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The role of chemokines and their receptors in dendritic cell biology

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1. ABSTRACT

Dendritic cells (DCs) are the chief inducers of adaptive immunity. Their normal life cycle begins with the generation of their precursors in the bone-marrow, followed by their release into the blood stream, continues with their entry into non-lymphoid tissues and commences with steady-state or infection-induced migration into draining lymph nodes. Each of these migration steps is controlled by distinct chemokine-chemokine receptor interactions, facilitated by dynamic changes in chemokine receptor expression. In this review, we describe current knowledge on the role of chemokines and their receptors in the control of DC migratory behavior, as well as other influences on DC biology.

2. PRINCIPLES OF THE ROLE OF DENDRITIC CELLS IN IMMUNITY

Adaptive immune responses against infectious pathogens, tumor cells or vaccines depend on the activation of antigen-specific T cells. In order to avoid autoimmunity by autoreactive T cells that have escaped thymic censorship (1), T cell activation is tightly regulated, for example by its restriction to professional antigen-presenting cells that possess various means of distinguishing between self antigens and pathogens. Dendritic cells (DCs) are generally regarded as the most important antigen-presenting cells that facilitate T cell activation (2, 3). After their discovery by the seminal studies of Steinman and colleagues, knowledge

Table 1. Features of murine dendritic cells

DC Subset	Phenotype	Function
1a. Conventional $CD8^-$ DC (previously termed "myeloid" DC)	$CD11c^+$ $CD11b^+$ $CD8\alpha\alpha^-$ $DEC205^-$ $DCIR^+$	Occur in all tissues, migrate to draining LNs, activate $CD4^+$ T cells
1b. Conventional $CD8^+$ DC (previously termed "lymphoid" DC)	$CD11c^+$ $CD11b^-$ $CD8\alpha\alpha^+$ $DEC205^+$ mannose $receptor^+$	Restricted to lymphatic tissues, activation or tolerization of $CD8^+$ and $CD4^+$ T cells, cross-presentation
2. Langerhans cell	$CD11c^+$ $CD11b^+$ $CD8\alpha\alpha^-$ $DEC205^+$ $Langerin^+$ $CD1a^+$	Antigen transport from skin to cutaneous LNs, T cell activation?
3. Plasmacytoid DC	$CD11c^{int}$, $CD11b^-$ $CD8\alpha\alpha^-$ $DEC205^-$ $CD45RO^+$ $Gr\text{-}1^+$	IFNα production in viral infections
TIP DC	$CD11c^+$ $CD11b^{int}$ $CD8\alpha\alpha^-$ $CCR2^+$	TNFα and iNOS production in certain bacterial infections

on these cells has expanded enormously and continues to do so. Much of the current model of DC biology has been extrapolated from the analysis of DCs in lymphatic tissues of mice, and –with some exceptions- is corroborated by observations in human biopsy material. Research on DCs in non-lymphoid organs has been pioneered by studies on skin cells originally discovered by Paul Langerhans more than 100 years ago, which now have been recognized as a distinct DC subset that performs functions different to those of conventional DCs (4-6). As a further fundamental cellular subset, plasmacytoid DC have to be distinguished, which perform important innate immune functions in viral infections, such as the secretion of type I interferons, while their role as antigen-presenting cells is still unclear. In addition to distinct functionality, these DC subsets are also thought to represent distinct cell lineages that are not interconvertable when fully differentiated (7). DCs are usually categorized by determining their cell surface molecule expression. The most commonly employed DC marker in the murine system is the integrin chain CD11c, whereas DC-SIGN seems to be more specific for human DCs (8). In this review, we will focus on murine conventional DC and hereafter use the term "DC" to refer only to such DC. The complex biology of plasmacytoid DC has recently been reviewed elsewhere (9).

Murine (but not human) conventional DC are often further subdivided into $CD11b^-$ $CD8^+$ and $CD11b^+$ $CD8^-$ DC. In the past, these subsets had been referred to as "lymphoid" and "myeloid" DCs owing to the assumption that they were derived from different developmental lineages. Authoritative reviews nowadays consider these terms obsolete (3, 10). $CD8^+$ DCs have been shown to exhibit cross-presenting ability important for activation of cytotoxic $CD8^+$ T cells (CTL) in antiviral and anti-tumor immune responses (4, 11-13). They are further distinguished by expression of certain antigen uptake receptors of the C-lectin type, such as DEC-205 (14) or the mannose receptor (13), the latter of which plays a functional role in the unique capability of DC to cross-present exogenous antigen to naïve T cells (11, 15). In the lung, cross-presenting DC were characterized by expression of the CD103 integrin (16). $CD11b^+$ $CD8^-$ DCs possess different endocytotic C-lectin type and are specialized at activating $CD4^+$ T cells (13, 14). Human analogs of these two subtypes of conventional DCs remain to be defined. Further DC subtypes have been distinguished, such as TNFα- and iNOS-producing (TIP) DCs, which were essential in the innate defense against listeria monocytogenes infection (17). Table 1 summarizes the different DC subtypes and their main features.

DCs originate from hematopoietic stem cell precursors that are released into the blood (3, 18). Many details of the DC lineage remain to be resolved, such as the question whether a common precursor, such as the monocyte, supplies tissues with both macrophages and DC subtypes (18-20), or whether a distinct blood-borne DC precursor gives rise to DCs only (21). It has been suggested that monocytes convert to DCs only during inflammation (3). Recent data indicate that adoptively transferred monocytes can become DCs (22, 23), raising the possibility that DCs in peripheral organs may arise at least to some extent from monocytes in the steady state. In lymphoid organs such as the spleen, *in vivo* tracking experiments supported the view that monocytes do not contribute to the DC populations in the steady state (3, 18, 22). However, this has recently been questioned by a study that mathematically modeled splenic DC turnover in parabiosis experiments (24). Most authorities agree that monocytes can differentiate into specialized DCs under infectious or inflammatory conditions (3, 25, 26).

Following precursor entry into lymphoid and non-lymphoid tissue, immature DCs reside in virtually all tissues as sentinels (3, 27) and sample their environment using various endocytic mechanisms that are highly active at this stage (28). Immature DCs are also equipped with a series of receptors for microbial molecular patterns such as Toll-like receptors (TLRs), and for inflammatory cytokines. TLR signaling fundamentally changes the chemokine receptor expression profile and initiates DC migration towards the organ-draining LNs. Upon reaching these organs, matured DCs have downregulated their endocytic activity, but upregulated expression of molecules required to activate T cells, such as MHC and co-stimulatory molecules and secreted cytokines (28-30). Naïve T cells recirculate through secondary lymphatic tissues and scan immigrated DCs for presentation of their cognate antigen. T cells bearing a receptor specific for antigen captured in peripheral organs become activated and undergo vigorous proliferation, change their chemokine receptor expression profile and emigrate from the lymph nodes. Activated T cells then can enter peripheral tissues to perform immune effector functions (31), or migrate to B cell areas in secondary lymphatic tissues where they promote antibody production.

DC biology also comprises so-called steady-state migration, where immature tissue DCs in the absence of inflammatory or infectious stimuli after some time constitutively leave the organ (3, 32-36). Such

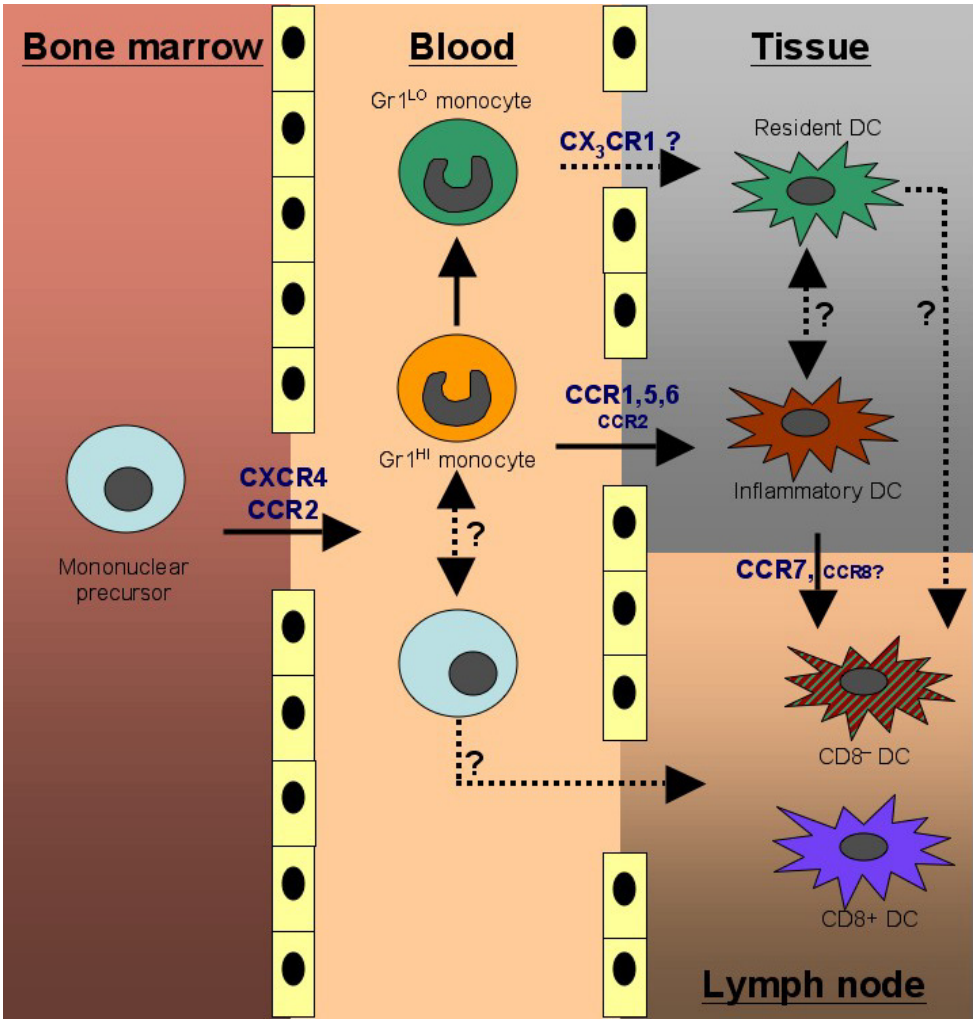

Figure 1. Chemokine receptors affecting migration of DCs at different stages of their life-cycle.

immature DCs transport self antigen to draining LNs, where they usually cause T cell tolerance (3, 15, 19, 20, 33, 37).

In addition to migratory DCs arriving from the periphery, secondary lymphoid organs also contain resident DCs, which include $CD8^+$ and $CD8^-$ subpopulations. These obtain antigen arriving via the lymph or from migrating DCs. Antigen handover from migratory to draining LN-resident DCs has been documented in herpes virus infection, resulting in the induction of T cell-mediated immunity (12, 38). A further exception to the classical paradigm of DCs as antigen shuttles and T cell activators represent non-migratory DCs, which remain in peripheral tissues despite ongoing inflammation or infection, in order to locally sustain or functionally modify immigrating effector T cells that had been activated by migratory DCs (3, 39). Phenotypic differences between such tissue-resident DCs and migratory DCs remain to be defined.

3. OVERVIEW ON THE ROLE OF CHEMOKINES AND THEIR RECEPTORS IN DC BIOLOGY

3.1. Selective use of chemokines to direct migration at distinct stages of the DC life cycle

The stages of the DC life cycle are characterized by distinct cell migration patterns that are regulated by characteristic chemokine-chemokine receptor interactions (Figure 1). These patterns are facilitated through controlled expression of discrete chemokine receptors, allowing cell subset-selective *in vivo* responses to particular chemokine signals (overview see Table 2).

The release of many DC precursors from the bone marrow is controlled by CXCR4 / CXCL12 (SDF-1) (40). In inflammatory conditions such as bacterial infections, the CCR2 ligand CCL2 (MCP-1) can stimulate the release of inflammatory monocytes from the bone marrow, thereby increasing the availability of precursors for inflammatory DCs and macrophages (41, 42).

Table 2. Chemokine receptors expressed by DCs

Chemokine receptor	Expression profile	Biological effect	Chemokine ligands
CCR1	Th2 cells Immature DCs	Recruitment of Th2 cells DC migration in humans	CCL3 (MIP1α) CCL5 (RANTES) CCL7 (MCP-3) CCL8 (MCP-2) CCL9 (MRP-2) CCL14 (HCC1) CCL16 (HCC4)
CCR2	DC precursors in blood and BM $Gr1^{HI}$ monocytes Regulatory T cells	DC recruitment to inflammatory sites DC precursor emigration out of the bone marrow	CCL2 (MCP-1) CCL7 (MCP-3) CCL12 (MCP-5) CCL8 (MCP-2) CCL16 (HCC4)
CCR3	Th2 cells, eosinophils, basophils	Th2 responses	CCL11 (Eotaxin) CCL5 (RANTES) CCL7 (MCP-3) CCL8 (MCP-2) CCL28 (MEC)
CCR4	DCs,Th2 cells Activated T cells Some memory cells Regulatory T cells	Recruitment of skin homing T cells/memory cells to skin Recruitment of Th2 cells to inflammatory sites	CCL17 (TARC) CCL19 (MDC, ABCD-1)
CCR5	DC precursors in the blood, Monocytes, Regulatory T cells	Recruitment to inflammatory sites Recruitment of naïve T cells to licensed DCs Costimulation of T cells	CCL3 (MIP-1α) CCL4 (MIP-1β) CCL5 (RANTES) CCL8 (MCP-2) CCL11 (eotaxin) CCL14 (HCC1) CCL16 (HCC4)
CCR6	Gut DCs	Langerhans cell migration, DC migration into the gut DC localization in PP Recruitment of LC precursors to skin during infection	CCL20 (MIP-3α, LARC)
CCR7	DCs, Naïve T cells Central memory T cells Regulatory T cells	Migration of DC from tissue to secondary lymphoid organ Migration of naïve T cells and Treg Induces maturation of DCs Enhances endocytosis by DCs	CCL19 (MIP-3β, ELC) CCL21 (6Ckine, SLC)
CCR8	Th2 cells DCs	Recruitment of Th2 cells to inflammatory sites; Migration of monocyte-derived DC from skin to LN	CCL1 (TCA3)
CCR9	intestinal T cells pDCs,	T cell recruitment to gut pDC recruitment to inflamed gut	CCL25 (TECK)
CCR10	Skin, mucosal tissue salivary gland mammary gland	T cell recruitment to inflamed skin IgA^+ plasma cell migration to mucosa	CCL27 (CTACK) CCL28 (MEC)
CXCR4	BM, thymus Germinal center	Monocytes egress from BM	CCL12 (SDF-1)
CX3CR1	DCs, monocytes	DC sentinel function	CX3CR1 (Fractalkine)
CXCR3	NK cells Activated T cells	Recruitment of Th1 cells	CXCL9 (MIG) CXCL10 (IP10) CXCL11 (ITAC)

The recruitment of DC precursors from the blood into inflamed peripheral tissues is thought to be controlled by CCR2 (25, 43-47), although recent studies have proposed that CCR2 signaling in fact mediates DC precursor release from the bone marrow to the blood (41, 42). DC (precursor) immigration into peripheral tissues is affected by several further chemokine receptors, in particular CCR1, CCR5 and CCR6 (46, 48-50). The differential roles of these receptors are poorly understood. It is possible that they serve to selectively respond to the various chemokines released from the different tissues of our body, or in response to individual inflammatory or infectious conditions. Alternatively, it is conceivable that these receptors are used redundantly to avoid microbial immune escape strategies, since inhibition of several chemokine receptors is more difficult to achieve by mutation and selection than of only one mediator. A further unresolved question pertains to the mechanisms mediating tissue entry of DCs under homeostatic conditions, in order to populate tissues with resident sentinels. In some models, a role of CX_3CR1 has been described (25, 46).

The step of triggered DC migration from peripheral tissues into tissue-draining LNs is under control of CCR7, which guides activated DCs and naïve T cells towards each other in the priming phase of immune responses (51). After exposure to inflammatory stimuli in peripheral tissues, DCs undergo maturation, and upregulate CCR7 (52), whereas chemokine receptors facilitating entry into inflamed tissues, such as CCR2 or CCR5 are downregulated (53). The CCR7 chemokine ligands CCL19 (ELC, MIP-3β) and CCL21 (SLC, 6Ckine) are expressed

Table 3. Some chemokines produced by DCs

Chemokine	Expression profile	Chemokine receptor	Biological effect
CCL17 (TARC)	Lung, LN, PP	CCR4	Attraction of Th2 cells Attraction of regulatory T cells skin homing of memory T cells
CCL19 (ELC)		CCR7	DC migration DC maturation DC survival
CCL21 (SLC)		CCR7	DC migration DC maturation DC survival
CCL22 (MDC)		CCR4	Attraction of Th2 cells
CXCL9 (MIG)	DC, MΦ, tissue cells	CXCR3	Attraction of Th1 cells
CXCL10 (IP-10)	DC, MΦ, tissue cells	CXCR3	Attraction of Th1 cells
CXCL11 (ITAC)	DC, MΦ, tissue cells	CXCR3	Attraction of Th1 cells

by stromal cells in secondary lymphatic tissues (19, 20, 54). There is evidence that also steady-state DC migration into draining LNs is controlled by CCR7 (32, 34, 35). The role of chemokines in entry of DC precursors from the blood-stream into secondary lymphatics is unclear (Figure 1).

3.2. Tissue-specific DC recruitment by distinct chemokines

The expression profile of some chemokines, which DCs are responsive to, shows preference for certain organs, which can facilitate tissue-specific recruitment of cells expressing the cognate chemokine receptor(s). Thus, DCs expressing CCR6 and CCR9 can be attracted to mucosal tissues, where their chemokine ligands, CCL20 (LARC) and CCL25 (TECK), respectively, are produced (55, 56). In contrast, CCL17 (TARC) or CCL22 (MDC) can be produced in the skin by DC, resulting in preferential recruitment of $CCR4^+$ T cells towards this organ (57-59). CXCL16 produced by skin epithelial cells attracted precursors of DCs and Langerhans cells expressing the chemokine receptor CXCR6 to the epidermis (60).

3.3. Role of DC-derived chemokines in T helper-subtype differentiation

DCs not only respond to chemokines, they can also produce distinct chemokines, in order to selectively facilitate generation of Th1 and Th2-biased immune responses, and thereby recruit immune effectors suitable for the defense against viral and bacterial pathogens, or parasites, respectively (see Table 3). Th1 cells preferentially express CXCR3 and CCR5, and DCs can selectively produce CXCR3 ligands to attract them (61-63). Th2 cells express higher amounts of CCR3, CCR4 or CCR8 (53, 64-66), and DCs have been shown to secrete chemokines targeting CCR4 (67). CCR3 is even more specifically expressed by Th2 cells (64). Its ligands such as CCL11 (Eotaxin) are produced by tissue cells and macrophages (68), whereas evidence for selective production by DCs is weak. CCL1 (TCA3) is produced by Th2 cells and can attract $CCR8^+$ cells, which includes other Th2 cells and DCs (26, 66).

Following DC-induced Th1 differentiation, primed CD4 T cells downregulate expression of chemokine receptors enabling lymphoid tissue homing, such as CCR7 and CXCR5, the latter of which facilitates entry into B cell areas. Instead, they up-regulate Th1 effector cell-targeting chemokine receptors such as CCR5 or CXCR6 (69). A similar switch towards Th2 effector cell-targeting chemokine receptors such as CCR3 or CCR4 occurs as a consequence of DC-induced Th2 differentiation. Thus, chemokine receptor expression dynamically changes during the life-cycle of migratory immune cells, such as DCs or T cells, in order to permit homing to sites where cells of a distinct functionality are required (53, 64, 70).

The role of chemokines in DC biology is not restricted to regulating migration of immune cells. Chemokine signaling also modifies intrinsic cell functions such as the antigen presentation capability of DCs or the proliferation of T cells stimulated by DCs. In the following, we will review in more detail some of the most extensively investigated chemokine-chemokine receptor interactions relevant for DC biology:

4. DISTINCT CHEMOKINE-CHEMOKINE RECEPTOR INTERACTIONS RELEVANT IN DC BIOLOGY

4.1. Role of CXCR4 / CXCL12 (SDF-1) in egress of DC precursors from the BM into the blood

DCs in peripheral tissues can originate from blood borne precursors, such as monocytes (24, 71, 72). The bone-marrow contains a clonogenic progenitor of monocytes that can differentiate both into DCs and macrophages (18). The egress of monocytes from the bone marrow into the circulation under non-inflammatory conditions is controlled by the chemokine CXCL12 (SDF-1), which is expressed on stromal cells (73, 74). By interacting with its receptor CXCR4 on monocyte and DC precursors, cell surface integrins are upregulated (75), which retain the precursors in the bone-marrow (76). Thereby, the immune system can control the supply with DC precursors by modifying CXCL12 (SDF-1) expression (40). CXCL12 (SDF-1) is downregulated in infectious conditions, thereby releasing more monocytes and DC precursors into the circulation (40).

A further role of CXCR4 in DC biology has been suggested based on the recent detection of CXCR4 on plasmacytoid DCs (77). This raised the possibility that these DCs may be infected by X4-tropic HIV, which uses this chemokine receptor to infect activated T cells (78). The biology of plasmacytoid DCs has been reviewed recently (9).

4.2. Role of CCR2 / CCL2 (MCP-1) in recruitment of DC precursors into inflamed tissue

Under infectious conditions, tissue DCs (and macrophages) can originate from monocyte precursors, whose release from the bone marrow is under control of CCR2 / CCL2 (MCP-1) (41). This precursor population is characterized by high expression levels of CCR2 and Gr-1 (Ly6C/G), as opposed to $CCR2^{LO}$ $Gr1^{LO}$ CX_3CR1^{HI} monocytes, which are thought to serve as sentinels that patrol the circulation under homeostatic conditions (25). Thus, blood monocytes consist of two main subsets of monocytes, defined by different expression levels of CCR2, CX_3CR1 and Gr1. It has recently become possible to track $Gr1^{HI}$ or $Gr1^{LO}$ blood monocytes, e.g. by using distinct labeling protocols utilizing fluorescent latex beads, genetic labeling or adoptive cell transfer studies (reviewed in (47)). These techniques permit identifying the precursor cell subset that gives rise to tissue DCs and the chemokine receptor pathways employed for recruitment.

$Gr1^{HI}$ monocytes have been shown to be recruited into inflamed skin or peritoneum (25, 79), retina (80), and after infection with Toxoplasma gondii (81) or Listeria monocytogenes (79). In most models of acute inflammation, $Gr1^{HI}$ monocyte recruitment was concluded to be critically dependent on CCR2 (44, 82), but not on CX_3CR1 (26). $Gr1^{HI}$ monocytes can give rise to macrophages, but also to conventional DC populations. Using specific monocyte-subset labeling, adoptive transfer and bone marrow chimera, $Gr1^{HI}$ monocytes were identified as the circulating precursors for epidermal Langerhans cells in a model of UV-induced skin inflammation (72).

The CCR2 ligand CCL2 (MCP-1) is produced in several organs in response to infection, and CCR2 deficient mice supported a role of this chemokine receptor in monocyte and DC infiltration into inflamed organs (83, 84). This traditional view of CCR2-mediated immigration of monocytes from the blood into inflamed or infected tissue (43, 44, 85) has recently been challenged by the demonstration that egress of monocytes from the bone marrow into the circulation requires their expression of CCR2 (41, 42). In this setting, CCL2 (MCP-1) produced in inflamed tissues might reach the bone-marrow via the blood stream, to promote egress of monocytes (Figure 1). These findings warrant revisiting prior findings showing reduced DC and macrophage recruitment into inflamed tissue of CCR2-deficient mice (43, 45). However, ample experimental evidence remains to support an additional role of this chemokine receptor in the tissue entry of DC precursors in infection (25, 44, 46, 47) and also in autoimmunity, as CCR2, but not CCR5 or CCR6 mediated infiltration of inflammatory DCs in allergic airway inflammation (86).

4.3. Role of CCR2 / CCL2 (MCP-1) in recruitment of DC involved in innate immunity

In addition to the well-described role of DCs as inducers of adaptive immune responses, recent studies have proposed a role of conventional DCs also in innate immunity against bacterial infection (41). In particular, a CCR2-dependent conventional DC subpopulation termed "Tip-DCs" produced TNFalpha and iNOS, which were critical for the defense against Listeria monocytogenes infection. Their absence in CCR2 deficient mice resulted in high susceptibility to this infection (17). Tip-DCs seem to be derived from $Gr1^{HI}$ monocytes (41) and have also been observed in Salmonella infection (87) and in a murine model of bacterial urinary tract infection by uropathogenic *E. coli* (85). However, their contribution to overall production of these two mediators in urinary tract infection was small, and their absence in CCR2-deficient mice did not increase susceptibility to infection. Thus, Tip-DCs do not seem to be generally required for anti-bacterial innate immunity.

4.4. Role of CCR1, CCR5, CCR6, CCR8 and CCR9 in DC recruitment and migration

DCs also express the inflammatory chemokine receptors CCR1, CCR5, CCR6, CCR8 and CCR9 and appear to use them for recruitment to inflamed sites and/or to LNs (Figure 1). In mucosal immunity against entero-invasive *Salmonella typhimurium*, $CCR6^+$ DCs were recruited from the interfollicular regions of the Peyer's patches to the dome-region, which is located right beneath the epithelium and therefore represents a strategic position to capture pathogens from the intestinal lumen (50). Indeed, these DCs colocalized with *Salmonella*-specific $CD4^+$ T cells and induced their proliferation and expansion, implying presentation of bacterial antigen. This process must have been functionally relevant, as lack of $CCR6^+$ DCs increased the number of bacteria in the liver (50).

In general, DCs in Peyer's patches and lamina propria differentially express CCR6, and $CCR6^+$ DCs in Peyer's patches are essential for local adaptive immune response against entero-invasive pathogens (88). CCR6-deficient mice mounted an impaired humoral immune response to orally administered antigens and to enteropathic rotavirus. In contrast, responses to subcutaneous antigens were normal in these animals, suggesting that CCR6 is a mucosa-specific regulator of humoral immunity and of lymphocyte homeostasis in the intestinal mucosa (88). In line, repopulation of inflamed skin by dermal DCs requires CCR2, but not CCR6 (89). In sterile lung inflammation, DCs also used CCR6 for recruitment from the bloodstream, in order to traverse alveolar epithelium (90). They also required CCR2 for this purpose, in order to cross vascular endothelium (90). Another chemokine receptor specifically relevant in DC migration in the intestine under inflammatory conditions may be CCR9, as CCR9-dependent recruitment of plasmacytoid DCs is a prerequisite for the rapid mobilization of conventional DCs from the lamina propria (91).

CCR5 contributed to inflammatory recruitment of mononuclear phagocytes and DCs in several models. In thermal cornea damage, it mediated recruitment of DCs towards inflammation (48). In diet-induced atherosclerosis in $ApoE^{-/-}$ mice, lack of CCR5, but not of CCR1, reduced monocyte infiltration and ameliorated atherosclerosis (92). CCR5 appears to be employed by both monocyte subsets

for emigration into atherosclerotic lesions (46). There is most likely functional redundancy between these receptors, since two of the three chemokine ligands of CCR5 also bind to CCR1 (CCL3=MIP-1a and CCL5=RANTES), as demonstrated using *in vitro* transmigration assays (93). Furthermore, CCR5 is expressed also on activated T cells (94), including regulatory T cells (95), so that biological effects observed in knockout mice often cannot be easily attributed to DCs. Apart from effects on DC migration and its role as co-receptor for HIV entry (see above), CCR5 has recently been shown to act as a pattern recognition receptor for a mycobacterial heat shock protein, which triggered DC maturation (96). Also, it has been shown to be recruited to the immunological synapse of DCs, where it increased costimulation of T cells during priming (49). Finally, an indirect role of CCR5 in DC biology has been described in classical cross-priming, where $CD4^+$ T cells engaged in licensing cross-presenting DCs (97) secreted the CCR5 ligands CCL3 (MIP-1a) and CCL4 (MIP-1b), which recruited naïve CD8 T cells towards the DCs for activation (98).

Little is known about the function of CCR8 that is highly expressed by monocyte-derived DCs in models using intradermal injection of particulate antigens. However, similar to CCR7, monocyte-derived DCs have been shown to use it for migration to the skin-draining lymph node (26).

4.5. CX3CR1-mediated effects on DCs

Virtually all organs contain a network of resident DCs, which is thought to serve as a sentinel system against microbes or other inflammatory challenges (27). Especially dense networks have been described in the kidney (99, 100) and in the gut (50). These resident DCs can be visualized particularly well with the use of transgenic mice expressing green fluorescent protein instead of one of the two CX_3CR1 genes under control of its natural promoter (25). Intravital microscopy revealed that interstitial GFP^+ DCs continually probed the surrounding tissue environment using dendrite extensions. These observations have led to the hypothesis that resident DCs use CX_3CR1 to enter non-inflamed tissues. Conclusive results have been found in the lung, where Gr-1^{LO} CX_3CR1^{HI} monocytes appeared to contribute to the turnover of pulmonary DC populations in the steady state (23). However, Gr-1^{HI} monocytes (expressing comparatively low levels of CX_3CR1) used CX_3CR1 for emigration into atherosclerotic lesions of chronically inflamed vasculature, as opposed to their Gr-1^{LO} counterparts (46). This suggests that different mechanisms may exist for CX_3CR1-dependent recruitment under homeostatic and inflammatory conditions. Furthermore, the expression of CX_3CR1 by DCs in the tissue does not allow to directly draw conclusions about their precursor, as cell may up- or downregulate CX_3CR1 during their differentiation.

In the small intestine, lamina propria DCs were reported to require CX_3CR1 for formation of transepithelial dendrites, which were required for acquisition of luminal bacterial antigens and for clearance of entero-invasive pathogens (50). The general relevance of these findings for intestinal infections is unclear, as it was later shown that TLR signaling by gut epithelial cells was responsible for such dendrite formation (101) and that acquisition of a fungal antigen did not require these dendrites at all (102). In the inflamed cornea, CX_3CR1 was required for DC recruitment into the stroma and epithelium (103). The involvement of CX_3CR1 in inflammatory DC recruitment sheds further doubt on the proposed dichotomy of CX_3CR1-dependent monocytes for homeostatic DCs, and CCR2-dependent monocytes for inflammatory DC recruitment.

4.6. CCL19 (ELC, MIP-3beta) and CCL21 (SLC, 6Ckine) -mediated effects on DCs via CCR7

DC migration triggered by microbial stimuli or by inflammatory cytokines (104) is accompanied by fundamental changes in the chemokine receptor expression profile, such as downregulation of CCR2 and CCR5 (53), which mediate tissue immigration from the bloodstream, and upregulation of CCR7 or CCR4 (52). CCR7 is the dominant chemokine receptor mediating migration of DCs to draining LNs (Figure 1) (51). In CCR7-deficient mice, DC migration from the skin, gut, eye and lung into draining LNs was reported to be severely impaired (32, 34, 35, 51, 105). In order to reach these LNs, DCs first have to enter the lymphatics possibly via adhesion molecules such as ICAM –1 or JAM-1 (20). DCs migrate towards CCL21 (SLC, 6Ckine)-leu expressed inside of lymphatic vessels, resulting in their arrival in the subcapsular sinus of the draining LN (19, 20, 106). There they are further directed towards the paracortex by CCL21 (SLC, 6Ckine) -ser or CCL19 (ELC, MIP-3β) derived from stroma cells and high endothelial venules in order to reach the site of T cell activation (19, 107). Maturing DCs can also produce CCL19 themselves, and thereby induce signaling involved in rearrangement of the cytoskeleton (52, 54). Therefore, DCs may use paracrine or autocrine mechanisms for CCR7-dependent migration. However, the expression of CCR7 alone is not sufficient for DC migration. Further signals such as lipid mediators, cysteinyl leukotriens, prostaglandin E_2, and CD38 are required to sensitize CCR7 to its ligands CCL19 (ELC, MIP-3beta) and CCL21 (SLC, 6Ckine) (20). Possibly, these mediators alter intracellular signaling pathways, but the exact mechanisms are unclear. Additional factors described to influence DC migration include sphingosine-1-phosphate (108), histamine, adenosine, and prostaglandin-D_2 (20).

In the absence of inflammation, CCR7-dependent constitutive migration of immature DCs to organ-draining LN has been observed, for example in the skin (35). Such "steady-state" DC migration is thought to be important for peripheral T cell tolerance against organ-derived antigens (2). Tolerogenic cross-presentation of antigen to $CD8^+$T cells (cross-tolerance) has been shown to apply to pancreatic or kidney self antigen in the respective organ-draining LN (15, 37). It is unresolved whether cross-tolerizing DCs were migratory or whether LN-resident $CD8^+$ DCs after capturing antigen from organ derived steady-state migrating ones mediated tolerance.

CCR7 not only acts as a chemotactic receptor on DCs. Both its ligands increase the endocytotic capability of

DCs (109). Furthermore, CCR7 protected human monocyte-derived DCs from apoptosis induced by serum deprivation (110). Both CCL19 and CCL21 have been reported to induce DC maturation, upregulation of costimulatory molecules such as CD80 and CD86 and result in secretion of inflammatory cytokines such as IL-12, TNFα and IL-1 (111). Furthermore, DCs from paucity of lymph nodes (plt) mice, a natural mutation deficient for CCL21-ser (SLC, 6Ckine) and CCL19 (ELC, MIP-3beta), showed reduced maturation (112). To mediate such diverse cellular effects, CCR7 engages various signaling pathways (54). In DCs, cdc42-rac mediates endocytosis, whereas PI3 kinase controls cell survival (54). The selective effects of CCL19 (ELC, MIP-3beta) and CCL21 (SLC, 6Ckine) in regulation of DC survival, maturation, and chemotaxis are generally difficult to distinguish.

4.7. Effect of CCL17 (TARC) and CCL22 (MDC) produced by DCs on T cells via CCR4

In mice, CCL17 (TARC) was originally identified by comparing gene expression profiles between macrophages and bone marrow-derived DCs (113). *In vivo* it is expressed by thymic DCs and by DCs in lymph nodes and in the lung. No expression was found in B or T cells (113, 114). Recombinant murine CCL17 (TARC) lacked chemotactic activity on naive $CD4^+$ T cells, but attracted antigen-primed $CD4^+$ T cells with preference for the Th2 phenotype by interacting with CCR4 (113). This *in vitro* observation was confirmed *in vivo* using murine Th2-dependent disease models, for example allergic airway inflammation (115) or atopic dermatitis (116). Mice deficient for CCL17 (TARC) showed diminished T-cell dependent contact hypersensitivity and delayed allogeneic rejection of heart transplants (114). Interestingly, CCL17 (TARC) was not detected in the spleen, even in the presence of systemic bacterial infection (114). A functional involvement of CCL17 (TARC) was demonstrated in LPS- and in *Propionibacterium acnes*-induced fulminant hepatitis, where it recruited IL-4 producing and liver-infiltrating $CCR4^+$ CD4 T cells (117).

The CCL17-receptor CCR4 has been detected on Langerhans cells, monocytes, NK cells, platelets, memory T cells and $CD25^+$ regulatory T cells (53, 114, 118). It also recognizes CCL22 (MDC=macrophage–derived chemokine) (67), whose function is less defined than that of CCL17 (TARC). CCR4 mediated homing of CD4 T cells to the skin, but not to mucosal tissue (59). Both the production of CCL17 (TARC) by mature DCs and the expression of CCR4 on T cells, as well as functional studies (119) suggest that it promotes T-cell–DC interaction during antigen specific activation. It is unknown whether CCL17 (TARC) exerts cell-intrinsic CCR4-mediated effects on T cells during priming. Recent studies highlighted an additional role of CCR4 for the trafficking of regulatory T cells in inflammatory models, e.g. of inflammatory bowel disease (120, 121).

Despite the often cited association of CCL17 (TARC) and CCR4 with Th2 polarization (67), the CCR4-deficient mouse showed unimpaired Th2 response, but unexpectedly was protected from LPS-induced endotoxic shock (122). Furthermore, allograft rejection was delayed in these animals (123). Consistent with these findings, CCL17 (TARC) is strongly upregulated in DCs in response to various TLR ligands, correlating with increased production of Th1 cytokines such as IL-12 (114). Thus, the paradigm of the Th2 association of CCR4-CCL17 responses seems to require further studies.

4.8. Effect of CXCL9 (MIG), CXCL 10 (IP10) and CXCL 11 (ITAC) produced by DCs on Th1 cells via CXCR3

Three related chemokines, CXCL9 (MIG), CXCL10 (IP10) and CXCL11 (ITAC) are ligands for the two isoforms of the chemokine receptor CXCR3 (124), which is expressed by activated $CD4^+$ Th1 cells, $CD8^+$ T cells and NK cells (61-63). Production of the three CXCR3 ligands is induced by IFNγ in various cells, including DCs and macrophages. Also some TLR ligands have been reported to further increase secretion of these chemokines (125).

In the T cell activation phase, DCs inducing Th1 responses selectively produced CXCR3 ligands in order to retain Th1-commited T cells in the lymph node for optimal priming (26). During the effector phase, CXCR3 ligands produced by tissue-resident DCs and/or by intrinsic tissue cells recruited Th1 effector T cells from the circulation to the site of injury, for example in delayed type hypersensitivity responses (126, 127). Interestingly, CXCR3 is used by activated $CD8^+$ effector T cells also for entry into lymph nodes and for killing CXCR3-ligand-producing DCs that present cognate antigen, perhaps in order to prevent further priming of specific $CD8^+$ T cells after sufficient of these cells have been generated (128). Thus, CXCR3 appears to drive Th1 responses not only in the priming phase of adaptive immunity in draining lymph nodes, but also in the effector phase in peripheral and lymphoid tissues. As all of the three CXCR3 ligands are specific agonists for this receptor (61, 62), and even appear to act as antagonists for the Th2 chemokine receptor CCR3 (129), it is currently thought that CXCR3 signaling is used by the immune system to selectively induce Th1 immunity.

Also in various Th1-type inflammatory diseases, a role of CXCR3-signaling has been observed, e.g. rheumatoid arthritis (65), multiple sclerosis (61), skin diseases (126, 130, 131), type 1 diabetes (132), lung, bowel and renal transplant rejection (62, 133, 134) and glomerulonephritis (127, 135), as evidenced by protection of CXCR3-deficient mice in murine models of these diseases. Concurrent expression of the three CXCR3 ligands is observed in many disease models, such as the tubulointerstitial kidney compartment (136, 137), where DCs are abundant (99) or in the lung (134). However, in most of these studies, the exact cellular source of these chemokines was not elucidated, so that the contribution of DCs to their production remains to be clarified. In HIV infection, virally infected DCs selectively expressed CXCL10 (IP10) and 11 (ITAC), which was interpreted as viral strategy to attract CD4 T cells towards infected cells for purposes of viral spreading.

Interestingly, in some disease models, genetic or antibody-mediated incapacitation of CXCL10 (IP10) was sufficient for protection (138, 139), demonstrating preferential use of only one of the three CXCR3 ligands. Similar observations were also made in infection models, which were exacerbated after blocking of individual chemokines (134, 140). It is unknown, whether this was due to differences in the cellular or tissue expression profile of the chemokines, or to particularities of the infectious condition studied.

5. VIRAL EXPLOITATION OF CHEMOKINES RECEPTORS EXPRESSED BY DCS

Many viruses exploit chemokines or their receptors for purposes of infection. Probably the best known example is the essential role of CCR5 in entry of C5-trophic HIV into monocytes, DCs and macrophages, which allows the virus to spread into deep tissue compartments (141, 142). Based on the resistance of individuals bearing a mutation of CCR5 to HIV infection, therapeutical trials using CCR5 inhibitors are currently being performed (143).

The human cytomegalovirus uses a different strategy to exploits the chemokine system: It downregulates CCR1 and CCR5 in infected DCs, and thereby inhibits induction of adaptive immunity by impairing DC migration (144). Moreover, it causes production of a soluble chemokine receptor analogon, which can bind and incapacitate several chemokines such as the CCR5 ligand CCL4 (MIP-1b) (145). A further example is the poxvirus *molluscum contagiosum*, which produces a CCR8 inhibitor capable of inhibiting migration of human monocytes and DCs (146). More information of these and several other cases of viral exploits of the chemokine system can be found in specialized reviews (147, 148).

6. CONCLUDING REMARKS

The different stages of the DC life cycle are stringently controlled by distinct chemokines and their receptors. Some of these mechanisms have recently been elucidated, but many remain unresolved or controversial. Exact knowledge of these mechanisms is crucial not only for understanding basic immune mechanisms, such as those regulating DC lineage and migration, or microbial immune escape, but may also facilitate the development of novel therapeutic strategies aimed at selectively modifying DC responses. Recent advances in the use of chemokine receptor inhibitors highlight their potential for designing more effective therapies with fewer side effects (149, 150).

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Abbreviations: APC: antigen-presenting cell, BM: bone-marrow, DC: dendritic cell, IFN: interferon, IL: interleukin, iNOS: inducible NO-synthetase, LN: lymph node, TNF: tumor necrosis factor

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