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Dendritic cell biology and regulation of dendritic cell trafficking by chemokines

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Abstract. DC (dendritic cells) represent an heterogeneous family of cells which function as sentinels of the immune system. They traffic from the blood to the tissues where, while immature, they capture antigens. Then, following inflammatory stimuli, they leave the tissues and move to the draining lymphoid organs where, converted into mature DC, they prime naive T cells. The key role of DC migration in their sentinel function led to the investigation of the chemokine responsiveness of DC populations during their development and maturation. These studies have shown that immature DC respond to many CC and CXC chemokines (MIP-1α, MIP-1β, MIP-3α, MIP-5, MCP-3, MCP-4, RANTES, TECK and SDF-1) which are inducible upon inflammatory stimuli. Importantly, each immature DC population displays a unique spectrum of chemokine responsiveness. For examples, Langerhans cells migrate selectively to MIP-3α (via CCR6), blood CD11c$^+$ DC to MCP chemokines (via CCR2), monocytes derived-DC respond to MIP-1α/β (via CCR1 and CCR5), while blood CD11c$^-$ DC precursors do not respond to any of these chemokines. All these chemokines are inducible upon inflammatory stimuli, in particular MIP-3α, which is only detected within inflamed epithelium, a site of antigen entry known to be infiltrated by immature DC. In contrast to immature DC, mature DC lose their responsiveness to most of these inflammatory chemokines through receptor down-regulation or desensitization, but acquire responsiveness to ELC/MIP-3β and SLC/6Ckine as a consequence of CCR7 up-regulation. ELC/MIP-3β and SLC/6Ckine are specifically expressed in the T-cell-rich areas where mature DC home to become interdigitating DC. Altogether, these observations suggest that the inflammatory chemokines secreted at the site of pathogen invasion will determine the DC subset recruited and will influence the class of the immune response initiated. In contrast, MIP-3β/6Ckine have a determinant role in the accumulation of antigen-loaded mature DC in T cell-rich areas of the draining lymph node, as illustrated by recent observations in mice deficient for CCR7 or SLC/6Ckine. A better understanding of the regulation of DC trafficking might offer new opportunities of therapeutic interventions to suppress, stimulate or deviate the immune response.

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Introduction: life cycle of dendritic cells

Dendritic cells (DC) are bone marrow-derived leukocytes which function as sentinels of the immune system [4, 87, 102]. DC precursors migrate from the bone marrow through the blood stream to almost every tissue, where they eventually become resident immature DC. Langerhans cells (LC) in the epidermis are the best studied example of immature DC, which show a high ability for antigen uptake but a low capacity for antigen presentation. During pathogen invasion, immature DC capture intruder antigens, and quickly leave the epidermis. They crawl through the dermis, cross the endothelium of lymphatic vessels and migrate to the draining lymph node. During their migration from the peripheral tissues, DC undergo phenotypical and functional maturation. Most remarkably, they stop to capture antigens while up-regulating the expression of co-stimulatory molecules. After reaching the subcapsular sinus of the lymph node, DC move to the areas (T cell areas) through which T cells, recruited from the blood, percolate. Recognized there as interdigitating DC (IDC), they are actively involved in the presentation of antigen to naive T cells. The presentation of antigen to the appropriate T cells seems to be the ultimate mission of the DC recruited from the periphery, as most of them disappear in the T cell areas, most likely by apoptosis.

The complex pattern of DC migration favors the presentation of antigen, captured at the periphery, to the rare antigen-specific T cells, and the activation and subsequent clonal expansion of these T cells.

DC perform different functions in distinct anatomical sites

Steps of DC maturation

From the outlines of their life cycle, DC appear as migratory cells moving from one site to the next to perform specific functions for which they acquire specific abilities through a stepwise maturation. Although oversimplifying the reality, the characterization of four individual steps of DC maturation has been possible through the analysis of in vitro generated DC either from monocytes cultured in the presence of GM-CSF and IL-4 [86] or from $CD34^+$-hematopoietic progenitor cells (HPC) cultured in GM-CSF plus TNF-α [15]. Step 1 represents a probably heterogeneous stage of DC precursors that corresponds to cells found in vivo in the bone marrow and blood stream which displays the ability to secrete large amounts of profinflammatory and/or anti-viral cytokines. Step 2 represents a stage of immature DC in the periphery characterized by very active receptor-dependent and -independent endocytic activity and by the lack of expression of co-stimulatory molecules, for which LC represent an in vivo example. Step 3 represents a stage in which maturing DC, after perceiving the "danger" signal provided by bacterial products (LPS) or inflammatory mediators (IL-1, TNF-α), lose their expression of endocytic receptors such as the mannose receptor, the asialoglycoprotein receptor, or Langerin [85, 109, 110] and their capacity to uptake antigen (Fig. 1). In contrast, these mature DC exhibit the phenotype and functions of antigen-presenting cells able to efficiently prime naive $CD4^+$ T cells. In particular, co-stimulatory molecules (CD54, CD58, CD80 and CD86) are up-regulated and importantly, a

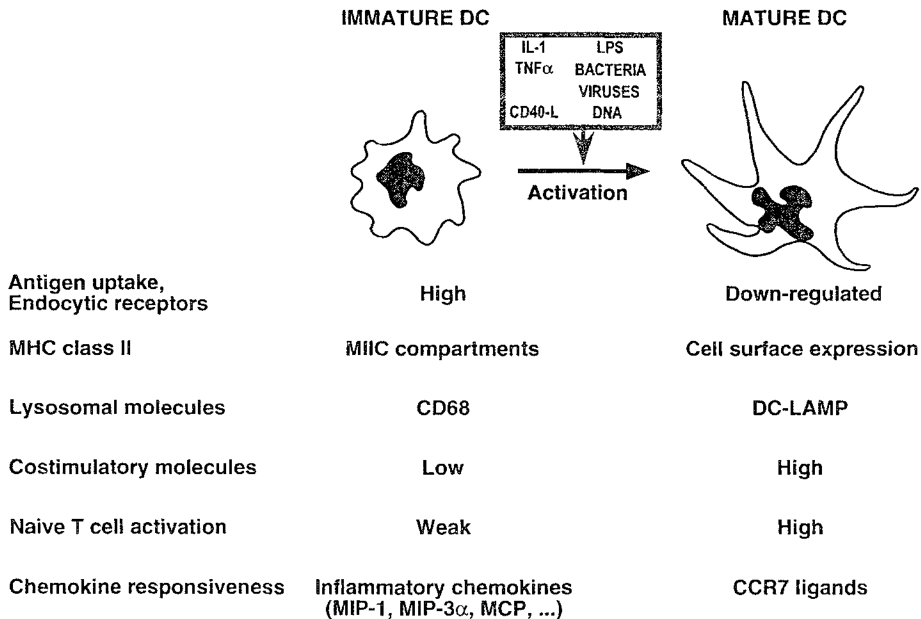

Fig. 1. Inflammatory stimuli and T cell signals trigger dendritic cell (DC) maturation. During infection, inflammatory cytokines (IL-1, TNF-α), bacterial and viral products (LPS, CpG, double-strand RNA), cell death and T cell factors [CD40 ligand (L)] trigger DC maturation characterized by changes in morphology, phenotype and functions. DC activation allows DC survival and induces loss of antigen uptake capacity, up-regulation of co-activation molecules, secretion of regulatory cytokines (IL-10, IL-12) and chemokines, changes in lysosomal protein expression (DC-LAMP>>CD68), translocation of MHC class II at cell surface and up-regulation of the capacity to activate naive T cells. Also DC activation induces loss of responsiveness to various inflammatory chemokines (MIP-1α, MIP-3α, RANTES) and induction of migration in response to ELC/MIP-3β and SLC/6Ckine related to CCR7 up-regulation. The immature stage of DC corresponds to peripheral DC such as Langerhans cells. The mature stage of DC corresponds to interdigitating cells of secondary lymphoid organs

shift in lysosome membrane glycoprotein content occurs with down-regulation of CD68 and up-regulation of DC-LAMP [25]. Finally, the MHC class II molecules are translocated from the lysosomal MHC class II compartments to the cell surface [18, 74]. Stage 4 represents further activation, i.e., through CD40L, which has been suggested to endow a "mature-activated" DC with the capacity to present antigen to naive $CD8^+$ T cells [2, 52].

Heterogeneity among populations of immature DC

DC form an heterogeneous family of cells with characteristic features. Their heterogeneity in terms of origin and functions is not yet fully elucidated. Although this represents an over-simplification, immature DC can be classified into four distinct groups of related cells: the epithelial DC (LC), the interstitial DC (dermal DC), the monocyte derived-DC, and the $CD11c^-$ DC precursors.

Epithelial DC

LC represent a population of DC only found in epithelia, and whose specific function remains unclear. LC are characterized by the selective expression of CD1a, a non-polymorphic class I-like molecule probably involved in glycolipid presentation [65]. Furthermore, LC contain a unique organelle, the Birbeck granule, which is formed from the cell surface through engagement of Langerin, a recently identified C-type lectin [110]. Its unique expression on LC suggests that Langerin provides LC with unique antigen uptake and migration capacities. The origin of LC is still a matter of controversy, but several studies have shown that LC are regulated independently from other DC populations. In particular, they develop from CD34^{+} progenitor from independent precursors [17]. Importantly, transforming growth factor (TGF)-β has been identified as an essential factor for the selective development of LC, both in vitro and in vivo.

Interstitial DC

Interstitial DC were initially characterized in heart, using monoclonal antibodies (mAb) against HLA class II or CD45; DC have subsequently been identified in the interstitium of most organs and tissues (liver, kidney, pancreas, ureter, bladder, thyroid, gut, dermis) [44]. The interstitial DC sit in the extravascular areas and their dendritic processes extend into the interstitium for a considerable distance away from the cell body. In these tissues, the DC are loosely bound to blood vessels and possibly lymphatics. These cells are characterized by the expression of CD68 and Factor XIIIa, and the lack of LC markers [55, 68]. They might be related to circulating blood CD11c^{+} DC, which themselves are phenotypically identical to germinal center (GC) DC [39]. In terms of origin, they have been proposed to derive from CD14 precursors which develop from CD34 progenitors [17]. They also display phenotypic and functional similarities with monocyte-derived DC (MDDC).

Monocyte-derived DC

Monocytes can differentiate in vitro, without proliferation, into $CD1_a^+$ DC upon culture with GM-CSF and IL-4 [82, 86]. Monocytes can also differentiate into DC in vitro upon reverse migration through endothelial cell layer [76]. Furthermore, this differentiation event has recently been reported to occur in vivo following inflammatory stimuli [78]. This pathway of DC development probably represents physiological events occurring during inflammatory reactions, as opposed to constitutive surveillance performed by resident interstitial or epithelial DC.

CD11c^{-} plasmacytoid DC precursors

In humans, another population of DC has been identified, the CD11c^{-}CD13^{-}DR+ CD123^{++} plasmacytoid DC precursors [40]. These cells have been identified in blood, tonsils and thymus. The pathway leading to the development of these cells from CD34^{+} HPC has not yet been documented. However, these cells probably represent an inde-

pendent population, and it has been suggested that they share a common precursor with lymphoid cells [79]. These cells might be related to the lymphoid DC described in mice by Shortman et al. [96]. The CD11c$^-$ precursors are dependent on IL-3 for survival in vitro and acquire the capacity to stimulate naive T cells when cultured with IL-3 and/or CD40 ligand (CD40L). Blood CD11c$^-$ DC precursors have recently been shown to correspond to the blood natural IFN-α producing cells (NIPC) involved in high level of IFN-α production during viral infection [97]. Although the physiology of this cell type remains obscure, it is likely that it plays an important role at the interface between innate and acquired immunity.

Germinal center DC

A population of large dendritic CD11c$^+$CD4$^+$CD3$^-$ cells was identified within the GC of human lymph nodes, tonsils and spleens [39]. These cells are characterized by a strong MHC class II expression, a morphology of DC, and a potent stimulatory activity on CD4$^+$ T cells. It is likely that these DC stimulate the GC T cells required for the generation of memory B cells. In addition, these cells also directly interact with GC B cells to sustain a high rate of proliferation, in particular in presence of IL-2 [28]. The presence of similar CD4$^+$CD11c$^+$ DC in blood suggests that GCDC might derive from precursors in blood.

Functional heterogeneity among DC subpopulations

In addition to the heterogeneity related to their origin, DC populations differ in their function.

Interaction with B cells

In particular, human DC subsets have been reported to exert different functions with regard to the regulation of B cell activation. CD14-derived DC (interstitial-type DC) and CD11c$^+$ DC from blood or B cell follicles in tonsils (GCDC) trigger naive B cell differentiation, an activity not shared by LC. DC populations with the ability to transfer antigen to B cells or to sustain B cell differentiation also have recently been described in mouse [34, 118]. Thus, some DC populations such as the interstitial DC might be involved in the regulation of humoral responses, while others such as epidermal DC might be mainly involved in cellular immune responses.

Modulation of T cell differentiation

Different studies in human and mouse have established that DC populations differ in their capacity to regulate the differentiation of T cell responses towards type I or type II. In man, it has been proposed that CD11c$^-$-derived DC play a role in the induction of Th2 cells [80], in contrast to MDDC which are recognized as being involved in Th1 responses through IL-12 production [20]. In mouse, the lymphoid-derived DC have been shown to induce in vivo the development of Th1 immune re-

sponses, through IL-12 production, while myeloid DC preferentially induce a Th2 response [60, 75].

Other functions

It has been suggested that mouse lymphoid DC play a role in the negative regulation of T cell activation, contributing to the maintenance of peripheral tolerance [96]. Finally, blood $CD11c^-$ DC corresponding to the blood NIPC [97] might play an important role in the initiation of antiviral immune responses.

Different immature DC populations are recruited by different chemokines

Each step of DC trafficking involved in either their steady-state distribution in peripheral and lymphoid organs, or in their recruitment upon inflammation / injury, is likely to be controlled, at least partially, by soluble chemotactic factors known as chemokines.

In vivo evidence for DC recruitment during inflammation

Newly generated DC migrate, presumably through the blood stream, from the bone marrow to non-lymphoid tissues where they eventually become resident cells. In the lung, DC accumulate rapidly (within an hour) in the respiratory tract mucosa after local challenge with a broad spectrum of stimuli including bacteria, viruses, soluble protein antigens, and haptens [63, 64, 71, 104, 120]. Furthermore, DC in blood are constitutively poised at the interface of blood and skin, and cutaneous inflammation results in a rapid recruitment of DC from the blood to tissues [81].

Finally, skin inflammation has also been shown to induce monocyte recruitment from blood which, following antigen uptake, differentiate into DC and emigrate through lymphatic vessels to draining lymph nodes [78]. In this context, accelerated influx of DC into draining lymph node also occurs following skin parasite infection [92].

As for other leukocytes, DC recruitment, across endothelium into tissue, is a multistep process that involves selectin-supported rolling, followed by a triggering event mediated by chemokines and then firm integrin-mediated adhesion [12]. The E- and P-selectins have been shown to be involved in DC rolling on endothelium in vivo [81]. The integrin CD18 also appears to be involved in the recruitment of DC within lung tissues [95]. In addition, DC produce several matrix-metalloproteases (MMP), including a recently identified member of the membrane anchor MT-MMP (de Saint Vis, submitted), probably involved in the breaching of the basal membrane, a required activity for DC trafficking.

Differential responsiveness to chemokines (Tables 1 and 2)

The above-described accumulations of DC probably represent recruitment of circulating DC precursors through the production of chemokine upon local inflammation.

Table 1. Each DC subset expresses a restricted set of chemokine receptors

Receptor	Ligands	Monocytes	MDDC	CD1a-DC	CD14⁻DC	Blood 11c⁺	Blood 1c⁻
CCR1	MIP-α	+	++	–/low	+	+	+
CCR2	MCP-1	++	–	–	++	++	+
CCR3[a]	Eotaxin	–	+	–/low	–/low	–/+	–/+
CCR4[b]	TARC,MDC	ND	–	–	–	–	–
CCR5	MIP-1β, RANTES	+	+	–	–	+	+
CCR6	MIP-3α	–	–	+++	++	–	–
CCR7	MIP-3β, 6Ckine	–	++ (mature)	++ (mature)	++ (mature)	++ (mature)	++ (mature)
CCR8[b]	1309, TARC	–	–	–	–	–	–
CCR9[b]	TECK	–	+	+	+	ND	ND
CXCR1	IL-8	–	–	–	–	–	–
CXCR2	IL-8	–	–	–	–	–	–
CXCR3[c]	IP-10, MIG	–	–	–	–	low/+	+++
CXCR4[d]	SDF-1	+	low/+	low/+	low/+	++	++
CXCR5	BCA-1	–	–	–	–	ND	ND
XCR1[e]	Lymphotactin	–	–	–	–	ND	ND
CX3CR[e]	Fractalkine	+	–	ND	ND	ND	ND

Unless specified, the results represent cell surface expression determined by FACS analysis
[a] CCR3 expression was usually not detected at cell surface but expression was observed by intracytoplasmic staining and/or by PCR
[b] CCR4, CCR8 and CCR9 expressions were only studied by PCR
[c] CXCR3 expression was detected by FACS and PCR
[d] CXCR4 expression at cell surface was only detected following a few hours incubation at 37°C
[e] XCR1 and CX3CR1 expression were only detected by PCR

In vitro, immature DC respond to a large spectrum of chemokines such as MIP-1α, MIP-1β, MIP-3α, MIP-3β, MIP-5, MCP-3, MCP-4, RANTES, MDC, TECK, 6Ckine and SDF-1 [23, 24, 26, 91, 99–101, 119]. Furthermore, most of these responses have been confirmed in trans-endothelial migration assays [23, 58]. The chemokines listed above transduce a chemotactic signal, probably through CCR1, CCR2, CCR5, CCR6, CCR7 and CXCR4. Conversely, lymphotactin, eotaxin-1, TARC, IL-8, GRO-β, IP-10 and ENA-78 appear inactive on DC in vitro [24, 100, 101, 119]

It appears that many chemokines can induce DC migration in vitro. However, determination of the maturation level of DC, their origin and the signals regulating secretion of various chemokines, is a prerequisite to understanding the regulation of the migration of DC in vivo.

Recruitment of monocyte-derived DC

Monocytes and MDDC can respond to many inflammatory chemokines. Monocytes respond to the CC chemokines MCP-1 to 4, MIP-1α, MIP-1β, and RANTES, probably as a consequence of CCR1, -2 and -5 expression [61]. In addition, monocytes also respond to the CX3C chemokine fractalkine [5], while, with regard to CXC chemokines, they only respond to SDF-1 [8].

Table 2. Each DC subset responds to restricted set of chemokines. The results represent induction of migration and/or induction of calcium flux

		Monocytes	MDDC	CD1a-DC	CD14⁻DC	Blood 11c⁺	Blood 11c⁻
Chemokines	Receptors						
MIP-α	CCR1,5	++	+++	low/+	+	–	–
MCP-1	CCR2	++	–	–	++	+++	low/+
MCP-4	CCR2 + ?	++	++	–	++	+++	low/+
Eotaxin	CCR3?	–	–/low	–/low	–	+	low
TARC	CCR4	–	–	–	–	ND	ND
MDC	?	–	+	ND	ND	ND	ND
MIP-1 β	CCR5	++	++	–	–/low	–	–
RANTES	CCR1,3,5?	++	++	low/+	++	+	low/+
MIP-3α	CCR6	–	–	+++	++	–	–
MIP-3β, 6Ckine	CCR7,10?	–	++ (mature)	++ (mature)	++ (mature)	++ (mature)	++ (mature)
1309	CCR8	ND	–	–	–	ND	ND
TECK	CCR9,10?	–	–	ND	ND	ND	ND
IL-8	CXCR1	–	–	ND	ND	ND	ND
IL-8	CXCR2	–	–	ND	ND	ND	ND
IP-10, MIG	CXCR3	+ (IP-10)	–	–	–	–	–
SDF-1	CXCR4	+	low/+	low	low	+++	+++
BCA-1	CXCR5	–	–	ND	ND	ND	ND
Lymphotactin	XCR1	–	ND	ND	ND	ND	ND
Fractalkine	CX3CR	+	ND	ND	ND	ND	ND

The results in Tables 1 and 2 represent a compilation of studies referred to in the text as well as personal observations

MDDC, generated after 5–7 days of culture in the presence of GM-CSF + IL-4, have an overlapping pattern of chemokine responsiveness with monocytes ([91, 100, 101] and Caux, in preparation). MDDC respond to MCP-2, 3 and 4, but not to MCP-1, as a consequence of CCR2 down-regulation. The receptor(s) used by MCP-2, 3 and 4 on these MDDC have not yet been defined. MDDC respond to MIP-1α, MIP-1β and RANTES probably through CCR1 and CCR5. They have been reported to respond to eotaxin, although CCR3 is not always detected at the cell surface but is present inside the cells ([93] and Granelli-Piperno, reported at the 1999 Langerhans cell New York meeting). In addition, the chemokine MDC has been shown to induce potent migration of MDDC through a receptor other than CCR4 [9, 37]. The responsiveness of DDC to fractalkine has not been documented.

Thus, there are significant differences between MDDC and monocytes, such as the lack of MCP-1 response and the acquisition of MDC response.

Recruitment of blood CD11c⁺ DC

There is no extensive published information regarding the response of blood CD11c⁺ DC to chemokines. We have investigated this specific question, and have observed that blood CD11c⁺ DC respond to the CC chemokines MCP-1 to 4, RANTES, and to a lesser extent, to eotaxin. These responses probably involve CCR2 and CCR3. CCR3 expression, however, which would explain the response to eotaxin

(as well as to RANTES and some MCP), has never been detected at the cell surface, but has been strongly detected by PCR. In contrast to monocytes and MDDC, blood CD11c+ failed to respond to MIP-1α and MIP-1β over a wide range of concentrations, although CCR1 and CCR5 are expressed at the cell surface and can be modulated by these chemokines. Furthermore, the infection of these blood DC in vitro by HIV has been shown to be blocked by MIP-1α and MIP-1β [31. This would suggest that CCR1 and CCR5 might not be appropriately coupled to mediate chemotaxis, and are unlikely to be involved in RANTES-mediated migration. Regarding MDC, we have so far been unable to reach a conclusion due to lack of consistent positive migration with CD11c+ DC. Regarding CXC chemokines, SDF-1 induced a potent migration of CD11c+ DC, while CXCR1, 2 and 3 ligands were inactive.

In conclusion, the absence of CCR1- and CCR5-dependent chemotaxis of blood CD11c+ DC represents a major difference between these DC and monocytes and MDDC.

Key role of MIP-3α in epithelial DC recruitment (Fig. 2)

Among DC populations, LC have a unique anatomical localization at the epithelial surfaces. The elements that control this specificity are now starting to be understood,

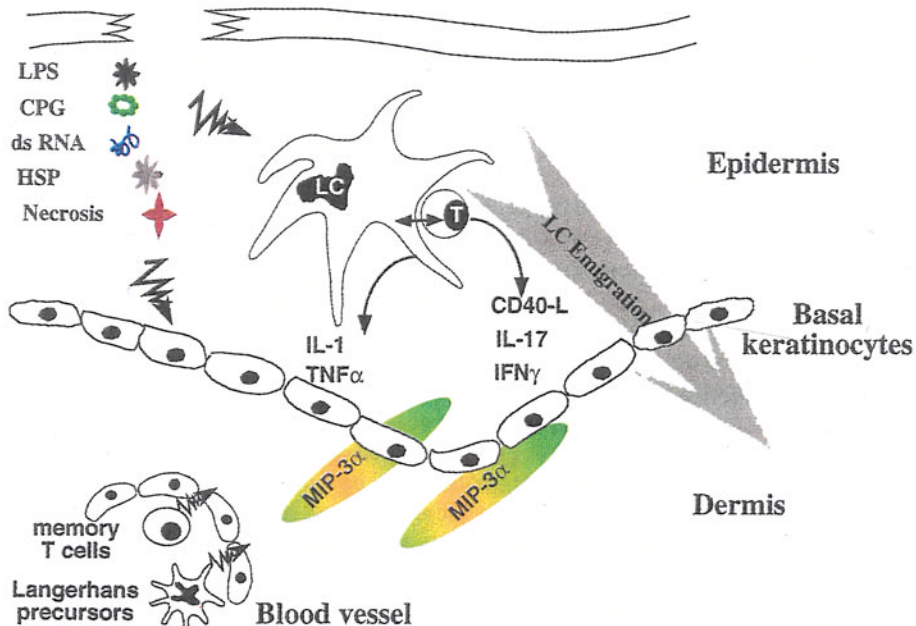

Fig. 2. Regulation of MIP-3α expression and Langerhans cell (LC) turnover at epithelial surfaces. During infection, many mediators released during inflammation directly activate LC that secrete cytokines such as IL-1 before emigration, and activate epithelial cells. Eventually, infectious antigens are presented locally to T cells that secrete cytokines such as IFN-γ, IL-17, and CD40L. All these factors cooperate to activate epithelial cells that produce chemokines, in particular MIP-3α. Thus, during infection, signals triggering LC emigration, allow, via the induction of MIP-3α secretion, the recolonization of epithelium by LC precursors as well as CCR6+ effector T cells with epithelial tropism

and include the potentially unique origin of LC [17, 103], chemotactic factors (i.e. chemokines) that are required for LC precursor recruitment (Dieu, submitted), an epithelial environment (i.e., TGF-β) that conditions their final differentiation [11, 16], and homing/adhesion molecules (i.e., CLA, E-cadherin) involved in their residency [106].

In contrast with the numerous chemokines inducing the migration of MDDC, relatively few chemokines can sustain the migration of LC. On CD34-derived LC precursors, activities of RANTES, MCP-3 and, to a lesser extent, MIP-lα were observed; the activity of eotaxin was inconsistent. No activity of MCP-1, 2 and 4, and MIP-lβ, and CXC chemokines except SDF-1 was detected (see Table 1 and Dieu, submitted).

Importantly, MIP-3α [46, 47, 83] appears to be the chemokine inducing the most potent responses of CD34-derived CDla+ LC precursors compared to RANTES or MCP-3 (Dieu, submitted). The activity of MIP-3α has been confirmed on ex vivo isolated LC [22] (Dieu, submitted), and so far only CD34-derived DC and ex vivo isolated LC have been shown to respond to MIP-3α in accordance with CCR6 expression (the only known receptor for MIP-3α). Neither monocytes, MDDC, nor ex vivo isolated blood DC populations respond to MIP-3α (Dieu, submitted). However, it has recently been shown that MDDC can express CCR6 and respond to MIP-3α when cultured with TGF-β [123], a factor previously reported as supporting LC differentiation from monocytes [35].

Regarding receptor expression, CD34-derived LC precursors express high levels of CCR6, and moderate levels of CCR1 and CCR5, but CCR2, CCR3, and CCR4 are undetectable, at least by cell surface staining. Thus, independent of their origin, MIP-3α appears to induce the selective migration of LC and LC precursors.

In humans, MIP-3α has recently been reported as being constitutively expressed by keratinocytes in the epidermal layer of the skin [22]. We have also observed MIP-3a expression in normal skin epithelium; however, the expression was weak and limited to the stratum corneum (Dieu, submitted). In vitro, using a specific ELISA, the spontaneous expression of MIP-3α was found to be restricted to cell lines of epithelial origin. The expression of MIP-3α was found to be up-regulated by inflammatory stimuli such as IL-1 and TNF-β, in particular in epithelial cells such as skin keratinocytes (Dieu 2, submitted). In addition, T cell factors such as CD40L, IL-17 and IFN-γ cooperate to induce strong levels of MIP-3α production by such cells. These observations might be particularly relevant to disease conditions involving epidermal infiltration by immune cells, as observed in psoriasis. Indeed, MIP-3α and CCR6 are strongly up-regulated in this pathology (Homey, submitted; Dieu, submitted). These observations suggest that, upon inflammation, the up-regulation of MIP-3α production may play an important role in the recruitment of LC precursors in the skin. However, this does not exclude a role for this chemokine in the constitutive recruitment of LC.

Interestingly, the expression of MIP-3α in situ in breast adenocarcinoma has been recently reported to be correlated with infiltration by DC with LC features [6], again arguing for a selective role of this chemokine in LC recruitment in epithelial tissues.

In vivo, MIP-3α is expressed at other epithelial surfaces. In the particular, MIP-3α has been shown in mice and humans to be abundantly expressed in the mucosa of the gut [105]. In human tonsils (a mucosa-associated lymphoid organ), we have observed a very strong expression of MIP-3α in the epithelial crypt, but not in the strat-

ified epithelium surrounding the lymphoid structure [26] (Dieu, submitted). This may reflect the fact that epithelial crypts are exposed to pathogens, while stratified epithelia are protected. Alternatively, it may reflect a difference in the type of epithelial cells, in particular the epithelial crypt contains specialized cells called "spongiform" cells, which probably correspond to the M cells of the gut involved in antigen/pathogen transport into the lymphoid structure. More recent observations have reported that, in the gut, MIP-3α was highly expressed in the epithelium of the dome of the Peyer's patches (Kelsall, reported at Keystone 2000; Cook, personal communication). This suggests that specialized epithelia involved in antigen/pathogen transport through M cells or "spongiform" cells and associated with mucosal lymphoid structures have the selective capacity to produce MIP-3α. Furthermore, the expression of MIP-3α in these epithelia is associated with CCR6-expressing cells in close vicinity of epithelial cells (Kelsall, reported at Keystone 2000; Dieu, submitted). These cells probably include memory B cells and memory T cells, known to respond to MIP-3α [56] and to be located in such areas in tonsils and Peyer's patches [59]. Furthermore, in the Peyer's patches a subset of DC, corresponding to $CD11b^+$ myeloid DC, which lines the dome epithelial layer, expresses CCR6 and represents the only DC population responding to MIP-3α (Kelsall, reported at Keystone 2000).

These observations suggest a key role for MIP-3α in the recruitment of immune cells, in particular a myeloid DC population, in the epithelium of Peyer's patches or the crypt of the tonsil, the site of antigen/pathogen entry.

The relationship between the mouse Peyer's patches $CD11b^+$ DC and LC is currently unknown; however, a population of DC percolating the epithelial crypt of human tonsils expresses CD1a, and thus is likely to be related to LC.

Finally, β defensins have been recently demonstrated to mediate chemotaxis of DC through CCR6 [122]. β defensins are also secreted by epithelial cells, and may represent alternative mediators of LC recruitment at epithelial surfaces. Altogether, these observations illustrate the key role of MIP-3α/CCR6 in the recruitment of LC type DC and other immune cells at the epithelial surface and argue for a unique role of this chemokine and LC in the regulation of epithelial immunity.

Selective migration of blood $CD11c^-$ DC precursors?

Through the production of high levels of IFN-α during viral infection, blood $CD11c^-$ DC precursors are likely to play an important role at the interface between innate and acquired immunity.

Regarding their recruitment, little information is available. However, among DC populations, generated in vitro or isolated ex-vivo, the $CD11c^-$ DC precursors represent the only population expressing L-selectin [19, 40] and thus are potentially directly recruited into secondary lymphoid organs from blood through high endothelial venules (HEV). Chemokines involved in such recruitment from blood have been described for lymphocytes, in particular the ligands for CCR7 (SLC/6Ckine, ELC/MIP-3β) play a key role in the traffic of naive T cells in the lymph nodes. However, resting $CD11c^-$ DC precursors do not respond to CCR7 ligands (unpublished observations). Other chemokines are likely to be involved in the entry of naive B cells and $CD11c^-$ DC precursors into lymph nodes from the blood. Most of the inflammatory chemokines active on other DC subsets appear to be unable to induce $CD11c^-$ DC migration. However, they have been described to express high levels of

CXCR3 [19], but migration induced by CXCR3 ligands has not yet been documented. The known ligands for CXCR3 are IP-10, MIG and I-TAC, three chemokines selectively induced by IFN-γ [29]. In addition, CXCR3 has been shown to be associated with T cells of Thl phenotype [10, 89]. This may represent a link between the role of CD11c⁻ DC precursors (NIPC) in antiviral responses and Thl-mediated immunity. These ligands have been proposed to play a role in the recruitment of effector cells at the site of inflammation.

Further studies will be required (1) to decipher whether the recruitment of CD11c⁻ precursors occurs at the site of inflammation or in lymphoid organs and (2) to identity the chemokines controlling their trafficking.

Conclusion

These observations support the notion that the different DC populations will probably not be recruited at the same anatomic site during a particular response, and that which one is recruited will depend in part on the chemokine gradient released at the site of injury. The type of resulting immune response will probably be dependent on the DC subpopulation recruited and, thus, on chemokines secreted.

Sequential chemokine responsiveness to reach the site of injury (Fig. 3)

Modulation of chemokine receptor expression during DC development/differentiation

The previous section illustrates that different DC populations are differentially responsive to chemokines. It is also apparent, however, that some populations derive from others, in a stepwise fashion, conditioned by the environment. In particular, monocytes can differentiate into DC, as a consequence of a combined action of GM-CSF and IL-4, or during reverse endothelial migration, both in vitro and in vivo [76, 78]. In this context, intradermal injection of a chemokine active on monocytes results in their local recruitment, as well as an increase in DC numbers in the draining lymph nodes, resulting in an enhanced immune response (A. Vicari, unpublished). Thus, monocytes represent precursors of DC that might be recruited into the tissue through chemokines not active on MDDC, such as MCP-1, known to be expressed by activated endothelial cells [51]. On the other hand, differentiating MDDC acquire new chemokine responsiveness, such as to MDC, potentially involved in trafficking through the tissue to reach the inflammatory site.

Along the same line, we have not succeeded in identifying circulating blood DC or DC precursors expressing CCR6. Furthermore, on CD14-derived DC from CD34 progenitors, a response to MCP chemokines precedes that of MIP-3α (Caux, in preparation). It can be hypothesized that, in vivo, LC precursors enter the tissue via an initial chemokine gradient (MCP?), and then, as a consequence of a specific microenvironment (TGF-β in the vicinity of epithelium?), CCR6 is up-regulated and the LC precursors are recruited to epidermis in response to MIP-3a. Alternatively, LC precursors might be present at a too low frequency in blood to be visualized in steady-state conditions, but upon ongoing responses their frequency in blood might increase as a consequence of GM-CSF release in the circulation.

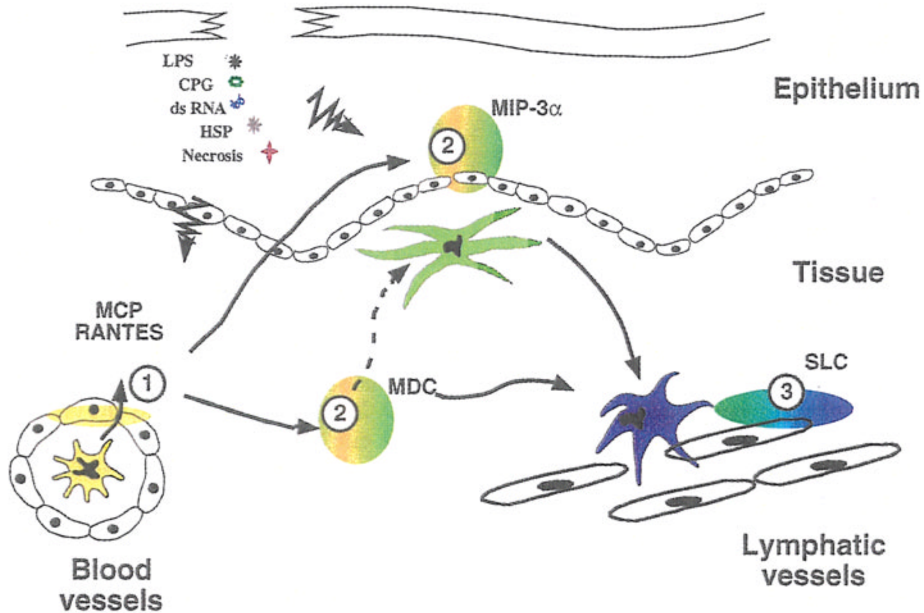

Fig. 3. Recruitment of DC at inflammatory sites involves the sequential action of different chemokines. During infection, inflammatory stimuli diffuse into the microenvironment and trigger chemokine production by the different cellular components. Activated endothelial cells expressing selectins secrete chemokines such as MCP and RANTES that allow circulating DC precursors to extravasate into the tissue (*1*). Depending on the type of DC precursor recruited and the cytokine milieu, other chemokine receptors are expressed on the infiltrating DC. The ligands for these receptors, produced by other cellular components, are probably involved in the navigation of the infiltrating DC (2). MDC, probably produced by resident interstial DC themselves, may allow trafficking of monocyte-derived DC into the interstitial space of the tissue up to the infected area, while MIP-3α expressed by the epithelial cells selectively allows LC recruitment in the epithelium. Following antigen capture, inflammatory stimuli trigger DC maturation characterized by the early expression of CCR7. SLC/6Ckine expressed by inflamed lymphatic endothelium, in return, facilitates migration through the lymphatic stream (*3*). The production of chemokines by resident DC, at the site of pathogen invasion, may be an important component of their sentinel function

Regulation of chemokine receptor expression by cytokines and other environmental factors

Cytokines produced at the site of injury can also influence the recruitment of DC precursors through modulation of chemokine receptors. In particular, IL-4 induces a down-regulation of CCR6 on CD34-derived DC ([14], and Dieu, in preparation), thus preventing their recruitment at the site of MIP-3α production. In addition to IL-4, IFN-γ also blocks CCR6 expression (Dieu, in preparation). In contrast, TGF-β has been shown to induce CCR6 expression on MDDC [93, 123]. We have also observed that IL-10 can induce CCR6 on MDDC (Dieu, in preparation).

Besides the induction of CCR6 on MDDC, TGF-β also increases the expression of other chemokine receptors (CCR1, CCR3, CCR5) and reciprocally blocks TNF-α-induced CCR7 expression [72, 93]. As CCR7 is a key receptor involved in the emigration of maturing DC out of the tissue (see below), TGF-β may control the turnover of LC both at the level of their recruitment and migration. In this context,

TGF-β has been reported to prevent maturation induced by inflammatory stimuli but not that induced by CD40L [36].

Source of chemokine production?

The chemokine produced will depend on the tissue itself and on the cytokine milieu. Each tissue has the capacity to produce a restricted set of chemokines differentially regulated by cytokines. In addition to endothelial cells, fibroblast and epithelial cells, infiltrating cells also contribute to the network of chemokines. In particular, the production of chemokines by DC has been suggested to play an important role in the recruitment of immune cells at the site of injury. As an example, MDDC rapidly produce large amounts of MIP-1α and MIP-1β [90] that can be released at the site of inflammation before emigration of the activated DC. In addition, MDC is a DC chemokine that has been reported to be expressed at the site of injury by DC [113]. These chemokines may be involved in the recruitment of other DC precursors at the site of injury to increase the efficiency of antigen uptake and secondary presentation to initially primed T cells in the draining node. In addition, DC chemokines may be involved in the recruitment of effector T cells. The production of chemokines by immature DC might represent an important contribution to their sentinel function.

Altogether, these observations show that DC recruitment into tissue probably requires sequential involvement of different chemokine receptors (blood extravasation, then navigation into tissue), whose expression is regulated during DC differentiation and controlled by immunomodulatory cytokines.

Recruitment of maturing DC into draining node and initiation of the immune response (Fig. 4)

As discussed previously, during injury inflammatory mediators such as IL-1, TNF, infectious agent products (such as LPS, CpG, DNA) or T cell products (such as CD40L, IFN-γ) drive DC maturation and induce maturing DC to emigrate out of the inflammatory site. A first consequence of this DC maturation is the loss of functions characterizing immature DC, in particular they lose antigen uptake capacity as a consequence of cytoskeleton re-arrangement and endocytic receptor down-regulation. Furthermore, the responsiveness to most of the inflammatory chemokines (MIP-lα, MIP-lβ, MCP1–4, RANTES, MIP-3α) is rapidly lost as a consequence of (1) a desensitization process involving saturation of their receptors by an endogenous production of ligands by activated DC [90, 91] and (2) a down-regulation of their receptor expression at the mRNA level [26, 33, 91, 99].

Concomitant to the loss of this chemokine responsiveness, the CCR7 receptor, not expressed by immature DC, is rapidly induced at the cell surface of maturing DC.

The known ligands for CCR7 are SLC/6Ckine/Exodus-2 and ELC/MIP-3β/Exodus-3 [45, 47, 66, 83, 124]. In addition to CCR7, these chemokines also bind to CCR10 [38], and in mouse but not in human, SLC/6Ckine is also a ligand for CXCR3 [98].

Contrary to many CC-inflammatory chemokines, ELC/MIP-3β and SLC/6Ckine have no chemotactic activity on immature DC. Both ligands have been reported by several groups to mediate potent migration of human and mouse mature DC through CCR7 [21, 26, 50, 72, 84, 91, 99, 112, 121]. All human DC subsets (CD34-derived,

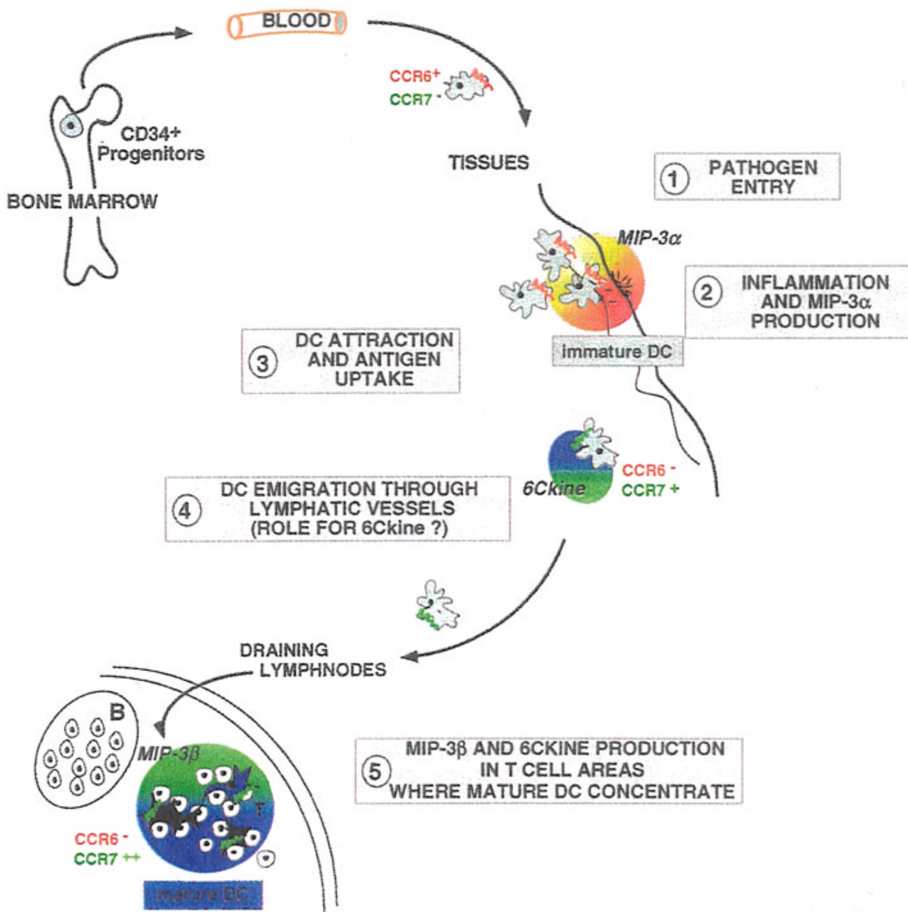

Fig. 4. Model of DC mobilization upon inflammation in vivo. It is tempting to speculate that during pathogen invasion (*1*), immature LC or their precursors, expressing CCR6, are attracted to the site of inflammation through the local production of chemokines such as MIP-3α (*2*). After antigen uptake (*3*), inflammatory stimuli turn off MIP-3α responsiveness (CCR6 down-regulation, desensitization), thereby enabling LC to escape the local gradient of MIP-3α. Maturing LC start to express CCR7 and emigrate to the lymph stream through SLC/6Ckine produced by activated lymphatic vessels (*4*). Maturing LC entering into the draining lymph node home to the paracortical area in response to the production of ELC/MIP-3β and/or SLC/6Ckine by cells spread over the T cell zone (*5*). As ELC/MIP-3β and/or SLC/6Ckine can attract mature DC and lymphocytes, they probably play a key role in helping antigen-loaded DC to meet specific T cells (*5*)

MDDC, Blood $CD11c^+$, $CD11c^-$) respond to MIP-3β and SLC/6Ckine upon maturation ([26], and unpublished data).

Entry into lymphatic vessels, a control step?

In the mouse, SLC/6Ckine has been shown to be expressed by endothelial lymphatic vessels draining non-lymphoid tissues [43]. Furthermore, still in mouse, exogenous

SLC/6Ckine has been shown to increase the yield of DC emigrating out of skin explants in vitro [50], and blocking SLC/6Ckine in vivo impaired emigration of DC out of the dermis [84]. In addition, we observed that SLC/6Ckine gene transfer in mouse tumors triggers a massive infiltration by CCR7-expressing DC (Vicari, submitted). Surprisingly, these DC display an immature phenotype, suggesting that in vivo SLC/6Ckine can recruit DC that are not fully mature, which might correspond to cells entering into the lymphatic stream. Finally, we have found that, although SLC/6Ckine is constitutively expressed on mouse lymphatic endothelium, its expression is strongly up-regulated a few hours following LPS injection. This might suggest that the entry into lymphatics by maturing $CCR7^+$ DC is regulated by the level of SLC/6Ckine expressed by lymphatic vessels, itself under the control of inflammatory stimuli. In addition, two genes encoding for SLC/6Ckine have been reported in mouse [111]; these two genes are differentially expressed in tissues and lymphoid organs. So far, only one gene encoding for human SLC/6Ckine has been described, and SLC/6Ckine has been documented in the T cell area of lymphoid organs [27] but not yet in non-lymphoid tissues. This might suggest that differences in the constitutive SLC/6Ckine expression in lymphatic endothelium could exist between mouse and man.

It is possible that expression of SLC/6Ckine on human lymphatic endothelium could be dependent on inflammatory stimuli. This possibility raises the question of accessibility of draining lymphatics for in vitro generated DC currently re-infused intradermally in DC-based anti-tumor immunotherapy clinical trials.

The notion that entry into the lymphatics by maturing DC could be a control step has already been suggested by the observation that antibody against the P-glycoprotein (MDR) blocks the reverse migration of DC, mimicking entry into the lymphatics [77]. Although the role of P-glycoprotein was not elucidated in this observation, it has been suggested that the anti-MDR blocks the release of certain eicosanoids such as LTC4 by activated DC. These molecules might deliver a signal to lymphatic endothelium for the control of vessel permeability.

Role of CCR7 ligands in the homing of antigen-loaded DC in the T cell area

In mouse secondary lymphoid organs, the expression of SLC/6Ckine has been reported on HEV [43]. Similarly, in human, we observed SLC/6Ckine expression in HEV as well as in numerous cells in the T cell-restricted areas [27].

In human inflamed tonsils and lymph nodes, ELC/MIP-3β expression is also restricted to T cell areas, the site to which mature IDC home. A similar observation has been reported for mice where ELC/MIP-3β is constitutively expressed within the T cell areas of different secondary lymphoid tissues (spleen, lymph nodes and Peyer's patches) [70].

Altogether, these observations suggest that, following inflammatory stimuli, DC undergoing maturation will express CCR7. Concomitantly SLC/6Ckine induced on the lymphatic endothelium during the inflammatory reaction trigger the emigration of maturing DC through the lymph stream. Mature DC entering the draining lymph nodes are driven into the paracortical area in response to the production of ELC/MIP-3β and/or SLC/6Ckine by cells spread over the T cell zone. The resistance of CCR7 to ligand-induced desensitization supports the hypothesis of a sequential role of SLC/6Ckine and MIP-3β through CCR7 during migration of maturing DC to the draining lymph node [90].

The key roles of SLC/6Ckine and ELC/MIP-3β in the recruitment of mature DC into the T cell area of lymphoid organs has been recently demonstrated in a naturally SLC/6Ckine-deficient mouse [41] and in mouse deficient in CCR7 [32]. In these mice, the anatomical structure of lymphoid organs is disorganized, with a strong defect in naive T cell homing in the T cell areas. In addition, in both animals, DC failed to accumulate in the lymphoid organs following injection or contact sensitization. As a consequence, these animals have impaired immune responses with severely delayed rates of antibody responses, a lack of contact sensitivity and delayed-type hypersensitivity reactions, and a markedly increased sensitivity to infections.

In this context, it is interesting to note that mice deficient for the TNF family member lymphotoxin (LT)-α1β2 have a deficiency in the production of ELC/MIP-3β [69].

These mice as well as LTβR-deficient mice have a decreased number of DC in lymphoid tissues with a randomized distribution [117]. This might either suggest that LT-α1β2 signaling is required for ELC/MIP-3β production or alternatively that LT-α1β2 is required for the development of a stromal element involved in ELC/MIP-3β production.

Recruitment of naive T cells in the draining node

Role of CCR7 ligands in the encounter between antigen-loaded DC and antigen-specific T and B cells

The passage of lymphocytes across the endothelium into lymph nodes and Peyer's patches is a multistep process that involves selectin-supported rolling, followed by a triggering event mediated by chemokines and then firm integrin-mediated adhesion [12]. The best candidate chemokine for this process is the CC chemokine SLC/6Ckine [43, 45, 47, 66, 116], which is active in inducing integrin-mediated adhesion of naive lymphocytes [13, 108]. The central role of SLC/6Ckine in T cell migration across HEV was suggested by the observation that mice deficient for SLC/6Ckine (plt mice) or CCR7 have defective T cell trafficking into lymph nodes [32, 41, 67].

Thus, concomitant to mature DC homing into the T cell areas, CCR7-expressing naive T cells will enter lymph nodes through the production of SLC/6Ckine by HEV. The naive T cells may then be driven to the T cell area through the increased ELC/MIP-3β gradient. The source of ELC/MIP-3β in the T cell area has been proposed to be IDC themselves [70], and in vitro generated DC can produce ELC/MIP-3β upon final maturation ([90], and personal observation). Thus, the newly arriving DC may themselves become a source of ELC/MIP-3β, allowing an amplification and/or a persistence of the chemotactic signals. Because ELC/MIP-3β and SLC/6Ckine can attract both mature DC and naive T cells, they are likely to play a key role in helping antigen-loaded DC to encounter antigen-specific T cells. The fact that DC themselves are a source of ELC/MIP-3β may contribute to the accumulation of mature DC at the initial site, allowing T cells undergoing activation to receive prolonged signals, which is a requirement for naive T cell activation [53].

Role of chemokines produced by DC?

In addition to ELC/MIP-3β, following interaction with T cells, DC produce other chemokines such as DC-CK-1 [1], MDC [37, 94, 107], TARC ([57, 90] and unpub-

lished observation), Teck [114], RANTES [90], and fractalkine [49, 73]. The production of this spectrum of chemokines probably favors interactions between activated CD4 T cells and CD8 T cells or B lymphocytes. In addition, the finding that many chemokines differ in their efficiency to attract cells of Th1 or Th2 phenotype [48] also points to a role for DC chemokine expression in promoting polarization of T cell responses. A subset of memory T cells termed "central memory" still express CCR7 and L-selectin [88], and thus can undergo another round of activation in the lymph nodes during secondary immune responses. It is possible that the recruitment of these memory T cells is favored by the production of DC chemokines with tropism for already pre-committed T cells such MDC and TARC.

Colonization of germinal center by DC?

While the colonization of the T cell area by mature DC and naive T cells is beginning to be understood, in particular through the elucidation of the key role of CCR7 ligands, the recruitment of B cells and other cellular components in the B cell follicle is less clear. In particular, $CD11c^{+}$ DC have been identified in the human GC [39]. Also, colonization of the B cell follicles by DC soon after immunization has recently been reported in mice [7]. These DC were characterized by their binding capacity for soluble mannose receptors [62], and are thought to play a role in antigen transport to B cells. These cells enter the node through the subcapsular sinus from the lymph and then reach the B cell follicle. The chemokines responsible for this selective homing are not known; however, BCA1/BLC, a ligand for CXCR5, plays a critical role in GC formation [31, 42, 54]. CXCR5 is spontaneously expressed on most circulating B cells and induced through OX40L activation on T cells [30, 115]. These observations suggest that BCA1 may play a similar role in the homing of GC B cells. The activity of BCA1, however, has not yet been documented on any DC population.

Conclusion

DC induce, sustain and regulate immune responses. Different DC subsets share biological functions, and display specific ones such as polarization of T cell responses towards type 1 or type 2, regulation of B cell responses, or induction of anti-viral immunity. Although DC can be resident cells such as LC in the epidermis, accumulating evidence shows that, during inflammatory reactions, they can be rapidly mobilized from blood at the site of injury. Chemokines are important effectors of the regulation of DC recruitment, and, depending on the chemokine gradient released at the site of injury, different DC populations will be recruited. It is expected that the type of immune response which results from this probably depends on the DC subpopulation recruited, and thus on the chemokines secreted.

According to their maturation stage, DC display functional specialization: (1) at the precursor stage they have the ability to secrete large amounts of proinflammatory and/or anti-viral cytokines, (2) at the immature stage they display high antigen uptake capacity, and (3) when they are mature they are characterized by the ability to activate and modulate T cell responses. To accomplish their different functions linked to the stage of maturation, DC migrate to different specific microenvironments.

This trafficking is also under the control of chemokines, and different chemokines regulate the recruitment of the precursors, the immature and the mature DC. At the site of injury, inflammatory chemokines act sequentially in parallel to the differentiation process that occurs during the recruitment of DC precursors from blood to tissues, and navigation within tissues (dermis to epidermis). The production of chemokines by DC during their precursor or immature stage represents an important contribution to their sentinel function (recruitment of other DC precursors or effector T cells). After antigen uptake, inflammatory stimuli turn off the response to the inflammatory chemokines and concomitantly DC acquire CCR7 expression. Maturing DC then enter the lymph stream, potentially directed by SLC/6Ckine expressed on lymphatic vessels, and leave the inflamed tissue. Mature DC entering the draining lymph nodes are driven into the paracortical area in response to the production of ELC/MIP-3β and/or SLC/6Ckine by cells spread over the T cell zone. Concomitantly, CCR7-expressing naive T cells enter lymph nodes via the production of SLC/6Ckine by HEV. The newly arriving DC may themselves become a source of ELC/MIP-3β, allowing an amplification and/or a persistence of the chemotactic signal. As these two chemokines can attract mature DC and lymphocytes, they may play a key role in helping antigen-loaded DC to encounter specific T cells. Following interaction with antigen-specific T cells, DC will produce many chemokines favoring interactions between activated $CD4^+$ T cells and $CD8^+$ T cells or B lymphocytes.

Thus, the control of DC trafficking appears to be a complex process with the intervention of several chemokines and many other molecules such as selectins, integrins or proteases. Further investigations are required to assess the role of chemokines in constitutive DC trafficking versus induced DC mobilization during inflammation. Such approaches may help elucidate the role of DC in peripheral tolerance maintenance versus immune induction. Studies of interaction between chemokines, DC and effector cells in disease conditions may open new avenues of therapeutic intervention. A better understanding of the regulation of DC trafficking may allow the in vivo manipulation of DC to increase (cancer, infectious diseases) or to suppress (transplantation, auto-immunity) immune responses.

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