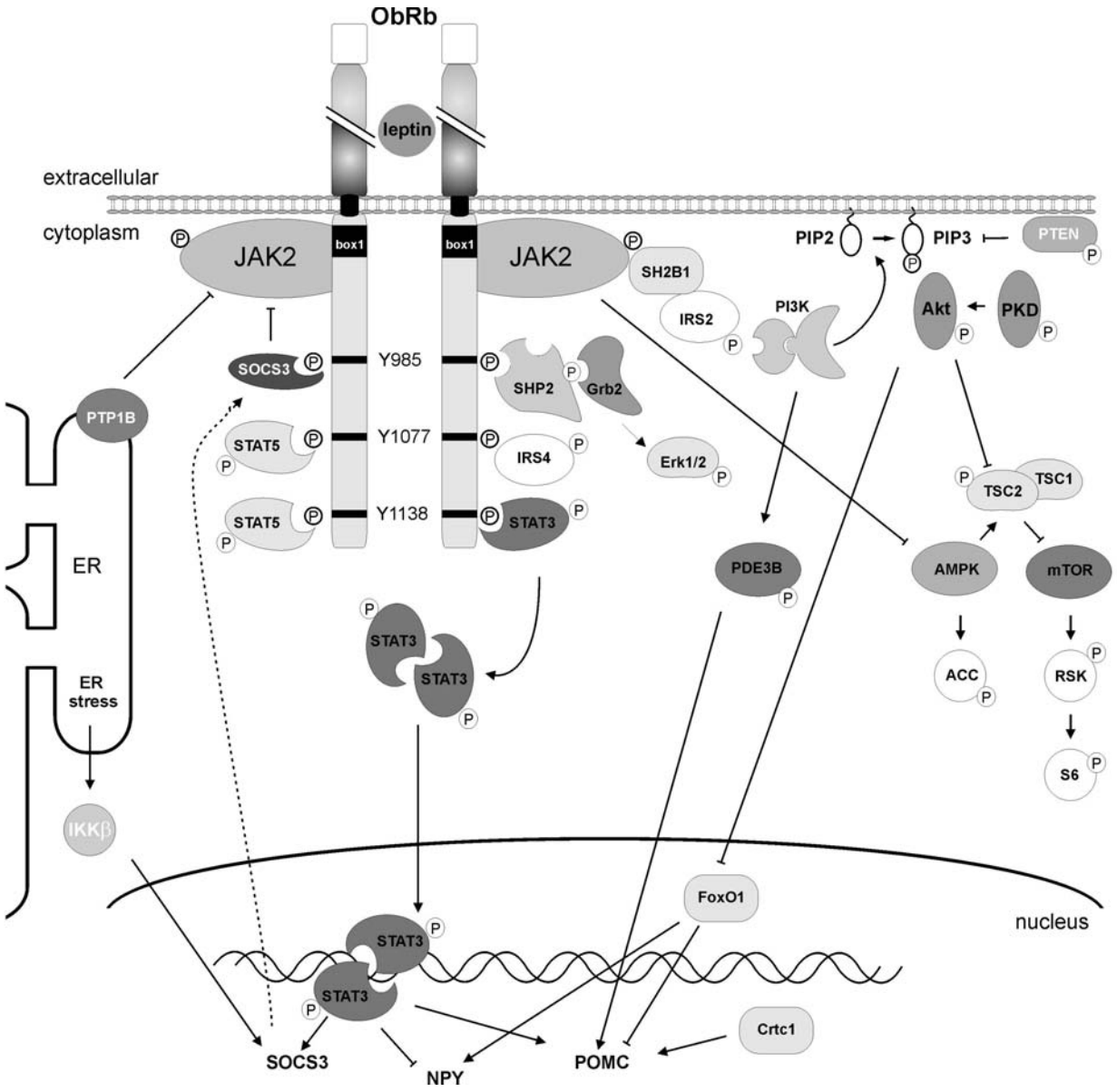

Figure 2. Schematic overview of leptin receptor signaling in the hypothalamus. The contribution of the several leptin-activated pathways is described in section 5. ObRb: leptin receptor long isoform, POMC: pro-opiomelanocortin; NPY: neuropeptide Y; JAK2: Janus kinase 2; STAT: signal transducers and activators of transcription; Erk: extracellular signal-regulated protein kinase; SHP2: SH2-containing protein tyrosine phosphatase 2; Grb2: growth factor receptor-bound protein-2; PI3K: phosphatidylinositol 3-kinase; AMPK: 5'-AMP-activated protein kinase; mTOR: mammalian target of rapamycin; ER: endoplasmic reticulum; SOCS: suppressor of cytokine signaling; IRS: insulin receptor substrate; PIP_2: phosphatidylinositol 4,5-diphosphate; PIP_3: phosphatidylinositol 3,4,5-triphosphate; PDK: 3-phosphoinositide dependent protein kinase; FoxO1: forkhead box O1; PTEN: phosphatase and tensin homologue; PDE3B: phosphodiesterase 3B; ACC: acetyl-CoA carboxylase; Ctrc1: Creb-regulated transcription coactivator-1; RSK: ribosomal S6 kinase; TSC: tuberous sclerosis protein; PTP1B: protein tyrosine phosphatase 1B; IKKβ: inhibitor of nuclear factor kappa-B kinase subunit beta; P: phosphate

and $STAT3^{S727A}$ knock-in mice (107-110). The kinase(s) responsible for STAT3 S727 phosphorylation upon leptin stimulation are still poorly investigated and a role for extracellular signal-regulated protein kinase (ERK) and c-Jun NH2-terminal kinase (JNK) has been suggested (111, 112). Recently, STAT3 was shown to be methylated by protein arginine N-methyltransferase 2 (PRMT2) on arginine 31 and that PRMT2-deficient mice are hypophagic, lean, have significantly reduced serum leptin levels and are more resistant to DIO (113). Although methylation of STAT3 seems to occur *in vivo*, the importance of arginine 31 in STAT signaling is still under debate (243). Additional posttranslational modifications of STAT3, like acetylation (114), may also influence STAT3

activity. However, acetylation of STAT3 after leptin stimulation was not demonstrated so far.

Homologous replacement of tyrosine 1138 with serine (ObR ^{S1138}) or deletion of neuronal STAT3 results in severe hyperphagia and morbid obesity, indicating that the JAK2-STAT3 pathway is indispensable for the hypothalamic anorectic actions of leptin (115-118). Biochemical blockage of STAT3 activation has pinpointed the essential role of STAT3 for the acute effects of leptin on food intake and glucose homeostasis (119). POMC expression is directly induced by leptin via a STAT3 responsive element in the POMC promoter (120) and ObR ^{S1138} mice display a suppression of hypothalamic melanocortin activity confirming that STAT3 participates in energy homeostatis by regulating POMC expression (115). Despite this however, genetic inactivation of STAT3 in POMC-expressing neurons did not completely abolish the anorexigenic effect of leptin and causes only mild obesity and no increased sensitivity to a high-fat diet. So, the STAT3-POMC pathway forms only part of the energy homeostatic response to leptin and/or STAT3-dependent effects in other cells are also involved (121). A second well-characterized effect of leptin is the negative regulation of the orexigenic neuropeptides NPY and AgRP. Mice lacking STAT3 expression in AgRP/NPY neurons are mildly hyperphagic, hyporesponsive to leptin and display increased levels of basal NPY expression while AgRP expression remains relatively constant (122, 123). Another STAT3-mediated effect of leptin is the upregulation of thyrotropin-releasing hormone (TRH) that enhances thyroid function and results in increased energy expenditure (124-126). Since STAT3 acts as a transcription factor, activation and translocation to the nucleus of STAT3 leads to the modulation of expression of several leptin-responsive genes, including several genes encoding neuropeptides (see above) and inflammation-related proteins (127). One very well-studied direct target of leptin, suppressor of cytokine signaling 3 (SOCS3), a feedback inhibitor of lepin signaling that has been suggested as a potential mediator of central leptin resistance (128, 129), will be discussed further in this review.

ObR ^{S1138} mice are less hyperglycemic compared to *db/db* mice and are still fertile (16, 115) indicating that STAT3-independent pathways are mediating the effects of leptin on other physiological processes like reproduction and glycemic control. This was also confirmed by the observation that although mice with a specific deletion of STAT3 in ObRb expressing cells are leptin resistant, hyperphagic and obese, they still exhibit normal fertility (130).

In addition to STAT3, leptin also induces phosphorylation of STAT1, STAT5 and STAT6 in cultured cells (22, 131, 132), but only leptin-induced STAT5 phosphorylation in the hypothalamic ARC of mice (133) and STAT5 nuclear translocation in rat hypothalamic nuclei (134) were detected. Upon leptin stimulation, STAT5 binds to phospo-Y1077 and phospho-Y1138 on the ObRb (100, 133, 135) and deletion of both STAT5A and STAT5B in the central nervous system causes leptin resistance, hyperphagia and obesity, but to a lesser extent than STAT3 deletion, indicating that the JAK2/STAT5 pathway may contribute to the leptin dependent regulation of energy balance and body weight (136). However, at present no specific target genes or effects mediated by leptin-induced STAT5 activation are known and these are difficult to assess given the shared pY1138 binding site on the ObRb with STAT3 which hampers mutational studies.

5.2. The SHP2/MAPK pathway

Leptin induces phosphorylation of Y985 in the ObRb, thereby creating a binding site for the carboxy-terminal SH2 domain of SH2-containing protein tyrosine phosphatase 2 (SHP2) (98, 137-139). SHP2 becomes itself phosphorylated, recruits the adaptor protein growth factor receptor-bound protein-2 (Grb2) and induces JAK2-dependent activation of the extracellular signal-regulated kinase 1/2 (ERK1/2) mitogen-activated protein kinase (MAPK) in cultured cells and the hypothalamus (73, 137, 140, 141). Leptin also activates, but to a lesser extent, the MAPK pathway independent of Y985 and phosphorylation of SHP2, probably via direct binding of Grb2 to JAK2 (137). A catalytic inactive SHP2 mutant blocks leptin-mediated ERK activation by the ObRb (137). The physiological importance of the SHP2/MAPK pathway is underscored by the observations that neuron-specific deletion of SHP2 results in early-onset obesity and leptin resistance and that pharmacological inhibition of ERK1/2 in the hypothalamus reverses the anorectic and weight-reducing effects of leptin (140, 141). Mice with POMC neuron-specific deletion of the gene encoding SHP2 have elevated adiposity, decreased leptin sensitivity, and reduced energy expenditure (142). ERK-dependent upregulation of the immediate early genes *egr-1* and *c-fos* has been demonstrated in cell culture and *in vivo* in the hypothalamus (137, 143, 144) and analysis of ObR ^{S1138} knock-in mice confirmed that *c-fos* upregulation is independent of STAT3 activation (145). Knock–in mice (*l/l*) homozygous for a Y985 to leucine mutation are neuroendocrinologically normal and fertile, but females demonstrate decreased feeding, decreased expression of orexigenic neuropeptides, protection from high-fat DIO, and increased leptin sensitivity in a sex-biased manner (146). More recently, young homozygous Y985F mice were shown to be slightly leaner, although they exhibit adult-onset or DIO (147). These phenotypes probably do not reflect the effect of the Y985F mutation on leptin-induced ERK activation, but are consistent with the known role of Y985 in the ObRb as a binding site for SOCS3, a negative regulator of leptin receptor signaling (see further).

A leptin-dependent increase of hypothalamic mammalian target of rapamycin (mTOR) activity and subsequent ribosomal protein S6 phosphorylation were shown to be required for leptin's anorectic effect (148, 149) (see further). Reduced hypothalamic mTOR signaling may contribute to the development of hyperphagia, weight gain, and leptin resistance during diet-induced obesity (150). *In vitro* studies have demonstrated that Y985 and ERK are required for the phosphorylation of S6 by the ribosomal S6 kinase (RSK), which enhances cap-dependent translation and protein synthesis (133).

Other members of the MAPK family (p38 and JNK) have also been reported to be activated by leptin in several cell types (144, 151), but the associated pathways have not been well characterized.

5.3. The PI3K pathway

ObRb activation induces phosphorylation of several members of the insulin receptor substrate (IRS) family (73, 152-154). IRS1 and particularly IRS2 are both recruited to the ObRb via SH2B1, an interaction partner of JAK2 (153, 155). Genetic deletion of SH2B1 results in severe leptin resistance, hyperphagia and morbid obesity in mice (156), while neuron-specific restoration of SH2B1 corrected the metabolic disorders in SH2B1 knock-out mice and improved JAK2-mediated leptin signaling and the regulation of orexigenic neuropeptide expression in the hypothalamus (157). Moreover, neuron-specific overexpression of SH2B1 dose-dependently protected against high-fat diet-induced leptin resistance and obesity (157). SH2B1 also enhances JAK2 activity, thereby promoting the activation of leptin-dependent pathways downstream of JAK2 (155). These observations suggest that neuronal SH2B1 regulates leptin sensitivity, energy balance and body weight. IRS4 was found to interact with the phospho-Y1077 motif of the ObRb using MAPPIT (MAmmalian Protein-Protein Interaction Trap), a cytokine receptor-based two-hyrid method and to function as an adaptor protein, interacting with the regulatory p85 subunit of the phosphatidylinositol 3-kinase (PI3K), phospholipase C gamma, and the SOCS family members SOCS2, SOCS6, and SOCS7 (152). IRS activation in turn recruits the regulatory p85 subunit and activates PI3K, leading to the accumulation of its product phosphatidylinositol 3,4,5-triphosphate (PIP_3). PIP_3 activation leads to sequential activation of 3-phosphoinositide-dependent protein kinase 1 (PDK1) and Akt culminating in the inhibition of the transcription factor Forkhead box O1 (FoxO1), which (when activated) stimulates the transcription of the orexigenic peptides NPY and AgRP, but suppresses the transcription of anorexigenic POMC. FoxO1 appears to antagonize STAT3 action in both AgRP and POMC neurons (158-160). Therefore, ARC-specific overexpression of a constitutively active FoxO1 mutant results in a loss of the ability of leptin to curtail food intake. Conversely, siRNA-mediated knockdown of FoxO1 in the ARC increases leptin sensitivity and decreases food intake and body weight (158, 159). Moreover, in hypothalamic cells leptin induces phosphorylation of PTEN (phosphatase and tensin homologue), a negative regulator of PI3K signaling, by casein kinase II (CK2) and glycogen synthase kinase 3 (GSK3) and thereby inhibits its phosphatase activity (161, 162).

Additionally, PI3K-dependent activation of cyclic nucleotide phosphodiesterase 3B (PDE3B), a cAMP-degrading enzyme, has been shown in the hypothalamus and intracerebroventricular (icv) injection of the PDE3 inhibitor cilostamide, blocked the inhibitory effect of leptin on food intake and body weight (163). Cilostamide completely reversed leptin-induced POMC expression in the rat hypothalamus suggesting a PDE3B-dependent POMC induction mechanism (164).

A crucial role for the PI3K pathway in leptin signaling is underscored by several observations. $IRS2^{-/-}$ mice are hyperphagic and obese (165, 166) and neuron-specific deletion of IRS2 causes an obese, hyperphagic phenotype in mice, establishing a crucial role for IRS2 in brain control of energy homeostasis (167, 168), although IRS2 deletion from POMC neurons has no apparent body weight phenotype (169). PI3K signaling in POMC neurons seems essential for the acute suppression of food intake elicited by leptin, but is not a major contributor to the regulation of long-term energy homeostasis (170). *In vivo* studies implicate the PI3K/PDE3B pathway in the suppression of NPY/AgRP neurons in the ARC (171, 172). PI3K-dependent leptin signaling has been shown to open ATP-sensitive K^+ channels in rat hypothalamic neurons (173) and in rat and mouse insulin-secreting cells (161, 174), resulting in cell hyperpolarization and inhibition of firing. K^+ channel activation by leptin is dependent on actin depolymerization in both cell types (161, 173). The connection between leptin-driven PI3K activity, actin re-modeling, and K^+ channel opening appears not to be due simply to increased PIP_3, but may also require coincident inhibition of PTEN protein and lipid phosphatase activity through increased PTEN phosphorylation (162).

Leptin-stimulated activation of hypothalamic PI3K is impaired in DIO (175) and pharmacological inhibition of PI3K activity blocks the anorectic effect of leptin (163, 176), while chronic activation of the hypothalamic PI3K pathway by ObR neuron-targeted deletion of the PIP_3 phosphatase PTEN increases leptin sensitivity and decreases adiposity (177). In contrast, deletion of PTEN in POMC neurons results in leptin resistance and obesity (178). Finally, specific deletion of PDK1 in POMC expressing neurons leads to a modest obese phenotype which can be reversed by inhibiting FoxO1 activation (179). In conclusion, these studies suggest that the PI3K pathway in non-POMC hypothalamic neurons appears to mediate the long-term anorectic effects of leptin.

Next to leptin, insulin has been identified as fuel sensor acting in part through its hypothalamic receptors to inhibit food intake and stimulate energy expenditure. As their intracellular signaling converges at the PI3K pathway, leptin and insulin may coordinately act to control energy homeostasis (176, 180-182). Neuron-specific insulin receptor knockout mice display obesity with leptin resistance (183), while expression of the ObRb in the ARC of genetically obese, ObR-deficient Koletsky rats improved insulin sensitivity in a PI3K-dependent way (184). Although the relative contributions of insulin and leptin in functional hypothalamic signaling are difficult to assess, the importance of the PI3K pathway is clear.

5.4. The AMPK pathway

The 5'-AMP-activated protein kinase (AMPK) is activated by elevated AMP/ATP ratios and acts a cellular energy sensor in multiple cell types (185, 186). AMPK phosphorylates and inactivates acetyl-CoA carboxylase (ACC), a key enzyme in fatty acid biosynthesis. Leptin regulates AMPK activity in a tissue-specific manner: leptin activates AMPK in muscle tissue and hepatocytes (58,

187), but inhibits AMPK activity in multiple hypothalamic regions, including the ARC and PVH, thereby stimulating hypothalamic ACC and inhibiting food intake (188-190). Dominant negative AMPK expression in the hypothalamus is sufficient to reduce food intake and body weight. Furthermore, inhibition of hypothalamic AMPK is necessary for leptin's anorexigenic effects on food intake and body weight, as constitutively active AMPK attenuates these effects (188, 189). However, more recent results indicate that targeted deletion of AMPK alpha 2 in POMC and NPY/AgRP neurons did not affect the appetite suppressing effect of leptin but specifically prevented glucose sensing (186).

The precise mechanism of AMPK activation by leptin is still unknown but requires JAK kinase activity and does not seem to depend on intracellular phosphotyrosine motifs in the ObR (187). The Ca^{2+}/calmodulin (CaM)-dependent protein kinase kinase 2 (CaMKK2) is an upstream activator of AMPK in the hypothalamus, and inhibition of CaMKK2 reduces appetite and body weight, consistent with decreased NPY and AgRP mRNAs. Moreover, the loss of CaMKK2 protects mice from high-fat DIO and glucose intolerance (191). One downstream effect of AMPK is the inhibition of the protein kinase mTOR, which also integrates responses to changes in cellular energy levels (see further).

The cyclic AMP responsive element-binding protein-1 (Creb1)-regulated transcription coactivator-1 (Crtc1) was shown to be required for energy balance and reproduction. Hypothalamic Crtc1 is phosphorylated and inactive in *ob/ob* mice, while leptin administration increases the amount of dephosphorylated nuclear Crtc1, thereby enhancing the expression of anorexigenic neuropeptides (192). Since the AMPK pathway is known to regulate Crtc activity (193) and central AMPK activity is inhibited by leptin (189), the AMPK pathway may also mediate effects of leptin on Crtc1.

5.5. The mTOR pathway

The mammalian Target of Rapamycin (mTOR) protein is a serine-threonine kinase that regulates cell-cycle progression and growth by sensing changes in energy status. Leptin increases hypothalamic mTOR activity, and inhibition of mTOR signaling by rapamycin attenuates leptin's anorectic effect (148). Systemic deletion of the ribosomal p70 S6 kinase 1 (RSK), a major physiological downstream effector of mTOR, or selective expression of a dominant negative RSK mutant in the ARC blunts leptin's acute anorexigenic action in mice (150, 194). Exposure to high-fat diet decreased mTOR signaling within the hypothalamus, suggesting that reduced hypothalamic mTOR activity contributes to the development of hyperphagia, weight gain, and leptin resistance during DIO (150). mTOR is inhibited by the TSC1/TSC2 complex. Akt was shown to phosphorylate and inactivate TSC2 (195), while under energy starvation conditions AMPK differentially phosphorylates TSC2 and enhances its activity (196). These data indicate that there may exist cross-talk between different pathways to co-regulate leptin's downstream effects. Surprisingly, in mice TSC1 deletion in POMC neurons resulted in leptin resistance and hyperphagic obesity (197). Likewise, chronic activation of the PI3K/Akt pathway in POMC neurons causes a similar phenotype in mice with POMC neuron-specific deletion of PTEN (178). These observations support the idea that the PI3K/Akt pathway stimulates the mTOR pathway in POMC neurons and that chronic activation may alter synaptic transmission in POMC neurons and/or neural wiring in the hypothalamus, resulting in leptin resistance. The recent observation that genetic ablation of ObR expression in POMC neurons induces alterations at synapses on POMC neurons in the ARC supports this hypothesis (198).

6. CONTROL OF LEPTIN RECEPTOR EXPRESSION

Trafficking dynamics and the availability of ObR at the cell surface are also involved in the regulation of leptin receptor signaling (Figure 3). The amount of receptors at the cell surface is determined by the equilibrium between receptor synthesis and transport to the plasma membrane, internalization and recycling, degradation and ectodomain shedding. At steady state, both the ObRa and ObRb are localized in the *trans*-Golgi network, in endosomes, and to a lesser extent, at the cell surface. Newly synthesized leptin receptors are partially retained in the Golgi complex or in a post-Golgi intracellular compartment and both isoforms are constitutively endocytosed in a ligand-independent manner leading to degradation in the lysosomes with no evidence of recycling to the cell surface or to the *trans*-Golgi network (199-201). Both ObRa and ObRb isoforms are ubiquitinated and internalized by clathrin-mediated endocytosis but this ubiquitination seems only essential for ObRa endocytosis (202). ObRb levels in the ARC and VMH nuclei were increased after fasting and decreased by refeeding. Leptin challenge increased ObRb expression in the ARC, but not after high-fat feeding (203).

Bardet-Biedl syndrome (BBS) proteins mediate ObRb trafficking to the plasma membrane and BBS1 was shown to interact with the ObRb (204). Deletion of BBS proteins therefore impairs cell surface expression, resulting in leptin resistance and obesity (204, 205). The ObR gene-related protein (Ob-RGRP) (also known as leptin receptor overlapping transcript (LEPROT)), whose transcript is genetically linked to the ObR transcript, controls ObR function by negatively regulating its cell surface expression (206). Silencing of Ob-RGRP prevents DIO (206) and therefore, Ob-RGRP is a potential target for obesity treatment.

Recently, our group identified RING finger protein RNF41 as an interaction partner of the ObRb (82). Our studies highlight the importance of RNF41 as a controller of receptor exposure and shedding and demonstrates that RNF41 determines steady-state cell surface levels and signaling of several JAK2-associated cytokine receptors, including the ObRb. Moreover, RNF41 prevents the degradation of constitutively endocytosed receptors and re-routes them to cellular compartments for

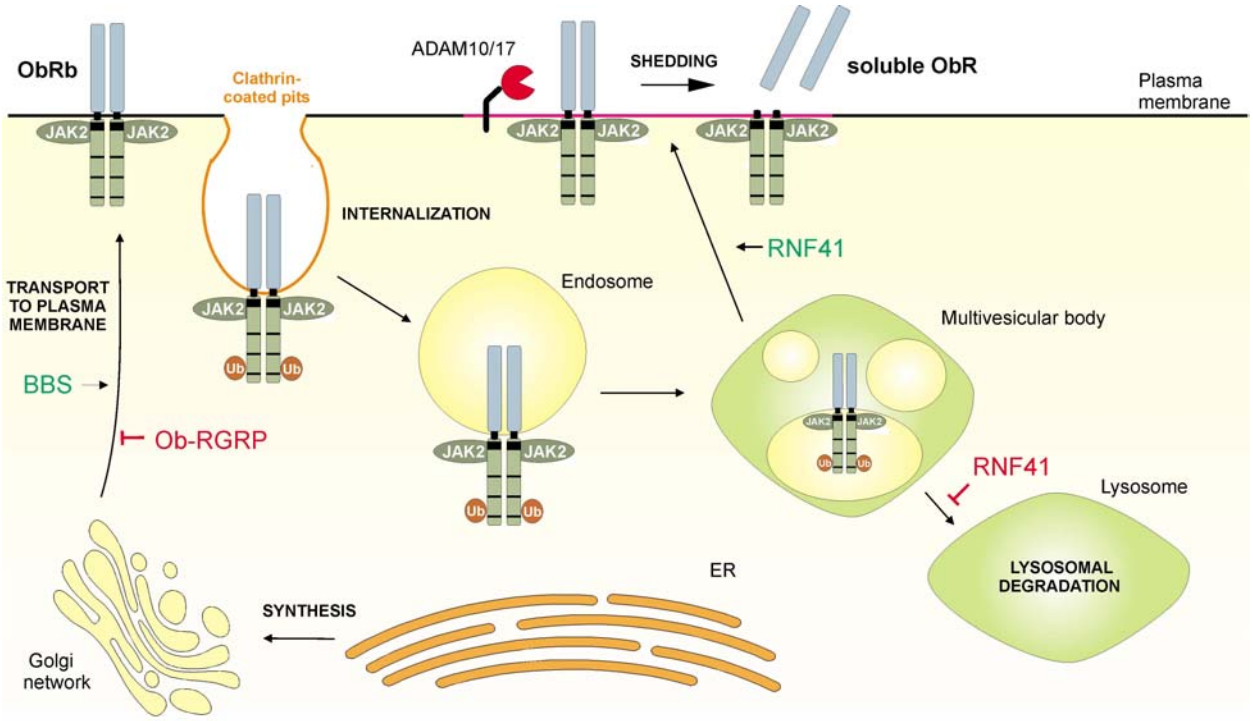

Figure 3. The 'life cycle' of the leptin receptor and the control of leptin receptor expression are further described in section 6. After receptor synthesis, folding and maturation in the ER and Golgi network, the ObRb is transported to the plasma membrane. This transport is positively and negatively influenced by BBS proteins and Ob-RGRP, respectively. After cell surface exposure, the ObRb is internalized by clathrin-dependent endocytosis. In contrast to the ObRa, the role of ubiquitination or other internalization motifs for ObRb internalization is still unclear. Via (early) endosomes and multivesicular bodies, the ObRb is targeted to the lysosomes for degradation. However, upon expression of RNF41, the ObRb is send to subcellular locations (most likely on the plasma membrane) where shedding by the metalloproteases ADAM10 and ADAM17 occurs. ObRb: leptin receptor long isoform, JAK2: Janus kinase 2; Ub: ubiquitin; ER: endoplasmic reticulum; RNF41: ring finger protein 41; ADAM: a disintegrin and metalloprotease; BBS: Bardet-Biedl syndrome; Ob-RGRP: ObR gene-related protein

ectodomain shedding by the metalloproteases ADAM10 and ADAM17 (82). These findings imply the novel concept that lysosomal degradation and ectodomain shedding are coupled phenomena with a single protein, RNF41, determining the balance between both.

7. POSSIBLE MECHANISMS OF LEPTIN RESISTANCE

The reduced ability of leptin to suppress appetite and promote energy expenditure is a primary risk factor for the development of obesity. The term, leptin resistance is used to describe the apparent paradox of elevated circulating leptin levels in the majority of obese individuals. The underlying mechanisms responsible for this phenomenon are multiple and include defective leptin transport across the blood-brain barrier (BBB), impaired leptin receptor expression and signaling and ER stress.

Leptin itself might play an important role in the development of leptin resistance, the so called 'leptin-induced leptin resistance'. Emerging evidence suggests that leptin resistance predisposes diet-induced obesity, which in turn raises leptin levels further leading to a vicious cycle of weight gain (207).

7.1. Negative regulation of leptin receptor signaling

During the last years, research concerning the onset of leptin resistance was mainly focused on the contribution of defects in negative feedback mechanisms (like SOCS3 and PTP1B) that dampen leptin receptor signaling and prevent overactivation of leptin signaling pathways (Figure 2). The JAK/STAT pathway is negatively regulated by members the Suppressor of Cytokine Signaling (SOCS) family. Leptin signaling via Y1138 and STAT3 induces SOCS3 expression (106, 129, 208), which in turn switches off signaling by binding to Y985 and inhibiting phosphorylation/activation of JAK2 (128, 135, 209). Overexpression of SOCS3 is therefore been proposed as one of the main mechanisms for the onset of leptin resistance (129, 210). Indeed, hypothalamic SOCS3 expression is significantly increased in several leptin resistant animal models (45, 129). Immunohistochemical studies suggest that the ARC is selectively leptin resistant in DIO mice and that this may be caused by elevated SOCS3 in this hypothalamic nucleus (211).

Mutation of Y985 to leucine (*l/l*) increases leptin sensitivity in female mice (146). However, in contrast to female *l/l* mice, both male and female Y985F mice showed increased susceptibility to high fat diet-induced obesity,

supporting a positive action of signaling via Y985 in attenuating diet-induced impairment of energy metabolism (147). SOCS3-haploinsufficient mice or neuron-specific SOCS3-deficient mice show enhanced leptin-induced hypothalamic STAT3 phosphorylation as well as POMC induction, resulting in a greater body weight loss, suppression of food intake and an attenuation of diet-induced leptin resistance compared to wild-type mice (212, 213). Deletion of SOCS3 in POMC neurons enhanced leptin sensitivity and improved glucose homeostasis (214), while transgenic SOCS3 overexpression in POMC neurons leads to impairment of STAT3 and mTOR/S6 kinase signaling, with subsequent leptin resistance, obesity and glucose intolerance, establishing that specific SOCS3 upregulation in POMC neurons is sufficient to cause leptin resistance and obesity (215).

Next to SOCS3, CIS (Cytokine-inducible SH2-containing protein) and SOCS2 were also shown to interact with the ObRb (216). CIS binds with the conserved Y985 and Y1077 motifs in the cytosolic domain of the ObRb, while SOCS2 only interacts with the Y1077 motif, but with higher binding affinity and thereby competes with CIS and STAT5a recruitment at this site (216). MAPPIT analysis also indicated that SOCS2 interacts with other members of the SOCS family, including SOCS3, and can function as a molecular bridge between a ubiquitin ligase complex and SOCS proteins, targeting them for proteasomal turnover (217). However, in the context of leptin signaling a physiological role for CIS and SOCS2 *in vivo* has not been established so far.

Localized to the cytoplasmic face of the endoplasmic reticulum (ER), PTP1B (Protein Tyrosine Phosphatase 1B) inhibits leptin signaling by binding and dephosphorylating JAK2 (218, 219). PTP1B is expressed in hypothalamic regions harboring leptin-responsive neurons (219). Both systemic, neuron-specific and POMC neuron-specific deletion of PTP1B improves leptin sensitivity and protects from DIO (142, 219-222). Since the expression of hypothalamic PTP1B is increased in leptin resistant animals, a role for PTP1B in the onset of leptin resistance has been suggested (223, 224). Overexpression of SH2B1, an endogenous enhancer of leptin sensitivity, counteracted PTP1B-mediated inhibition of leptin signaling in cultured cells (156). PTP1B expression is increased by high-fat feeding and inflammation (225), but how PTP1B expression and activity is regulated after leptin stimulation or in case of DIO is still unclear.

7.2. Defective transport of leptin through the blood-brain barrier

To reach the ObRb-expressing neurons in the brain, leptin has to pass the blood-brain barrier (BBB). Leptin levels in the cerebrospinal fluid are decreased in cases of obesity, suggesting that defective leptin transport contributes to leptin resistance (226-228). Leptin enters the brain by a saturable transport system (227-229) and a role in this process for the short isoform ObRa, which is abundantly expressed in brain microvessels constituting the BBB, has been demonstrated (77, 78, 230). However, a distinct subpopulation of ARC neurons, that can be labeled by BBB impermeable fluorescent tracers, was shown to respond more rapidly and sensitively to circulating leptin compared with other hypothalamic ObRb neurons. These neurons might therefore make direct contact with the blood circulation by projections through the BBB (231, 232). Additional studies are needed to clarify the contribution of impaired leptin transport to the pathogenesis of leptin resistance. Additionally, these studies might generate important information for the development of leptin antagonists (67, 233) since these antagonists preferentially only block the (adverse) peripheral functions of leptin without perturbing its central effect on body weight.

7.3. Endoplasmic reticulum (ER) stress

Growing evidence provides an intriguing link between metabolic inflammation and dysfunction of leptin signaling via activation of IKKβ and ER stress. An imbalance between ER loading during the biosynthesis of nascent proteins and ER capacity to properly fold these proteins results in ER stress. ER stress triggers the unfolded protein response (UPR), which involves activation of several intracellular signaling pathways that help to maintain ER homeostasis by reducing protein synthesis and increasing both ER folding capacity and degradation of unfolded/misfolded proteins (234). ER stress was shown to be increased in multiple tissues in leptin-resistant and obese animals, including the hypothalamus, and inhibits leptin signaling (235-238). Reduced ER capacity in mice results in severe leptin resistance and leads to a significant augmentation of obesity on a high-fat diet (236). Overnutrition atypically activates hypothalamic IKKβ/NF-κB at least in part through elevated ER stress in the hypothalamus (237). While forced activation of hypothalamic IKKβ/NF-κB interrupts central leptin signaling and actions, suppression of IKKβ significantly protects against obesity and leptin resistance (237). The molecular mechanisms may involve PTP1B (238) and IKKβ-mediated elevation of SOCS3 (237). Physical exercise suppresses hyperphagia and associated hypothalamic IKKβ/NF-κB activation by a mechanism dependent upon the pro-inflammatory cytokines IL-6 and IL-10, linking physical activity to hypothalamic ER stress and inflammation (239).

Activation of inflammatory signaling has also been detected in the hypothalamus of obese rats (240, 241). Toll-like receptor 4 (TLR4) loss-of-function mutation protects from saturated fatty acid-induced ER stress activation**,** diet-induced weight gain and from fatty acid-induced hypothalamic cytokine expression (241).TLR4 signaling by fatty acids inhibits leptin-induced STAT3 activation. Mice deficient for the TLR adaptor molecule MyD88 in the brain are protected from high-fat diet induced weight gain and the concomitant development of leptin resistance, and from the induction of leptin resistance by acute central application of palmitate (242). This link between inflammatory signaling and obesity opens a new field of research which may provide the basis for a novel treatment of obesity.

8. CONCLUDING REMARKS

Obesity and obesity-related diseases impose an ever increasing risk to public health. The growing interest in the field of obesity research to unravel the mechanisms

that determine body weight is therefore not surprising. The discovery of leptin and its anorexic potential 16 years ago was a major breakthrough, but clinical applications await a better understanding of leptin biology. The molecular mechanisms underlying the onset of leptin resistance, a primary risk factor for obesity, seem to be multiple and might differ between leptin-resistant individuals. Additional studies deciphering this phenomenon are therefore indispensable. Many other nutrient signals like insulin and the gut peptide ghrelin contribute to the control of energy expenditure and food intake. Cross-talk and redundancy between these signals therefore complicate the development of a "golden anti-obesity drug" solely based on leptin biology. Furthermore, the leptin receptor is expressed on multiple neuronal cell types (e.g., POMC and AgRP/NPY neurons) in several hypothalamic and extra-hypothalamic regions and these leptin responsive neurons connect to other sites in the brain, leading to a sophisticated and dynamic neurocircuitry adding another level of complexity to the study of central leptin receptor signaling. Each set of ObRb expressing neurons throughout the brain integrates leptin with other nutrient signals to orchestrate a cell-specific response that contributes uniquely to the overall leptin signal. The importance of individual pathways to the cell-specific effects of leptin is difficult to assess and will require additional studies using sophisticated transgenic mice models, including mice with neuron-specific deletions of key ObR signaling mediators or tyrosine mutations in the intracellular domain of the ObRb. Additionally, the peripheral role of leptin should not be neglected, particularly in the context of enhanced immune responses in autoimmune diseases.

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10. REFERENCES

1. Y. Y. Zhang, R. Proenca, M. Maffei, M. Barone, L. Leopold & J. M. Friedman: Positional cloning of the mouse obese gene and its human homolog. *Nature*, 372, 425-432 (1994)

2. M. Maffei, J. Halaas, E. Ravussin, R. E. Pratley, G. H. Lee, Y. Zhang, H. Fei, S. Kim, R. Lallone, S. Ranganathan, P. A. Kern & J. M. Friedman: Leptin levels in human and rodent - measurement of plasma leptin and Ob RNA in obese and weight-rdeuced subjects. *Nat Med*, 1, 1155-1161 (1995)

3. L. A. Campfield, F. J. Smith, Y. Guisez, R. Devos & P. Burn: Recombinant mouse Ob protein - Evidence for a peripheral signal linking adiposity and central neural networks. *Science*, 269, 546-549 (1995)

4. J. M. Friedman & J. L. Halaas: Leptin and the regulation of body weight in mammals. *Nature*, 395, 763-770 (1998)

5. J. L. Halaas, K. S. Gajiwala, M. Maffei, S. L. Cohen, B. T. Chait, D. Rabinowitz, R. L. Lallone, S. K. Burley & J. M. Friedman: Weight-reducing effects of the plasma-protein encoded by the obese gene. *Science*, 269, 543-546 (1995)

6. M. A. Pelleymounter, M. J. Cullen, M. B. Baker, R. Hecht, D. Winters, T. Boone & F. Collins: Effects of the obese gene-product on body-weight regulation in ob/ob mice. *Science*, 269, 540-543 (1995)

7. J. A. Cioffi, A. W. Shafer, T. J. Zupancic, J. SmithGbur, A. Mikhail, D. Platika & H. R. Snodgrass: Novel B219/OB receptor isoforms: Possible role of leptin in hematopoiesis and reproduction. *Nat Med*, 2, 585-589 (1996)

8. P. Ducy, M. Amling, S. Takeda, M. Priemel, A. F. Schilling, F. T. Beil, J. H. Shen, C. Vinson, J. M. Rueger & G. Karsenty: Leptin inhibits bone formation through a hypothalamic relay: A central control of bone mass. *Cell*, 100, 197-207 (2000)

9. S. Takeda, F. Elefteriou, R. Levasseur, X. Y. Liu, L. P. Zhao, K. L. Parker, D. Armstrong, P. Ducy & G. Karsenty: Leptin regulates bone formation via the sympathetic nervous system. *Cell*, 111, 305-317 (2002)

10. G. Fantuzzi & R. Faggioni: Leptin in the regulation of immunity, inflammation, and hematopoiesis. *J Leukocyte Biol*, 68, 437-446 (2000)

11. M. R. Sierra-Honigmann, A. K. Nath, C. Murakami, G. Garcia-Cardena, A. Papapetropoulos, W. C. Sessa, L. A. Madge, J. S. Schechner, M. B. Schwabb, P. J. Polverini & J. R. Flores-Riveros: Biological action of leptin as an angiogenic factor. *Science*, 281, 1683-1686 (1998)

12. G. M. Lord, G. Matarese, L. K. Howard, R. J. Baker, S. R. Bloom & R. I. Lechler: Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. *Nature*, 394, 897-901 (1998)

13. G. Matarese, S. Moschos & C. S. Mantzoros: Leptin in immunology. *J Immunol*, 174, 3137-3142 (2005)

14. T. Morioka, E. Asilmaz, J. Hu, J. F. Dishinger, A. J. Kurpad, C. F. Elias, H. Li, J. K. Elmquist, R. T. Kennedy & R. N. Kulkarni: Disruption of leptin receptor expression in the pancreas directly affects beta cell growth and function in mice. *J Clin Invest*, 117, 2860-2868 (2007)

15. W. Huang, N. Dedousis, A. Bandi, G. D. Lopaschuk & R. M. O'Doherty: Liver triglyceride secretion and lipid oxidative metabolism are rapidly altered by leptin in vivo. *Endocrinology*, 147, 1480-1487 (2006)

16. S. H. Bates, R. N. Kulkarni, M. Seifert & M. G. Myers: Roles for leptin receptor/STAT3-dependent and -independent signals in the regulation of glucose homeostasis. *Cell Metab*, 1, 169-178 (2005)

17. L. A. Tartaglia, M. Dembski, X. Weng, N. H. Deng, J. Culpepper, R. Devos, G. J. Richards, L. A. Campfield, F. T. Clark, J. Deeds, C. Muir, S. Sanker, A. Moriarty, K. J. Moore, J. S. Smutko, G. G. Mays, E. A. Woolf, C. A. Monroe & R. I. Tepper: Identification and expression cloning of a leptin receptor, OB-R. *Cell*, 83, 1263-1271 (1995)

18. T. M. Fong, R. R. C. Huang, M. R. Tota, C. Mao, T. Smith, J. Varnerin, V. V. Karpitskiy, J. E. Krause & L. H. T. Van der Ploeg: Localization of leptin binding domain in the leptin receptor. *Mol Pharmacol*, 53, 234-240 (1998)

19. L. Zabeau, D. Defeau, H. Iserentant, J. Vandekerckhove, F. Peelman & J. Tavernier: Leptin receptor activation depends on critical cysteine residues in its fibronectin type III subdomains. *J Biol Chem*, 280, 22632-22640 (2005)

20. L. Zabeau, D. Defeau, J. Van der Heyden, H. Iserentant, J. Vandekerckhove & J. Tavernier: Functional analysis of leptin receptor activation using a Janus kinase/signal transducer and activator of transcription complementation assay. Mol Endocrinol, 18, 150-161 (2004)

21. L. Zabeau, D. Lavens, F. Peelman, S. Eyckerman, J. Vandekerckhove & J. Tavernier: The ins and outs of leptin receptor activation. FEBS Lett, 546, 45-50 (2003)

22. H. Baumann, K. K. Morella, D. W. White, M. Dembski, P. S. Bailon, H. K. Kim, C. F. Lai & L. A. Tartaglia: The full-length leptin receptor has signaling capabilities of interleukin 6-type cytokine receptors. Proc Natl Acad Sci USA , 93, 8374-8378 (1996)

23. H. Chen, O. Charlat, L. A. Tartaglia, E. A. Woolf, X. Weng, S. J. Ellis, N. D. Lakey, J. Culpepper, K. J. Moore, R. E. Breitbart, G. M. Duyk, R. I. Tepper & J. P. Morgenstern: Evidence that the diabetes gene encodes the leptin receptor: Identification of a mutation in the leptin receptor gene in db/db mice. Cell, 84, 491-495 (1996)

24. S. C. Chua, W. K. Chung, X. S. WuPeng, Y. Y. Zhang, S. M. Liu, L. Tartaglia & R. L. Leibel: Phenotypes of mouse diabetes and rat fatty due to mutations in the OB (leptin) receptor. *Science*, 271, 994-996 (1996)

25. G. H. Lee, R. Proenca, J. M. Montez, K. M. Carroll, J. G. Darvishzadeh, J. I. Lee & J. M. Friedman: Abnormal splicing of the leptin receptor in diabetic mice. *Nature*, 379, 632-635 (1996)

26. P. Cohen, C. Zhao, X. Cai, J. M. Montez, S. C. Rohani, P. Feinstein, P. Mombaerts & J. M. Friedman: Selective deletion of leptin receptor in neurons leads to obesity. *J Clin Invest*, 108, 1113-21 (2001)

27. C. de Luca, T. J. Kowalski, Y. Zhang, J. K. Elmquist, C. Lee, M. W. Kilimann, T. Ludwig, S.-M. Liu & S. C. Chua: Complete rescue of obesity, diabetes, and infertility in db/db mice by neuron-specific LEPR-B transgenes. *J Clin Invest*, 115, 3484-3493 (2005)

28. G. J. Morton, K. D. Niswender, C. J. Rhodes, M. G. Myers, J. E. Blevins, D. G. Baskin & M. W. Schwartz: Arcuate nucleus-specific leptin receptor gene therapy attenuates the obesity phenotype of Koletsky (fa(k)/fa(k)) rats. *Endocrinology*, 144, 2016-2024 (2003)

29. T. J. Kowalski, S.-M. Liu, R. L. Leibel & S. C. Chua: Transgenic Complementation of Leptin-Receptor Deficiency. *Diabetes*, 50, 425-435 (2001)

30. J. Donato, R. J. Silva, L. V. Sita, S. Lee, C. Lee, S. Lacchini, J. C. Bittencourt, C. R. Franci, N. S. Canteras & C. F. Elias: The Ventral Premammillary Nucleus Links Fasting-Induced Changes in Leptin Levels and Coordinated Luteinizing Hormone Secretion. *J Neurosci*, 29, 5240-5250 (2009)

31. M. L. Hakansson, H. Brown, N. Ghilardi, R. C. Skoda & B. Meister: Leptin receptor immunoreactivity in chemically defined target neurons of the hypothalamus. *J Neurosci*, 18, 559-572 (1998)

32. R. L. Leshan, D. M. Opland, G. W. Louis, G. M. Leinninger, C. M. Patterson, C. J. Rhodes, H. Munzberg & M. G. Myers: Ventral Tegmental Area Leptin Receptor Neurons Specifically Project to and Regulate Cocaine- and Amphetamine-Regulated Transcript Neurons of the Extended Central Amygdala. *J Neurosci*, 30, 5713-5723 (2010)

33. G. M. Leinninger, Y. H. Jo, R. L. Leshan, G. W. Louis, H. Y. Yang, J. G. Barrera, H. Wilson, D. M. Opland, M. A. Faouzi, Y. S. Gong, J. C. Jones, C. J. Rhodes, S. Chua, S. Diano, T. L. Horvath, R. J. Seeley, J. B. Becker, H. Munzberg & M. G. Myers: Leptin Acts via Leptin Receptor-Expressing Lateral Hypothalamic Neurons to Modulate the Mesolimbic Dopamine System and Suppress Feeding. *Cell Metab*, 10, 89-98 (2009)

34. G. M. Leinninger, Y. H. Jo, R. L. Leshan, G. W. Louis, H. Y. Yang, J. G. Barrera, H. Wilson, J. C. Jones, C. J. Rhodes, S. Chua, S. Diano, T. L. Horvath, R. J. Seeley, J. B. Becker, H. Munzberg & M. G. Myers: Leptin Receptor Neurons in the Lateral Hypothalamus Regulate the Mesolimbic Dopamine System and Energy Balance. Diabetes, 58, A396-A396 (2009)

35. M. G. Myers, H. Munzberg, G. M. Leinninger & R. L. Leshan: The Geometry of Leptin Action in the Brain: More Complicated Than a Simple ARC. *Cell Metab*, 9, 117-123 (2009)

36. M. M. Scott, J. L. Lachey, S. M. Sternson, C. E. Lee, C. F. Elias, J. M. Friedman & J. K. Elmquist: Leptin Targets in the Mouse Brain. *J Comp Neurol*, 514, 518-532 (2009)

37. M. W. Schwartz, R. J. Seeley, L. A. Campfield, P. Burn & D. G. Baskin: Identification of targets of leptin action in rat hypothalamus. *J Clin Invest*, 98, 1101-1106 (1996)

38. T. M. Hahn, J. F. Breininger, D. G. Baskin & M. W. Schwartz: Coexpression of Agrp and NPY in fasting-activated hypothalamic neurons. *Nat Neurosci*, 1, 271-272 (1998)

39. A. S. Chen, D. J. Marsh, M. E. Trumbauer, E. G. Frazier, X. M. Guan, H. Yu, C. I. Rosenblum, A. Vongs, Y. Feng, L. H. Cao, J. M. Metzger, A. M. Strack, R. E. Camacho, T. N. Mellin, C. N. Nunes, W. Min, J. Fisher, S. Gopal-Truter, D. E. MacIntyre, H. Y. Chen & L. H. T. Van der Ploeg: Inactivation of the mouse melanocortin-3 receptor results in increased fat mass and reduced lean body mass. *Nat Genet*, 26, 97-102 (2000)

40. D. Huszar, C. A. Lynch, V. FairchildHuntress, J. H. Dunmore, Q. Fang, L. R. Berkemeier, W. Gu, R. A. Kesterson, B. A. Boston, R. D. Cone, F. J. Smith, L. A. Campfield, P. Burn & F. Lee: Targeted disruption of the melanocortin-4 receptor results in obesity in mice. *Cell*, 88, 131-141 (1997)

41. J. E. Thornton, C. C. Cheung, D. K. Clifton & R. A. Steiner: Regulation of Hypothalamic Proopiomelanocortin mRNA by Leptin in ob/ob Mice. *Endocrinology*, 138, 5063-5066 (1997)

42. C. C. Cheung, D. K. Clifton & R. A. Steiner: Proopiomelanocortin neurons are direct targets for leptin in the hypothalamus. *Endocrinology*, 138, 4489-4492 (1997)

43. M. A. Cowley, J. L. Smart, M. Rubinstein, M. G. Cordan, S. Diano, T. L. Horvath, R. D. Cone & M. J. Low: Leptin activates anorexigenic POMC neurons through a neural network in the arcuate nucleus. *Nature*, 411, 480-484 (2001)

44. L. Huo, K. Gamber, S. Greeley, J. Silva, N. Huntoon, X.-H. Leng & C. Bjørbæk: Leptin-Dependent Control of Glucose Balance and Locomotor Activity by POMC Neurons. *Cell Metab*, 9, 537-547 (2009)

45. P. J. Enriori, A. E. Evans, P. Sinnayah, E. E. Jobst, L. Tonelli-Lemos, S. K. Billes, M. M. Glavas, B. E. Grayson, M. Perello, E. A. Nillni, K. L. Grove & M. A. Cowley: Diet-induced obesity causes severe but reversible leptin resistance in arcuate melanocortin neurons. *Cell Metab*, 5, 181-194 (2007)

46. M. M. Ollmann, B. D. Wilson, Y. K. Yang, J. A. Kerns, Y. R. Chen, I. Gantz & G. S. Barsh: Antagonism of central melanocortin receptors in vitro and in vivo by Agouti-related protein. *Science*, 278, 135-138 (1997)

47. N. Balthasar, R. Coppari, J. McMinn, S. M. Liu, C. E. Lee, V. Tang, C. D. Kenny, R. A. McGovern, S. C. Chua, J. K. Elmquist & B. B. Lowell: Leptin receptor signaling in POMC neurons is required for normal body weight homeostasis. *Neuron*, 42, 983-991 (2004)

48. E. van de Wall, R. Leshan, A. W. Xu, N. Balthasar, R. Coppari, S. M. Liu, Y. H. Jo, R. G. MacKenzie, D. B. Allison, N. J. Dun, J. Elmquist, B. B. Lowell, G. S. Barsh, C. de Luca, M. G. Myers, G. J. Schwartz & S. C. Chua: Collective and individual functions of leptin receptor modulated neurons controlling metabolism and ingestion. *Endocrinology*, 149, 1773-1785 (2008)

49. S. M. Sternson, G. M. G. Shepherd & J. M. Friedman: Topographic mapping of VMH [rarr] arcuate nucleus microcircuits and their reorganization by fasting. *Nat Neurosci*, 8, 1356-1363 (2005)

50. H. Dhillon, J. M. Zigman, C. P. Ye, C. E. Lee, R. A. McGovern, V. S. Tang, C. D. Kenny, L. M. Christiansen, R. D. White, E. A. Edelstein, R. Coppari, N. Balthasar, M. A. Cowley, S. Chua, J. K. Elmquist & B. B. Lowelll: Leptin directly activates SF1 neurons in the VMH, and this action by leptin is required for normal body-weight homeostasis. *Neuron*, 49, 191-203 (2006)

51. S. Pinto, A. G. Roseberry, H. Liu, S. Diano, M. Shanabrough, X. Cai, J. M. Friedman & T. L. Horvath: Rapid Rewiring of Arcuate Nucleus Feeding Circuits by Leptin. *Science*, 304, 110-115 (2004)

52. S. G. Bouret, J. N. Gorski, C. M. Patterson, S. Chen, B. E. Levin & R. B. Simerly: Hypothalamic Neural Projections Are Permanently Disrupted in Diet-Induced Obese Rats. *Cell Metab*, 7, 179-185 (2008)

53. V. Emilsson, Y. L. Liu, M. A. Cawthorne, N. M. Morton & M. Davenport: Expression of the functional leptin receptor mRNA in pancreatic islets and direct inhibitory action of leptin on insulin secretion. *Diabetes*, 46, 313-316 (1997)

54. R. N. Kulkarni, Z. L. Wang, R. M. Wang, J. D. Hurley, D. M. Smith, M. A. Ghatei, D. J. Withers, J. V. Gardiner, C. J. Bailey & S. R. Bloom: Leptin rapidly suppresses insulin release from insulinoma cells, rat and human islets and, in vivo, in mice. *J Clin Invest*, 100, 2729-2736 (1997)

55. M. Y. Wang, Y. Lee & R. H. Unger: Novel form of lipolysis induced by leptin. *J Biol Chem*, 274, 17541-17544 (1999)

56. L. Jiang, Q. Wang, Y. Yu, F. Zhao, P. Huang, R. Zeng, R. Z. Qi, W. Li & Y. Liu: Leptin Contributes to the Adaptive Responses of Mice to High-Fat Diet Intake through Suppressing the Lipogenic Pathway. *Plos One*, 4, e6884 (2009)

57. M. Y. Wang, L. Orci, M. Ravazzola & R. H. Unger: Fat storage in adipocytes requires inactivation of leptin's paracrine activity: Implications for treatment of human obesity. *Proc Natl Acad Sci USA* , 102, 18011-18016 (2005)

58. Y. Minokoshi, Y. B. Kim, O. D. Peroni, L. G. D. Fryer, C. Muller, D. Carling & B. B. Kahn: Leptin stimulates fatty-acid oxidation by activating AMP-activated protein kinase. *Nature*, 415, 339-343 (2002)

59. D. M. Muoio, G. L. Dohn, F. T. Fiedorek, E. B. Tapscott & R. A. Coleman: Leptin directly alters lipid

partitioning in skeletal muscle. *Diabetes*, 46, 1360-1363 (1997)

60. Y. Lee, M. Y. Wang, T. Kakuma, Z. W. Wang, E. Babcock, K. McCorkle, M. Higa, Y. T. Zhou & R. H. Unger: Liporegulation in diet-induced obesity - The antisteatotic role of hyperleptinemia. *J Biol Chem*, 276, 5629-5635 (2001)

61. W. Huang, N. Dedousis, B. A. Bhatt & R. M. O'Doherty: Impaired activation of phosphatidylinositol 3-kinase by leptin is a novel mechanism of hepatic leptin resistance in diet-induced obesity. *J Biol Chem*, 279, 21695-21700 (2004)

62. K. Y. Guo, J. E. McMinn, T. Ludwig, Y. H. Yu, G. Q. Yang, L. Chen, D. Loh, C. Li, S. Chua & Y. Y. Zhang: Disruption of peripheral leptin signaling in mice results in hyperleptinemia without associated metabolic abnormalities. *Endocrinology*, 148, 3987-3997 (2007)

63. A. Batra, B. Okur, R. Glauben, U. Erben, J. Ihbe, T. Stroh, I. Fedke, H.-D. Chang, M. Zeitz & B. Siegmund: Leptin: A Critical Regulator of CD4+ T-cell Polarization in Vitro and in Vivo. *Endocrinology*, 151, 56-62 (2010)

64. C. Martín-Romero, J. Santos-Alvarez, R. Goberna & V. Sánchez-Margalet: Human Leptin Enhances Activation and Proliferation of Human Circulating T Lymphocytes. *Cell Immunol*, 199, 15-24 (2000)

65. V. Sanchez-Margalet, C. MartÍN-Romero, J. Santos-Alvarez, R. Goberna, S. Najib & C. Gonzalez-Yanes: Role of leptin as an immunomodulator of blood mononuclear cells: mechanisms of action. *Clin Exp Immunol*, 133, 11-19 (2003)

66. V. De Rosa, C. Procaccini, G. Calì, G. Pirozzi, S. Fontana, S. Zappacosta, A. La Cava & G. Matarese: A Key Role of Leptin in the Control of Regulatory T Cell Proliferation. *Immunity*, 26, 241-255 (2007)

67. F. Peelman, H. Iserentant, S. Eyckerman, L. Zabeau & J. Tavernier: Leptin, immune responses and autoimmune disease. Perspectives on the use of leptin antagonists. *Curr Pharm Des*, 11, 539-548 (2005)

68. G. Matarese, A. La Cava, V. Sanna, G. M. Lord, R. I. Lechler, S. Fontana & S. Zappacosta: Balancing susceptibility to infection and autoimmunity: a role for leptin? *Trends Immunol*, 23, 182-187 (2002)

69. A. La Cava & G. Matarese: The weight of leptin in immunity. *Nat Rev Immunol*, 4, 371-379 (2004)

70. J. K. Howard, G. M. Lord, G. Matarese, S. Vendetti, M. A. Ghatei, M. A. Ritter, R. I. Lechler & S. R. Bloom: Leptin protects mice from starvation-induced lymphoid atrophy and increases thymic cellularity in ob/ob mice. *J Clin Invest*, 104, 1051-1059 (1999)

71. N. Busso, A. So, V. Chobaz-Peclat, C. Morard, E. Martinez-Soria, D. Talabot-Ayer & C. Gabay: Leptin Signaling Deficiency Impairs Humoral and Cellular Immune Responses and Attenuates Experimental Arthritis. *J Immunol*, 168, 875-882 (2002)

72. A. Palacio, M. Lopez, F. Perez-Bravo, F. Monkeberg & L. Schlesinger: Leptin Levels Are Associated with Immune Response in Malnourished Infants. *J Clin Endocrinol Metab*, 87, 3040-3046 (2002)

73. C. Bjorbaek, S. Uotani, B. da Silva & J. S. Flier: Divergent signaling capacities of the long and short isoforms of the leptin receptor. *J Biol Chem*, 272, 32686-32695 (1997)

74. T. Murakami, T. Yamashita, M. Iida, M. Kuwajima & K. Shima: A short form of leptin receptor performs signal transduction. *Biochem. Biophys. Res. Commun*, 231, 26-29 (1997)

75. C. Kloek, A. K. Haq, S. L. Dunn, H. J. Lavery, A. S. Banks & M. G. Myers: Regulation of Jak kinases by intracellular leptin receptor sequences. *J Biol Chem*, 277, 41547-41555 (2002)

76. G. Bahrenberg, I. Behrmann, A. Barthel, P. Hekerman, P. C. Heinrich, H. G. Joost & W. Becker: Identification of the critical sequence elements in the cytoplasmic domain of leptin receptor isoforms required for Janus kinase/signal transducer and activator of transcription activation by receptor heterodimers. *Mol Endocrinol*, 16, 859-872 (2002)

77. S. M. Hileman, D. D. Pierroz, H. Masuzaki, C. Bjorbaek, K. El-Haschimi, W. A. Banks & J. S. Flier: Characterizaton of short isoforms of the leptin receptor in rat cerebral microvessels and of brain uptake of leptin in mouse models of obesity. *Endocrinology*, 143, 775-783 (2002)

78. S. M. Hileman, J. Tornoe, J. S. Flier & C. Bjorbaek: Transcellular transport of leptin by the short leptin receptor isoform ObRa in Madin-Darby Canine Kidney cells. *Endocrinology*, 141, 1955-1961 (2000)

79. S. Uotani, C. Bjorbaek, J. Tornoe & J. S. Flier: Functional properties of leptin receptor isoforms internalization and degradation of leptin and ligand-induced receptor downregulation. *Diabetes*, 48, 279-286 (1999)

80. M. Maamra, M. Bidlingmaier, M. C. Postel-Vinay, Z. Wu, C. J. Strasburger & R. J. Ross: Generation of human soluble leptin receptor by proteolytic cleavage of membrane-anchored receptors. *Endocrinology*, 142, 4389-93 (2001)

81. H. F. Ge, L. Huang, T. Pourbahrami & C. Li: Generation of soluble leptin receptor by ectodomain shedding of membrane-spanning receptors in vitro and in vivo. *J Biol Chem*, 277, 45898-45903 (2002)

82. J. Wauman, L. De Ceuninck, N. Vanderroost, S. Lievens & J. Tavernier: RNF41 (Nrdp1) controls type 1 cytokine receptor degradation and ectodomain shedding. *J Cell Sci*, in press, (2010)

83. G. Brabant, R. Horn, A. von zur Muhlen, B. Mayr, U. Wurster, F. Heidenreich, D. Schnabel, A. Gruters-Kieslich, T. Zimmermann-Belsing & U. Feldt-Rasmussen: Free and protein bound leptin are distinct and independently controlled factors in energy regulation. *Diabetologia*, 43, 438-42 (2000)

84. S. E. Cohen, E. Kokkotou, S. B. Biddinger, T. Kondo, R. Gebhardt, J. Kratzsch, C. S. Mantzoros & C. R. Kahn: High circulating leptin receptors with normal leptin sensitivity in liver-specific insulin receptor knock-out (LIRKO) mice. *J Biol Chem*, 282, 23672-8 (2007)

85. P.-H. Lou, G. Yang, L. Huang, Y. Cui, T. Pourbahrami, G. K. Radda, C. Li & W. Han: Reduced Body Weight and Increased Energy Expenditure in Transgenic Mice Over-Expressing Soluble Leptin Receptor. *Plos One*, 5, e11669 (2010)

86. G. Q. Yang, H. F. Ge, A. Boucher, X. X. Yu & C. Li: Modulation of direct leptin signaling by soluble leptin receptor. *Mol Endocrinol*, 18, 1354-1362 (2004)

87. H. Tu, A. J. Kastin, H. Hsuchou & W. Pan: Soluble receptor inhibits leptin transport. *J Cell Physiol*, 214, 301-305 (2008)

88. J. J. Zhang & P. J. Scarpace: The soluble leptin receptor neutralizes leptin-mediated STAT3 signalling and anorexic responses in vivo. *Br J Pharmacol*, 158, 475-482 (2009)

89. N. Ghilardi & R. C. Skoda: The leptin receptor activates janus kinase 2 and signals for proliferation in a factor-dependent cell line. *Mol Endocrinol*, 11, 393-399 (1997)

90. R. Devos, Y. Guisez, J. VanderHeyden, D. W. White, M. Kalai, M. Fountoulakis & G. Plaetinck: Ligand-independent dimerization of the extracellular domain of the leptin receptor and determination of the stoichiometry of leptin binding. *J Biol Chem*, 272, 18304-18310 (1997)

91. D. W. White & L. A. Tartaglia: Evidence for ligand-independent homo-oligomerization of leptin receptor (OB-R) isoforms: A proposed mechanism permitting productive long-form signaling in the presence of excess short-form expression. *J Cell Biochem*, 73, 278-288 (1999)

92. F. Peelman, C. Couturier, J. Dam, L. Zabeau, J. Tavernier & R. Jockers: Techniques: New pharmacological perspectives for the leptin receptor. *Trends Pharmacol Sci*, 27, 218-225 (2006)

93. C. Couturier & R. Jockers: Activation of the Leptin Receptor by a Ligand-induced Conformational Change of Constitutive Receptor Dimers. *J Biol Chem*, 278, 26604-26611 (2003)

94. J. Bacart, A. Leloire, A. Levoye, P. Froguel, R. Jockers & C. Couturier: Evidence for leptin receptor isoforms heteromerization at the cell surface. *FEBS Lett*, 584, 2213-2217 (2010)

95. F. Peelman, H. Iserentant, A. S. De Smet, J. Vandekerckhove, L. Zabeau & J. Tavernier: Mapping of binding site III in the leptin receptor and modeling of a hexameric leptin:leptin receptor complex. *J Biol Chem*, 281, 15496-15504 (2006)

96. T. Matsuda, J. Feng, B. A. Witthuhn, Y. Sekine & J. N. Ihle: Determination of the transphosphorylation sites of Jak2 kinase. *Biochem. Biophys. Res. Commun*, 325, 586-594 (2004)

97. J. Feng, B. A. Witthuhn, T. Matsuda, F. Kohlhuber, I. M. Kerr & J. N. Ihle: Activation of Jak2 catalytic activity requires phosphorylation of Y-1007 in the kinase activation loop. *Mol Cell Biol*, 17, 2497-2501 (1997)

98. A. S. Banks, S. M. Davis, S. H. Bates & M. G. Myers: Activation of downstream signals by the long form of the leptin receptor. *J Biol Chem*, 275, 14563-14572 (2000)

99. D. W. White, K. K. Kuropatwinski, R. Devos, H. Baumann & L. A. Tartaglia: Leptin receptor (OB-R) signaling - Cytoplasmic domain mutational analysis and evidence for receptor homo-oligomerization. *J Biol Chem*, 272, 4065-4071 (1997)

100. P. Hekerman, J. Zeidler, S. Bamberg-Lemper, H. Knobelspies, D. Lavens, J. Tavernier, H. G. Joost & W. Becker: Pleiotropy of leptin receptor signalling is defined by distinct roles of the intracellular tyrosines. *Febs J*, 272, 109-119 (2005)

101. L. Jiang, J. You, X. X. Yu, L. Gonzalez, Y. Yu, Q. Wang, G. Q. Yang, W. J. Li, C. Li & Y. Liu: Tyrosine-dependent and -independent actions of leptin receptor in control of energy balance and glucose homeostasis. *Proc Natl Acad Sci USA* , 105, 18619-18624 (2008)

102. S. Robertson, R. Ishida-Takahashi, I. Tawara, J. Hu, C. M. Patterson, J. C. Jones, R. N. Kulkarni & M. G. Myers: Insufficiency of Janus Kinase 2-autonomous Leptin Receptor Signals for Most Physiologic Leptin Actions. *Diabetes*, 59, 782-790 (2010)

103. L. Jiang, Z. Q. Li & L. Y. Rui: Leptin stimulates both JAK2-dependent and JAK2-independent signaling pathways. *J Biol Chem*, 283, 28066-28073 (2008)

104. N. Stahl, T. J. Farruggella, T. G. Boulton, Z. Zhong, J. E. Darnell & G. D. Yancopoulos: Choice of Stats and Other Substrates Specified by Modular Tyrosine-Based Motifs in Cytokine Receptors. *Science*, 267, 1349-1353 (1995)

105. C. Vaisse, J. L. Halaas, C. M. Horvath, J. E. Darnell, M. Stoffel & J. M. Friedman: Leptin activation of Stat3 in the hypothalamus of wildtype and ob/ob mice but not db/db mice. *Nat Genet*, 14, 95-97 (1996)

106. W. Waelput, A. Verhee, D. Broekaert, S. Eyckerman, J. Vandekerckhove, J. H. Beattie & J. Tavernier: Identification and expression analysis of leptin-regulated immediate early response and late target genes. *Biochem J*, 348 Pt 1, 55-61 (2000)

107. I. Goren, J. Pfeilschifter & S. Frank: Determination of leptin signaling pathways in human and murine keratinocytes. *Biochem. Biophys. Res. Commun*, 303, 1080-1085 (2003)

108. Z. L. Wen, Z. Zhong & J. E. Darnell: Maximal activation of transcription by STAT1 and STAT3 requires both tyrosine and serine phosporylation. *Cell*, 82, 241-250 (1995)

109. Y. H. Shen, K. Schlessinger, X. J. Zhu, E. Meffre, F. Quimby, D. E. Levy & J. E. Darnell: Essential role of STAT3 in postnatal survival and growth revealed by mice lacking STAT3 serine 727 phosphorylatione. *Mol Cell Biol*, 24, 407-419 (2004)

110. X. K. Zhang, J. Blenis, H. C. Li, C. Schindler & S. Chenkiang: Requirement of serine phosphorylation for formation of STAT-promoter complexes. *Science*, 267, 1990-1994 (1995)

111. T. Miyazaki, J. D. Bub & Y. Iwamoto: c-Jun NH2-terminal kinase mediates leptin-stimulated androgen-independent prostate cancer cell proliferation via signal transducer and activator of transcription 3 and Akt. *Biochim. Biophys. Acta* , 1782, 593-604 (2008)

112. L. O'Rourke & P. R. Shepherd: Biphasic regulation of extracellular-signal-regulated protein kinase by leptin in macrophages: role in regulating STAT3 Ser(727) phosphorylation and DNA binding. *Biochemical J*, 364, 875-879 (2002)

113. H. Iwasaki, J. C. Kovacic, M. Olive, J. K. Beers, T. Yoshimoto, M. F. Crook, L. H. Tonelli & E. G. Nabel: Disruption of Protein Arginine N-Methyltransferase 2 Regulates Leptin Signaling and Produces Leanness In Vivo Through Loss of STAT3 Methylation. *Circ Res*, 107, 992-1001 (2010)

114. Z.-l. Yuan, Y.-j. Guan, D. Chatterjee & Y. E. Chin: Stat3 Dimerization Regulated by Reversible Acetylation of a Single Lysine Residue. *Science*, 307, 269-273 (2005)

115. S. H. Bates, W. H. Stearns, T. A. Dundon, M. Schubert, A. W. K. Tso, Y. P. Wang, A. S. Banks, H. J. Lavery, A. K. Haq, E. Maratos-Flier, B. G. Neel, M. W. Schwartz & M. G. Myers: STAT3 signalling is required for leptin regulation of energy balance but not reproduction. *Nature*, 421, 856-859 (2003)

116. Y. X. Cui, L. Huang, F. Elefteriou, G. Q. Yang, J. M. Shelton, J. E. Giles, O. K. Oz, T. Pourbahrami, C. Y. H. Lu, J. A. Richardson, G. Karsenty & C. Li: Essential role of STAT3 in body weight and glucose homeostasis. *Mol Cell Biol*, 24, 258-269 (2004)

117. Q. Gao, M. J. Wolfgang, S. Neschen, K. Morino, T. L. Horvath, G. I. Shulman & X. Y. Fu: Disruption of neural signal transducer and activator of transcription 3 causes obesity, diabetes, infertility, and thermal dysregulation. *Proc Natl Acad Sci USA* , 101, 4661-4666 (2004)

118. S. H. Bates, T. A. Dundon, M. Seifert, M. Carlson, E. Maratos-Filer & M. G. Myers: LRb-STAT3 signaling is required for the neuroendocrine regulation of energy expenditure by leptin. *Diabetes*, 53, 3067-3073 (2004)

119. C. Buettner, A. Pocai, E. D. Muse, A. M. Etgen, M. G. Myers Jr & L. Rossetti: Critical role of STAT3 in leptin's metabolic actions. *Cell Metab*, 4, 49-60 (2006)

120. H. Munzberg, L. H. Huo, E. A. Nillni, A. N. Hollenberg & C. Bjorbaek: Role of signal transducer and activator of transcription 3 in regulation of hypothalamic proopiomelanocortin gene expression by leptin. *Endocrinology*, 144, 2121-2131 (2003)

121. A. W. Xu, L. Ste-Marie, C. B. Kaelin & G. S. Barsh: Inactivation of signal transducer and activator of transcription 3 in proopiomelanocortin (Pomc) neurons causes decreased Pomc expression, mild obesity, and defects in compensatory refeeding. *Endocrinology*, 148, 72-80 (2007)

122. L. Gong, F. Yao, K. Hockman, H. H. Heng, G. J. Morton, K. Takeda, S. Akira, M. J. Low, M. Rubinstein & R. G. MacKenzie: Signal transducer and activator of transcription-3 is required in hypothalamic agouti-related protein/neuropeptide Y neurons for normal energy homeostasis. *Endocrinology*, 149, 3346-3354 (2008)

123. C. B. Kaelin, L. J. Gong, A. W. Xu, F. Y. Yao, K. Hockman, G. J. Morton, M. W. Schwartz, G. S. Barsh & R. G. MacKenzie: Signal transducer and activator of transcription (Stat) binding sites but not Stat3 are required for fasting-induced transcription of Agouti-related protein messenger ribonucleic acid. *Mol Endocrinol*, 20, 2591-2602 (2006)

124. M. Harris, C. Aschkenasi, C. F. Elias, A. Chandrankunnel, E. A. Nillni, C. Bjorbaek, J. K. Elmquist, J. S. Flier & A. N. Hollenberg: Transcriptional regulation of the thyrotropin-releasing hormone gene by leptin and melanocortin signaling. *J Clin Invest*, 107, 111-120 (2001)

125. F. Guo, K. Bakal, Y. Minokoshi & A. N. Hollenberg: Leptin Signaling Targets the Thyrotropin-Releasing Hormone Gene Promoter in Vivo. *Endocrinology*, 145, 2221-2227 (2004)

126. L. H. Huo, H. Munzberg, E. A. Nillni & C. Bjorbaek: Role of signal transducer and activator of transcription 3 in regulation of hypothalamic trh gene expression by leptin. *Endocrinology*, 145, 2516-2523 (2004)

127. P. Hekerman, J. Zeidler, S. Korfmacher, S. Bamberg-Lemper, H. Knobelspies, L. Zabeau, J. Tavernier & W. Becker: Leptin induces inflammation-related genes in

RINm5F insulinoma cells. *Bmc Molecular Biology*, 8, 41 (2007)

128. C. Bjorbaek, H. J. Lavery, S. H. Bates, R. K. Olson, S. M. Davis, J. S. Flier & M. G. Myers: SOCS3 mediates feedback inhibition of the leptin receptor via Tyr(985). *J Biol Chem*, 275, 40649-40657 (2000)

129. C. Bjorbaek, J. K. Elmquist, J. D. Frantz, S. E. Shoelson & J. S. Flier: Identification of SOCS-3 as a potential mediator of central leptin resistance. *Molecular Cell*, 1, 619-625 (1998)

130. M. L. Piper, E. K. Unger, M. G. Myers & A. W. Xu: Specific physiological roles for signal transducer and activator of transcription 3 in leptin receptor-expressing neurons. *Mol Endocrinol*, 22, 751-759 (2008)

131. N. Ghilardi, S. Ziegler, A. Wiestner, R. Stoffel, M. H. Heim & R. C. Skoda: Defective STAT signaling by the leptin receptor in diabetic mice. *Proc Natl Acad Sci USA* , 93, 6231-6235 (1996)

132. C. I. Rosenblum, M. Tota, D. Cully, T. Smith, R. Collum, S. Qureshi, J. F. Hess, M. S. Phillips, P. J. Hey, A. Vongs, T. M. Fong, L. Xu, H. Y. Chen, R. G. Smith, C. Schindler & L. H. T. VanderPloeg: Functional STAT 1 and 3 signaling by the leptin receptor (OB-R); Reduced expression of the rat fatty leptin receptor in transfected cells. *Endocrinology*, 137, 5178-5181 (1996)

133. Y. Gong, R. Ishida-Takahashi, E. C. Villanueva, D. C. Fingar, H. Muenzberg & M. G. Myers: The long form of the leptin receptor regulates STAT5 and ribosomal protein S6 via alternate mechanisms. *J Biol Chem*, 282, 31019-31027 (2007)

134. J. Mutze, J. Roth, R. Gerstberger & T. Hubschle: Nuclear translocation of the transcription factor STAT5 in the rat brain after systemic leptin administration. *Neurosci Lett*, 417, 286-291 (2007)

135. T. Montoye, J. Piessevaux, D. Lavens, J. Wauman, D. Catteeuw, J. Vandekerckhove, I. Lemmens & J. Tavernier: Analysis of leptin signalling in hematopoietic cells using an adapted MAPPIT strategy. *FEBS Lett*, 580, 3301-7 (2006)

136. J. Y. Lee, H. Muenzberg, O. Gavrilova, J. A. Reed, D. Berryman, E. C. Villanueva, G. W. Louis, G. M. Leinninger, S. Bertuzzi, R. J. Seeley, G. W. Robinson, M. G. Myers & L. Hennighausen: Loss of Cytokine-STAT5 Signaling in the CNS and Pituitary Gland Alters Energy Balance and Leads to Obesity. *Plos One*, 3, 13 (2008)

137. C. Bjorbaek, R. M. Buchholz, S. M. Davis, S. H. Bates, D. D. Pierroz, H. Gu, B. G. Neel, M. G. Myers & J. S. Flier: Divergent roles of SHP-2 in ERK activation by leptin receptors. *J Biol Chem*, 276, 4747-4755 (2001)

138. L. R. Carpenter, T. J. Farruggella, A. Symes, M. L. Karow, G. D. Yancopoulos & N. Stahl: Enhancing leptin response by preventing SH2-containing phosphatase 2 interaction with Ob receptor. *Proc Natl Acad Sci U S A*, 95, 6061-6 (1998)

139. C. Li & J. M. Friedman: Leptin receptor activation of SH2 domain containing protein tyrosine phosphatase 2 modulates Ob receptor signal transduction. *Proc Natl Acad Sci U S A*, 96, 9677-82 (1999)

140. K. Rahmouni, C. D. Sigmund, W. G. Haynes & A. L. Mark: Hypothalamic ERK mediates the anorectic and thermogenic sympathetic effects of leptin. *Diabetes*, 58, 536-42 (2009)

141. E. E. Zhang, E. Chapeau, K. Hagihara & G. S. Feng: Neuronal Shp2 tyrosine phosphatase controls energy balance and metabolism. *Proc Natl Acad Sci U S A*, 101, 16064-9 (2004)

142. R. Banno, D. Zimmer, B. C. De Jonghe, M. Atienza, K. Rak, W. Yang & K. K. Bence: PTP1B and SHP2 in POMC neurons reciprocally regulate energy balance in mice. *The J Clin Invest*, 120, 720-734 (2010)

143. C. F. Elias, C. Aschkenasi, C. Lee, J. Kelly, R. S. Ahima, C. Bjorbaek, J. S. Flier, C. B. Saper & J. K. Elmquist: Leptin differentially regulates NPY and POMC neurons projecting to the lateral hypothalamic area. *Neuron*, 23, 775-786 (1999)

144. H. Cui, F. Cai & D. D. Belsham: Leptin signaling in neurotensin neurons involves STAT, MAP kinases ERK1/2, and p38 through c-Fos and ATF1. *FASEB J.*, 20, 2654-2656 (2006)

145. H. Munzberg, E. E. Jobst, S. H. Bates, J. Jones, E. Villanueva, R. Leshan, M. Bjornholm, J. Elmquist, M. Sleeman, M. A. Cowley & M. G. Myers: Appropriate inhibition of orexigenic hypothalamic arcuate nucleus neurons independently of leptin receptor/STAT3 signaling. *J Neurosci*, 27, 69-74 (2007)

146. M. Bjornholm, H. Munzberg, R. L. Leshan, E. C. Villanueva, S. H. Bates, G. W. Louis, J. C. Jones, R. Ishida-Takahashi, C. Bjorbaek & M. G. Myers: Mice lacking inhibitory leptin receptor signals are lean with normal endocrine function. *J Clin Invest*, 117, 1354-1360 (2007)

147. J. You, Y. Yu, L. Jiang, W. Li, X. Yu, L. Gonzalez, G. Yang, Z. Ke, W. Li, C. Li & Y. Liu: Signaling through Tyr985 of Leptin Receptor as an Age/Diet-Dependent Switch in the Regulation of Energy Balance. *Mol. Cell. Biol.*, 30, 1650-1659 (2010)

148. D. Cota, K. Proulx, K. A. B. Smith, S. C. Kozma, G. Thomas, S. C. Woods & R. J. Seeley: Hypothalamic mTOR signaling regulates food intake. *Science*, 312, 927-930 (2006)

149. E. C. Villanueva, H. Munzberg, D. Cota, R. L. Leshan, K. Kopp, R. Ishida-Takahashi, J. C. Jones, D. C. Fingar, R. J. Seeley & M. G. Myers: Complex Regulation

of Mammalian Target of Rapamycin Complex 1 in the Basomedial Hypothalamus by Leptin and Nutritional Status. *Endocrinology*, 150, 4541-4551 (2009)

150. D. Cota, E. K. Matter, S. C. Woods & R. J. Seeley: The role of hypothalamic mammalian target of rapamycin complex 1 signaling in diet-induced obesity. *J Neurosci*, 28, 7202-7208 (2008)

151. H.-J. Shin, J. Oh, S. M. Kang, J. H. Lee, M.-J. Shin, K.-C. Hwang, Y. Jang & J. H. Chung: Leptin induces hypertrophy via p38 mitogen-activated protein kinase in rat vascular smooth muscle cells. *Biochem. Biophys. Res. Commun*, 329, 18-24 (2005)

152. J. Wauman, A. S. De Smet, D. Catteeuw, D. Belsham & J. Tavernier: Insulin receptor substrate 4 couples the leptin receptor to multiple signaling pathways. *Mol Endocrinol*, 22, 965-977 (2008)

153. C. J. Duan, M. H. Li & L. Y. Rui: SH2-B promotes insulin receptor substrate 1 (IRS1)- and IRS2-mediated activation of the phosphatidylinositol 3-kinase pathway in response to leptin. *J Biol Chem*, 279, 43684-43691 (2004)

154. M. Kellerer, M. Koch, E. Metzinger, J. Mushack, E. Capp & H. U. Haring: Leptin activates PI-3 kinase in C2C12 myotubes via janus kinase-2 (JAK-2) and insulin receptor substrate-2 (IRS-2) dependent pathways. *Diabetologia*, 40, 1358-1362 (1997)

155. Z. Q. Li, Y. J. Zhou, C. Carter-Su, M. G. Myers & L. Rui: SH2B1 enhances leptin signaling by both janus kinase 2 Tyr(813) phosphorylation-dependent and -independent mechanisms. *Mol Endocrinol*, 21, 2270-2281 (2007)

156. D. C. Ren, M. H. Li, C. J. Duan & L. Y. Rui: Identification of SH2-B as a key regulator of leptin sensitivity, energy balance, and body weight in mice. *Cell Metab*, 2, 95-104 (2005)

157. D. C. Ren, Y. J. Zhou, D. Morris, M. H. Li, Z. Q. Li & L. Y. Rui: Neuronal SH2B1 is essential for controlling energy and glucose homeostasis. *J Clin Invest*, 117, 397-406 (2007)

158. M.-S. Kim, Y. K. Pak, P.-G. Jang, C. Namkoong, Y.-S. Choi, J.-C. Won, K.-S. Kim, S.-W. Kim, H.-S. Kim, J.-Y. Park, Y.-B. Kim & K.-U. Lee: Role of hypothalamic Foxo1 in the regulation of food intake and energy homeostasis. *Nat Neurosci*, 9, 901-906 (2006)

159. T. Kitamura, Y. Feng, Y. I. Kitamura, S. C. Chua, Jr., A. W. Xu, G. S. Barsh, L. Rossetti & D. Accili: Forkhead protein FoxO1 mediates Agrp-dependent effects of leptin on food intake. *Nat Med*, 12, 534-40 (2006)

160. G. Yang, C. Y. Lim, C. Li, X. Xiao, G. K. Radda, X. Cao & W. Han: FoxO1 inhibits leptin regulation of pro-opiomelanocortin promoter activity by blocking STAT3 interaction with specificity protein 1. *J Biol Chem*, 284, 3719-27 (2009)

161. K. Ning, L. C. Miller, H. A. Laidlaw, L. A. Burgess, N. M. Perera, C. P. Downes, N. R. Leslie & M. L. J. Ashford: A novel leptin signalling pathway via PTEN inhibition in hypothalamic cell lines and pancreatic [beta]-cells. *EMBO J*, 25, 2377-2387 (2006)

162. K. Ning, L. C. Miller, H. A. Laidlaw, K. R. Watterson, J. Gallagher, C. Sutherland & M. L. J. Ashford: Leptin-dependent Phosphorylation of PTEN Mediates Actin Restructuring and Activation of ATP-sensitive K+ Channels. *J Biol Chem*, 284, 9331-9340 (2009)

163. A. Z. Zhao, J. N. Huan, S. Gupta, R. Pal & A. Sahu: A phosphatidylinositol 3-kinase phosphodiesterase 3B-cyclic AMP pathway in hypothalamic action of leptin on feeding. *Nat Neurosci*, 5, 727-8 (2002)

164. A. Sahu: A role of phosphodiesterase-3B pathway in mediating leptin action on proopiomelanocortin and neurotensin neurons in the hypothalamus. *Neurosci Lett*, 479, 18-21 (2010)

165. D. J. Burks, J. F. de Mora, M. Schubert, D. J. Withers, M. G. Myers, H. H. Towery, S. L. Altamuro, C. L. Flint & M. F. White: IRS-2 pathways integrate female reproduction and energy homeostasis. *Nature*, 407, 377-382 (2000)

166. D. J. Withers, J. S. Gutierrez, H. Towery, D. J. Burks, J. M. Ren, S. Previs, Y. T. Zhang, D. Bernal, S. Pons, G. I. Shulman, S. Bonner-Weir & M. F. White: Disruption of IRS-2 causes type 2 diabetes in mice. *Nature*, 391, 900-904 (1998)

167. N. Kubota, Y. Terauchi, K. Tobe, W. Yano, R. Suzuki, K. Ueki, I. Takamoto, H. Satoh, T. Maki, T. Kubota, M. Moroi, M. Okada-Iwabu, O. Ezaki, R. Nagai, Y. Ueta, T. Kadowaki & T. Noda: Insulin receptor substrate 2 plays a crucial role in beta cells and the hypothalamus. *J Clin Invest*, 114, 917-27 (2004)

168. X. Lin, A. Taguchi, S. Park, J. A. Kushner, F. Li, Y. Li & M. F. White: Dysregulation of insulin receptor substrate 2 in beta cells and brain causes obesity and diabetes. *J Clin Invest*, 114, 908-16 (2004)

169. A. I. Choudhury, H. Heffron, M. A. Smith, H. Al-Qassab, A. W. Xu, C. Selman, M. Simmgen, M. Clements, M. Claret, G. MacColl, D. C. Bedford, K. Hisadome, I. Diakonov, V. Moosajee, J. D. Bell, J. R. Speakman, R. L. Batterham, G. S. Barsh, M. L. J. Ashford & D. J. Withers: The role of insulin receptor substrate 2 in hypothalamic and beta cell function. *J Clin Invest*, 115, 940-950 (2005)

170. J. W. Hill, K. W. Williams, C. P. Ye, J. Luo, N. Balthasar, R. Coppari, M. A. Cowley, L. C. Cantley, B. B. Lowell & J. K. Elmquist: Acute effects of leptin require PI3K signaling in hypothalamic proopiomelanocortin neurons in mice. *J Clin Invest*, 118, 1796-1805 (2008)

171. C. D. Morrison, G. J. Morton, K. D. Niswender, R. W. Gelling & M. W. Schwartz: Leptin inhibits hypothalamic Npy and Agrp gene expression via a mechanism that

requires phosphatidylinositol 3-OH-kinase signaling. *Am J Physiol*, 289, E1051-E1057 (2005)

172. D. Kohno, M. Nakata, F. Maekawa, K. Fujiwara, Y. Maejima, M. Kuramochi, T. Shimazaki, H. Okano, T. Onaka & T. Yada: Leptin Suppresses Ghrelin-Induced Activation of Neuropeptide Y Neurons in the Arcuate Nucleus via Phosphatidylinositol 3-Kinase- and Phosphodiesterase 3-Mediated Pathway. *Endocrinology*, 148, 2251-2263 (2007)

173. S. Mirshamsi, H. Laidlaw, K. Ning, E. Anderson, L. Burgess, A. Gray, C. Sutherland & M. Ashford: Leptin and insulin stimulation of signalling pathways in arcuate nucleus neurones: PI3K dependent actin reorganization and KATP channel activation. *BMC Neurosci*, 5, 54 (2004)

174. J. Harvey, N. G. McKay, K. S. Walker, J. Van der Kaay, C. P. Downes & M. L. J. Ashford: Essential Role of Phosphoinositide 3-Kinase in Leptin-inducedK ATP Channel Activation in the Rat CRI-G1 Insulinoma Cell Line. *J Biol Chem*, 275, 4660-4669 (2000)

175. A. S. Metlakunta, M. Sahu & A. Sahu: Hypothalamic phosphatidylinositol 3-kinase pathway of leptin signaling is impaired during the development of diet-induced obesity in FVB/N mice. *Endocrinology*, 149, 1121-8 (2008)

176. K. D. Niswender, G. J. Morton, W. H. Stearns, C. J. Rhodes, M. G. Myers & M. W. Schwartz: Intracellular signalling - Key enzyme in leptin-induced anorexia. *Nature*, 413, 794-795 (2001)

177. L. Plum, E. Rother, H. Munzberg, F. T. Wunderlich, D. A. Morgan, B. Hampel, M. Shanabrough, R. Janoschek, A. C. Konner, J. Alber, A. Suzuki, W. Krone, T. L. Horvath, K. Rahmouni & J. C. Bruning: Enhanced leptin-stimulated PI3K activation in the CNS promotes white adipose tissue transdifferentiation. *Cell Metab*, 6, 431-45 (2007)

178. L. Plum, X. S. Ma, B. Hampel, N. Balthasar, R. Coppari, H. Munzberg, M. Shanabrough, D. Burdakov, E. Rother, R. Janoschek, J. Alber, B. F. Belgardt, L. Koch, J. Seibler, F. Schwenk, C. Fekete, A. Suzuki, T. W. Mak, W. Krone, T. L. Horvath, F. M. Ashcroft & J. C. Bruning: Enhanced PIP3 signaling in POMC neurons causes K-ATP channel activation and leads to diet-sensitive obesity. *J Clin Invest*, 116, 1886-1901 (2006)

179. B. F. Belgardt, A. Husch, E. Rother, M. B. Ernst, F. T. Wunderlich, B. Hampel, T. Klockener, D. Alessi, P. Kloppenburg & J. C. Bruning: PDK1 deficiency in POMC-Expressing cells reveals FOXO1-dependent and -independent pathways in control of energy homeostasis and stress response. *Cell Metab*, 7, 291-301 (2008)

180. A. W. Xu, C. B. Kaelin, K. Takeda, S. Akira, M. W. Schwartz & G. S. Barsh: PI3K integrates the action of insulin and leptin on hypothalamic neurons. *J Clin Invest*, 115, 951-8 (2005)

181. Y.-B. Kim, S. Uotani, D. D. Pierroz, J. S. Flier & B. B. Kahn: In Vivo Administration of Leptin Activates Signal Transduction Directly in Insulin-Sensitive Tissues: Overlapping but Distinct Pathways from Insulin. *Endocrinology*, 141, 2328-2339 (2000)

182. K. D. Niswender & M. W. Schwartz: Insulin and leptin revisited: adiposity signals with overlapping physiological and intracellular signaling capabilities. *Frontiers in Neuroendocrinology*, 24, 1-10 (2003)

183. J. C. Bruning, D. Gautam, D. J. Burks, J. Gillette, M. Schubert, P. C. Orban, R. Klein, W. Krone, D. Muller-Wieland & C. R. Kahn: Role of Brain Insulin Receptor in Control of Body Weight and Reproduction. *Science*, 289, 2122-2125 (2000)

184. G. J. Morton, R. W. Gelling, K. D. Niswender, C. D. Morrison, C. J. Rhodes & M. W. Schwartz: Leptin regulates insulin sensitivity via phosphatidylinositol-3-OH kinase signaling in mediobasal hypothalamic neurons. *Cell Metab*, 2, 411-420 (2005)

185. B. B. Kahn, T. Alquier, D. Carling & D. G. Hardie: AMP-activated protein kinase: ancient energy gauge provides clues to modern understanding of metabolism. *Cell Metab*, 1, 15-25 (2005)

186. M. Claret, M. A. Smith, R. L. Batterham, C. Selman, A. I. Choudhury, L. G. D. Fryer, M. Clements, H. Al-Qassab, H. Heffron, A. W. Xu, J. R. Speakman, G. S. Barsh, B. Viollet, S. Vaulont, M. L. J. Ashford, D. Carling & D. J. Withers: AMPK is essential for energy homeostasis regulation and glucose sensing by POMC and AgRP neurons. *J Clin Invest*, 117, 2325-2336 (2007)

187. S. Uotani, T. Abe & Y. Yamaguchi: Leptin activates AMP-activated protein kinase in hepatic cells via a JAK2-dependent pathway. *Biochem. Biophys. Res. Commun*, 351, 171-175 (2006)

188. U. Andersson, K. Filipsson, C. R. Abbott, A. Woods, K. Smith, S. R. Bloom, D. Carling & C. J. Small: AMP-activated protein kinase plays a role in the control of food intake. *J Biol Chem*, 279, 12005-8 (2004)

189. Y. Minokoshi, T. Alquier, N. Furukawa, Y. B. Kim, A. Lee, B. Xue, J. Mu, F. Foufelle, P. Ferre, M. J. Birnbaum, B. J. Stuck & B. B. Kahn: AMP-kinase regulates food intake by responding to hormonal and nutrient signals in the hypothalamus. *Nature*, 428, 569-74 (2004)

190. S. Gao, K. P. Kinzig, S. Aja, K. A. Scott, W. Keung, S. Kelly, K. Strynadka, S. Chohnan, W. W. Smith, K. L. K. Tamashiro, E. E. Ladenheim, G. V. Ronnett, Y. Tu, M. J. Birnbaum, G. D. Lopaschuk & T. H. Moran: Leptin activates hypothalamic acetyl-CoA carboxylase to inhibit food intake. *Proc Natl Acad Sci USA* , 104, 17358-17363 (2007)

191. K. A. Anderson, T. J. Ribar, F. M. Lin, P. K. Noeldner, M. F. Green, M. J. Muehlbauer, L. A. Witters, B. E. Kemp & A. R. Means: Hypothalamic CaMKK2 contributes to the regulation of energy balance. *Cell Metab*, 7, 377-388 (2008)

192. J. Y. Altarejos, N. Goebel, M. D. Conkright, H. Inotiel, J. X. Xie, C. M. Arias, P. E. Sawchenko & M. Montminy: The Creb1 coactivator Crtc1 is required for energy balance and fertility. *Nat Med*, 14, 1112-1117 (2008)

193. S. H. Koo, L. Flechner, L. Qi, X. M. Zhang, R. A. Screaton, S. Jeffries, S. Hedrick, W. Xu, F. Boussouar, P. Brindle, H. Takemori & M. Montminy: The CREB coactivator TORC2 is a key regulator of fasting glucose metabolism. *Nature*, 437, 1109-1114 (2005)

194. C. Blouet, H. Ono & G. J. Schwartz: Mediobasal Hypothalamic p70 S6 Kinase 1 Modulates the Control of Energy Homeostasis. *Cell Metab*, 8, 459-467 (2008)

195. K. Inoki, Y. Li, T. Q. Zhu, J. Wu & K. L. Guan: TSC2 is phosphorylated and inhibited by Akt and suppresses mTOR signalling. *Nat Cell Biol*, 4, 648-657 (2002)

196. K. Inoki, T. Q. Zhu & K. L. Guan: TSC2 mediates cellular energy response to control cell growth and survival. *Cell*, 115, 577-590 (2003)

197. H. Mori, K. Inoki, H. Munzberg, D. Opland, M. Faouzi, E. C. Villanueva, T. Ikenoue, D. Kwiatkowski, O. A. MacDougald, M. G. Myers & K. L. Guan: Critical Role for Hypothalamic mTOR Activity in Energy Balance. *Cell Metab*, 9, 362-374 (2009)

198. S. K. Chun & Y.-H. Jo: Loss of leptin receptors on hypothalamic POMC neurons alters synaptic inhibition. *J Neurophysiol* 104, 2321-2328 (2010)

199. S. Belouzard, D. Delcroix & Y. Rouille: Low levels of expression of leptin receptor at the cell surface result from constitutive endocytosis and intracellular retention in the biosynthetic pathway. *J Biol Chem*, 279, 28499-28508 (2004)

200. V. A. Barr, K. Lane & S. I. Taylor: Subcellular localization and internalization of the four human leptin receptor isoforms. *J Biol Chem*, 274, 21416-21424 (1999)

201. A. Lundin, H. Rondahl, E. Walum & M. Wilcke: Expression and intracellular localization of leptin receptor long isoform-GFP chimera. *Biochimica Et Biophysica Acta-Molecular Cell Research*, 1499, 130-138 (2000)

202. S. Belouzard & Y. Rouille: Ubiquitylation of leptin receptor OB-Ra regulates its clathrin-mediated endocytosis. *Embo J*, 25, 932-942 (2006)

203. S. E. Mitchell, R. Nogueiras, A. Morris, S. Tovar, C. Grant, M. Cruickshank, D. V. Rayner, C. Dieguez & L. M. Williams: Leptin receptor gene expression and number in the brain are regulated by leptin level and nutritional status. *J Physiol*, 587, 3573-3585 (2009)

204. S. J. Seo, D. F. Guo, K. Bugge, D. A. Morgan, K. Rahmouni & V. C. Sheffield: Requirement of Bardet-Biedl syndrome proteins for leptin receptor signaling. *Hum Mol Genet*, 18, 1323-1331 (2009)

205. K. Rahmouni, M. A. Fath, S. Seo, D. R. Thedens, C. J. Berry, R. Weiss, D. Y. Nishimura & V. C. Sheffield: Leptin resistance contributes to obesity and hypertension in mouse models of Bardet-Biedl syndrome. *J Clin Invest*, 118, 1458-1467 (2008)

206. C. Couturier, C. Sarkis, K. Séron, S. Belouzard, P. Chen, A. Lenain, L. Corset, J. Dam, V. Vauthier, A. Dubart, J. Mallet, P. Froguel, Y. Rouillé & R. Jockers: Silencing of OB-RGRP in mouse hypothalamic arcuate nucleus increases leptin receptor signaling and prevents diet-induced obesity. *Proc Natl Acad Sci USA*, 104, 19476-19481 (2007)

207. P. J. Scarpace & Y. Zhang: Leptin resistance: a predisposing factor for diet-induced obesity. *Am J Physiol Regul Integr Comp Physiol*, 296, R493-500 (2009)

208. S. L. Dunn, M. Bjornholm, S. H. Bates, Z. B. Chen, M. Seifert & M. G. Myers: Feedback inhibition of leptin receptor/Jak2 signaling via Tyr(1138) of the leptin receptor and suppressor of cytokine signaling 3. *Mol Endocrinol*, 19, 925-938 (2005)

209. S. Eyckerman, D. Broekaert, A. Verhee, J. Vandekerckhove & J. Tavernier: Identification of the Y985 and Y1077 motifs as SOCS3 recruitment sites in the murine leptin receptor. *FEBS Lett*, 486, 33-7 (2000)

210. C. Bjorbaek, K. El-Haschimi, J. D. Frantz & J. S. Flier: The role of SOCS-3 in leptin signaling and leptin resistance. *J Biol Chem*, 274, 30059-30065 (1999)

211. H. Munzberg, J. S. Flier & C. Bjorbaek: Region-specific leptin resistance within the hypothalamus of diet-induced obese mice. *Endocrinology*, 145, 4880-4889 (2004)

212. H. Mori, R. Hanada, T. Hanada, D. Aki, R. Mashima, H. Nishinakamura, T. Torisu, K. R. Chien, H. Yasukawa & A. Yoshimura: Socs3 deficiency in the brain elevates leptin sensitivity and confers resistance to diet-induced obesity. *Nat Med*, 10, 739-743 (2004)

213. J. K. Howard, B. J. Cave, L. J. Oksanen, I. Tzameli, C. Bjorbaek & J. S. Flier: Enhanced leptin sensitivity and attenuation of diet-induced obesity in mice with haploinsufficiency of Socs3. *Nat Med*, 10, 734-738 (2004)

214. P. Kievit, J. K. Howard, M. K. Badman, N. Balthasar, R. Coppari, H. Mori, C. E. Lee, J. K. Elmquist, A. Yoshimura & J. S. Flier: Enhanced leptin sensitivity and improved glucose homeostasis in mice lacking suppressor of cytokine signaling-3 in POMC-expressing cells. *Cell Metab*, 4, 123-132 (2006)

215. A. S. Reed, E. K. Unger, L. E. Olofsson, M. L. Piper, M. G. Myers & A. W. Xu: Functional Role of Suppressor of Cytokine Signaling 3 Upregulation in Hypothalamic Leptin Resistance and Long-Term Energy Homeostasis. *Diabetes*, 59, 894-906 (2010)

216. D. Lavens, T. Montoye, J. Piessevaux, L. Zabeau, J. Vandekerckhove, K. Gevaert, W. Becker, S. Eyckerman & J. Tavernier: A complex interaction pattern of CIS and SOCS2 with the leptin receptor. *J Cell Sci*, 119, 2214-2224 (2006)

217. J. Piessevaux, D. Lavens, T. Montoye, J. Wauman, D. Catteeuw, J. Vandekerckhove, D. Belsham, F. Peelman & J. Tavernier: Functional cross-modulation between SOCS proteins can stimulate cytokine signaling. *J Biol Chem*, 281, 32953-66 (2006)

218. W. Kaszubska, H. D. Falls, V. G. Schaefer, D. Haasch, L. Frost, P. Hessler, P. E. Kroeger, D. W. White, M. R. Jirousek & J. M. Trevillyan: Protein tyrosine phosphatase 1B negatively regulates leptin signaling in a hypothalamic cell line. *Mol Cell Endocrinol*, 195, 109-118 (2002)

219. J. M. Zabolotny, K. K. Bence-Hanulec, A. Stricker-Krongrad, F. Haj, Y. Wang, Y. Minokoshi, Y.-B. Kim, J. K. Elmquist, L. A. Tartaglia, B. B. Kahn & B. G. Neel: PTP1B Regulates Leptin Signal Transduction In Vivo. *Dev Cell*, 2, 489-495 (2002)

220. K. K. Bence, M. Delibegovic, B. Xue, C. Z. Gorgun, G. S. Hotamisligil, B. G. Neel & B. B. Kahn: Neuronal PTP1B regulates body weight, adiposity and leptin action. *Nat Med*, 12, 917-924 (2006)

221. A. Cheng, N. Uetani, P. D. Simoncic, V. P. Chaubey, A. Lee-Loy, C. J. McGlade, B. P. Kennedy & M. L. Tremblay: Attenuation of Leptin Action and Regulation of Obesity by Protein Tyrosine Phosphatase 1B. *Dev Cell*, 2, 497-503 (2002)

222. P. K. Picardi, V. C. Calegari, P. de Oliveira Prada, J. Contin Moraes, E. Araujo, M. C. C. Gomes Marcondes, M. Ueno, J. B. C. Carvalheira, L. A. Velloso & M. J. Abdalla Saad: Reduction of Hypothalamic Protein Tyrosine Phosphatase Improves Insulin and Leptin Resistance in Diet-Induced Obese Rats. *Endocrinology*, 149, 3870-3880 (2008)

223. C. D. Morrison, C. L. White, Z. Wang, S.-Y. Lee, D. S. Lawrence, W. T. Cefalu, Z.-Y. Zhang & T. W. Gettys: Increased Hypothalamic Protein Tyrosine Phosphatase 1B Contributes to Leptin Resistance with Age. *Endocrinology*, 148, 433-440 (2007)

224. C. L. White, A. Whittington, M. J. Barnes, Z. Wang, G. A. Bray & C. D. Morrison: HF diets increase hypothalamic PTP1B and induce leptin resistance through both leptin-dependent and -independent mechanisms. *Am J Physiol Endocrinol Metab*, 296, E291-299 (2009)

225. J. M. Zabolotny, Y.-B. Kim, L. A. Welsh, E. E. Kershaw, B. G. Neel & B. B. Kahn: Protein-tyrosine Phosphatase 1B Expression Is Induced by Inflammation in Vivo. *J Biol Chem*, 283, 14230-14241 (2008)

226. K. El-Haschimi, D. D. Pierroz, S. M. Hileman, C. Bjorbaek & J. S. Flier: Two defects contribute to hypothalamic leptin resistance in mice with diet-induced obesity. *J Clin Invest*, 105, 1827-1832 (2000)

227. J. F. Caro, J. W. Kolaczynski, M. R. Nyce, J. P. Ohannesian, I. Opentanova, W. H. Goldman, R. B. Lynn, P. L. Zhang, M. K. Sinha & R. V. Considine: Decreased cerebrospinal-fluid/serum leptin ratio in obesity: A possible mechanism for leptin resistance. *Lancet*, 348, 159-161 (1996)

228. M. W. Schwartz, E. Peskind, M. Raskind, E. J. Boyko & D. Porte: Cerebrospinal fluid leptin levels: Relationship to plasma levels and to adiposity in humans. *Nat Med*, 2, 589-593 (1996)

229. W. A. Banks, A. J. Kastin, W. T. Huang, J. B. Jaspan & L. M. Maness: Leptin enters the brain by a saturable system independent of insulin. *Peptides*, 17, 305-311 (1996)

230. A. J. Kastin, W. H. Pan, L. M. Maness, R. J. Koletsky & P. Ernsberger: Decreased transport of leptin across the blood-brain barrier in rats lacking the short form of the leptin receptor. *Peptides*, 20, 1449-1453 (1999)

231. O. Cheunsuang & R. Morris: Astrocytes in the arcuate nucleus and median eminence that take up a fluorescent dye from the circulation express leptin receptors and neuropeptide YY1 receptors. *Glia*, 52, 228-233 (2005)

232. M. Faouzi, R. Leshan, M. Bjornholm, T. Hennessey, J. Jones & H. Munzberg: Differential accessibility of circulating leptin to individual hypothalamic sites. *Endocrinology*, 148, 5414-5423 (2007)

233. A. Gertler: Development of leptin antagonists and their potential use in experimental biology and medicine. *Trends Endocrinol Metab*, 17, 372-378 (2006)

234. D. Ron & P. Walter: Signal integration in the endoplasmic reticulum unfolded protein response. *Nat Res Mol Cell Biol*, 8, 519-529 (2007)

235. U. Ozcan, Q. Cao, E. Yilmaz, A.-H. Lee, N. N. Iwakoshi, E. Ozdelen, G. Tuncman, C. Gorgun, L. H. Glimcher & G. S. Hotamisligil: Endoplasmic Reticulum Stress Links Obesity, Insulin Action, and Type 2 Diabetes. *Science*, 306, 457-461 (2004)

236. L. Ozcan, A. S. Ergin, A. Lu, J. Chung, S. Sarkar, D. Nie, M. G. Myers Jr & U. Ozcan: Endoplasmic Reticulum Stress Plays a Central Role in Development of Leptin Resistance. *Cell Metab*, 9, 35-51 (2009)

237. X. Zhang, G. Zhang, H. Zhang, M. Karin, H. Bai & D. Cai: Hypothalamic IKK[beta]/NF-[kappa]B and ER Stress Link Overnutrition to Energy Imbalance and Obesity. *Cell*, 135, 61-73 (2008)

238. T. Hosoi, M. Sasaki, T. Miyahara, C. Hashimoto, S. Matsuo, M. Yoshii & K. Ozawa: Endoplasmic Reticulum Stress Induces Leptin Resistance. *Mol Pharmacol*, 74, 1610-1619 (2008)

239. E. R. Ropelle, M. B. Flores, D. E. Cintra, G. Z. Rocha, J. R. Pauli, J. Morari, C. T. de Souza, J. C. Moraes, P. O. Prada, D. Guadagnini, R. M. Marin, A. G. Oliveira, T. M. Augusto, H. F. Carvalho, L. A. Velloso, M. J. A. Saad & J. B. C. Carvalheira: IL-6 and IL-10 Anti-Inflammatory Activity Links Exercise to Hypothalamic Insulin and Leptin Sensitivity through IKKbeta and ER Stress Inhibition. *PLoS Biol*, 8, e1000465 (2010)

240. C. T. De Souza, E. P. Araujo, S. Bordin, R. Ashimine, R. L. Zollner, A. C. Boschero, M. J. A. Saad & L. A. Velloso: Consumption of a Fat-Rich Diet Activates a Proinflammatory Response and Induces Insulin Resistance in the Hypothalamus. *Endocrinology*, 146, 4192-4199 (2005)

241. M. Milanski, G. Degasperi, A. Coope, J. Morari, R. Denis, D. E. Cintra, D. M. L. Tsukumo, G. Anhe, M. E. Amaral, H. K. Takahashi, R. Curi, H. C. Oliveira, J. B. C. Carvalheira, S. Bordin, M. J. Saad & L. A. Velloso: Saturated Fatty Acids Produce an Inflammatory Response Predominantly through the Activation of TLR4 Signaling in Hypothalamus: Implications for the Pathogenesis of Obesity. *J. Neurosci.*, 29, 359-370 (2009)

242. A. Kleinridders, D. Schenten, A. C. Könner, B. F. Belgardt, J. Mauer, T. Okamura, F. T. Wunderlich, R. Medzhitov & J. C. Brüning: MyD88 Signaling in the CNS Is Required for Development of Fatty Acid-Induced Leptin Resistance and Diet-Induced Obesity. *Cell Metab*, 10, 249-259 (2009)

243.W. Komyod,U.M. Bauer, P.C. Heinrich, S. Haan, I. Behrmann: Are STATs arginine-methylated? *J Biol Chem*, 280, 21700-21705 (2005)

Abbreviations: ObR: leptin receptor, POMC: pro-opiomelanocortin; AgRP: agouti-related peptide; NPY: neuropeptide Y; CART: cocaine and amphetamine-related transcript; MSH: melanocyte-stimulating hormone; JAK: janus kinase; STAT: signal transducers and activators of transcription; ERK: extracellular signal-regulated protein kinase; JNK: c-Jun NH2-terminal kinase; PRMT2: protein arginine N-methyltransferase 2; SHP2: SH2-containing protein tyrosine phosphatase 2; Grb2: growth factor receptor-bound protein-2; MAPK: mitogen-activated protein kinase; PI3K: phosphatidylinositol 3-kinase; AMPK: 5'-AMP-activated protein kinase; mTOR: mammalian target of rapamycin; ER: endoplasmic reticulum; BBB: blood-brain barrier; CRH: cytokine receptor homology; Ig: immunoglobulin; FN III: fibronectin type III; ARC: arcuate nucleus; VMH: ventromedial hypothalamus; PVN: paraventricular nucleus; DMH: dorsomedial hypothalamus; LHA: lateral hypothalamic area; PMV: ventral premammillary nucleus; MC3R: melanocortin receptor 3; MC4R: melanocortin receptor 4; GABA: gamma-aminobutyric acid; SF-1: steroidogenic factor-1; DIO: diet-induced obesity; NK: natural killer; T_H1: T helper 1; T_{Regs}: regulatory T cells; RNF41: ring finger protein 41; ADAM: a disintegrin and metalloprotease; BRET: bioluminescence resonance energy transfer; SH2: src homology 2; TRH: thyrotropin-releasing hormone; SOCS: suppressor of cytokine signaling; RSK: ribosomal S6 kinase; IRS: insulin receptor substrate; MAPPIT: mammalian protein-protein interaction trap; PIP_3: phosphatidylinositol 3,4,5-triphosphate; PDK1: 3-phosphoinositide dependent protein kinase-1; FoxO1: forkhead box O1; PTEN: phosphatase and tensin homologue; CK2: casein kinase II; GSK3: glycogen synthase kinase 3; PDE3B: phosphodiesterase 3B; icv: intracerebroventricular; ACC: acetyl-CoA carboxylase; CaMKK2: Ca^{2+}/calmodulin-dependent protein kinase kinase 2; Creb: cyclic AMP responsive element-binding protein; Ctrc1: Creb-regulated transcription coactivator-1; TSC: tuberous sclerosis protein; BBS: Bardet-Biedl syndrome; Ob-RGRP: ObR gene-related protein; LEPROT: leptin receptor overlapping transcript; CIS: cytokine-inducible SH2-containing protein; PTP1B: protein tyrosine phosphatase 1B; IKKβ: inhibitor of nuclear factor kappa-B kinase subunit beta; NF-κB: nuclear factor-kappaB; UPR: unfolded protein response; IL: interleukin; TLR: toll-like receptor

Key Words: Leptin Receptor Signaling, Leptin Resistance; Leptin Receptor Activation, JAK/STAT, MAPK, PI3K, AMPK, SOCS3; PTP1B; ER stress, Review

Send correspondence to: Jan Tavernier, Albert Baertsoenkaai 3, B-9000 Ghent, Belgium, Tel: 32 92649302, Fax: 32 92649492, E-mail: jan.tavernier@vib-ugent.be

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