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Review

Dendritic cell migration and lymphocyte homing imprinting

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Summary. For an effective adaptive immune response to occur, dendritic cells (DC), which are the most efficient antigen-presenting cells, must be able to sample the peripheral microenvironment and migrate towards secondary lymphoid organs (SLO) where they activate naïve lymphocytes. Upon activation, lymphocytes proliferate and acquire the capacity to migrate to extralymphoid compartments. Although the molecular mechanisms controlling lymphocyte homing to lymphoid and to some extralymphoid tissues have been described in significant detail, it is much less clear how DC migration is controlled. Do DC obey similar adhesion cues that lymphocytes do, or do they have their own "zip codes"? This is relevant from a therapeutic standpoint because effective DC-based vaccines should be able to reach the appropriate tissues in order to generate protective immune responses. Here, we discuss some of the mechanisms used by DC to reach their target tissues. Once DC arrive at their destination, they are exposed to the tissue microenvironment, which likely modulates their functional properties in a tissue-specific fashion. This local DC "education" is probably responsible among other things; for the acquisition of tissue-specific homing imprinting capacity by which DC instruct lymphocytes to migrate to specific tissues. Finally, we discuss how dysregulation of these signals may play a key role in disease.

Key words: Dendritic cells, Homing, Gut, Skin

Introduction

DC and lymphocytes are essential for adaptive immunity. In order to generate an efficient immune response, these critical cells need to be properly positioned in the body. An essential component in this process is the expression of specific trafficking molecules on DC and lymphocytes. Thus, tissue-tropism is determined by association with and sequential action of adhesion molecules and chemoattractant receptors that control the multi-step process of leukocyte homing (Butcher, 1991; Springer, 1994). This process, which includes tethering and rolling, activation, firm adhesion and transendothelial migration, is largely dependent on the interaction of multiple molecules, such as selectins, chemokines and integrins with their respective ligands (von Andrian and Mackay, 2000; Garrood et al., 2006).

Lymphocyte tissue-specific tropism was originally reported more than 30 years ago (Rudzik et al., 1975a,b; McDermott and Bienenstock, 1979; Tseng, 1981) and it has been extensively studied during the last decade (Kunkel and Butcher, 2002; von Andrian and Mempel, 2003; Bono et al., 2007; Mora, 2007). Naïve T cells leave the thymus, enter the circulation and then traffic preferentially through SLO, such as the spleen, peripheral lymph nodes (PLN) and gut-associated lymphoid tissue (GALT) (von Andrian and Mackay, 2000; Garrood et al., 2006). In these locations, naïve T cells screen antigen-bearing DC in search of their cognate peptide-MHC complex. Once the specific encounter occurs, naïve T cells are primed by DC in a complex multistep process (Mempel et al., 2004). Primed CD4 or CD8 T cells differentiate into activated effector/memory T cells, which are equipped with new homing properties (Table 1). Once T cells leave the SLO, they enter the circulation through the efferent lymph vessels and migrate to extralymphoid tissues.

DC are located at the barriers between the internal compartments of the body and the external environment, such as the skin, lungs and gut mucosa, tissues where they sample antigens. However, despite their critical role in the immune response, little is known about how DC migrate to different tissues. In this review, we will discuss some adhesion pathways needed by DC to reach their target organs. We will also address the role of different DC subpopulations in imprinting lymphocytes with specific tissue-tropism.

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DC migration

In humans and mice, two main subtypes of DC are found under steady-state conditions. These are type-I interferon-producing plasmacytoid DC (pDC) and conventional DC (cDC) (Wu and Liu, 2007). They traffic as DC precursors or as immature DC (iDC) from the blood to peripheral tissues where they sense and capture antigens. Once iDC sense pathogens, they undergo a maturation process during which they upregulate co-stimulatory molecules (e.g., CD80, CD86). Mature DC (mDC) then migrate through the afferent lymph towards the lymph nodes (LN) where they prime naïve T cells (von Andrian and Mempel, 2003). Migration of DC to and from peripheral tissues depends on the expression of chemokine receptors and their respective chemokine ligands, as well as on adhesion molecules, such as integrins. DC express receptors for and respond to constitutive and inflammatory chemokines and also respond to other chemoattractants, such as lipids (e.g., platelet-activating factor) and formyl peptides (Allavena et al., 2000). Originally, responsiveness to several chemoattractants was studied using DC derived from circulating monocytes (Sozzani et al., 1995). Subsequent studies using DC differentiated from $CD34^+$ hematopoietic precursors and Langerhans cells (LC) (Allavena et al., 2000) demonstrated that such responsiveness is generally conserved among different DC populations (Table 1).

Migratory properties of mDC versus iDC

iDC are derived from bone marrow (BM) progenitor cells through either the common lymphoid or the common myeloid progenitor pathways. Precursor DC and differentiated DC migrate in the bloodstream to peripheral tissue where they remain in an immature state patrolling for invasive pathogens. A classic example of iDC resident in peripheral tissues is LC in the epidermis, which possess a high capacity for antigen uptake. Once iDC capture antigens, they undergo maturation, a process by which their homing tropism is modified to direct their migration to the SLO.

In the late 90s, several groups described the differential expression of chemokine receptors between iDC and mDC differentiated from monocytes (Sallusto et al., 1998; Sozzani et al., 1998), suggesting different tissue tropism between these two DC stages. Expression of CCR1, CCR2, CCR5, CXCR4 and CXCR1 characterizes iDC with preferential migration towards inflamed tissues (Sallusto et al., 1998; Sozzani et al., 1998). In addition, depending on their origin, different iDC subsets express different chemokine receptor repertoires. Purified circulating DC express CCR1, CCR2, CCR3, CCR5 and CXCR4 (Ayehunie et al., 1997), whereas pDC also express CXCR3, which is not expressed by monocyte-derived DC (MoDC) or blood

Table 1. DC and lymphocyte homing.

Dendritic cell tissue tropism and microenvironmental migration

Cell type	Receptor	Ligand	Target tissue
iDC	CCR1	CCL3 (MIP-1α), CCL5 (RANTES), CCL7 (MCP-3)	Inflamed tissue (after entering the gut)*
	CCR2	CCL2 (MCP-1), CCL7 (MCP-3), CCL13 (MCP-4)	Inflamed tissue (after entering the gut)
	CCR5	CCL3 (MIP-1α), CCL4 (MIP-1ß), CCL5 (RANTES)	Inflamed tissue (after entering the gut)
	CXCR1	CXCL6 (CKA-3), CXCL8 (IL-8)	Inflamed tissue (after entering the gut)
mDC	CCR7	CCL19 (ELC), CCL21 (SLC)	Lymph nodes (via afferent lymph)
	CXCR4	CXCL12 (SDF-1α)	Lymph nodes (via afferent lymph)
LC	CCR6	CCL20 (MIP-3α)	Skin (from blood)
Gut CD11b+ DC	CX3CR1	CX3CL1 (Fractalkine)	Lamina propria (after entering the gut)
	?	CCL9 (MIP-1γ)	Peyer's patches (after entering the gut; from blood?)
	CCR6	CCL20 (MIP-3α)	Peyer's patches (after entering the gut; from blood?)
Gut pDC	CCR9	CCL25 (TECK)	Small intestine (from blood)

Lymphocyte tissue-tropism: gut versus skin migration

Cell type	Receptor	Ligand	Target tissue
T cells, B cells, ASC	α4ß7	MAdCAM-1	Small intestine, colon (from blood)
	CCR9	CCL25 (TECK)	Small intestine (from blood)
B cells, ASC	CCR10	CCL28 (MEC)	Small intestine, colon (from blood)
T cells	E-Lig, P-Lig	E- and P-selectin	Skin (from blood)
	CCR4	CCL17 (TARC), CCL22 (MDC)	Skin (from blood)
	CCR10	CCL27 (CTACK)	Skin (from blood, after entering the skin?)

* Parentheses denote whether the receptors are involved in cell migration directly from the blood and/or after the cells have arrived to the tissue.

DC (Cella et al., 1999). Upon maturation induced by either LPS, CD40L or TNF-α, DC acquire SLO-tropism by expressing high levels of CCR7 and CXCR4, thereby obtaining responsiveness to their respective ligands ELC/CCL19 or SLC/CCL21 and SDF-1α/CXCL12, which are expressed in the lymphoid organs (Dieu et al., 1998; Sallusto et al., 1998). In contrast, mDC do not respond to inflammatory chemokines, which is consistent with their loss of CCR1, CCR5 and CXCR1 surface expression upon exposure to maturation stimuli (Sallusto et al., 1998). Therefore, DC maturation results in a coordinated chemokine receptor switch from an inflamed/peripheral tissue-tropism to SLO-tropism (Fig. 1). Interestingly, uncoupling the chemokine receptor switch could be a means for pathogens to escape from the immune system. For example, infection of immature MoDC with human cytomegalovirus (HCMV) impairs DC migration to inflammatory chemokines by downregulating CCR1 and CCR5 surface expression without upregulating CCR7 (Varani et al., 2005).

Phenotypical and functional changes from iDC to mDC with the accompanying switch in tissue-tropism are the product of activation by danger/alarm signals from injured cells (Matzinger, 2002). Among these danger signals are pathogen-associated molecular patterns (PAMPs), which signal through Toll-like receptors (e.g., LPS, double-stranded RNA, single-stranded DNA, flagellin) (Matzinger, 2002). Interestingly, most of these signals induce iDC chemotaxis towards the danger signal's origin. High motility group box protein 1 (HMGB1) is a danger signal released by necrotic cells or secreted by activated macrophages which acts as chemoattractant for human monocyte-derived iDC, whereas mature DC do not respond to HMGB1 (Dumitriu et al., 2007; Yang et al., 2007). Also, receptors for the complement protein C1q are expressed on iDC and induce chemoattraction to inflamed tissue, whereas mDC are not C1q sensitive (Vegh et al., 2006). Thus, danger signals can specifically attract iDC towards the inflamed tissue, while mDC are insensitive to these stimuli.

In order to reach the inflamed tissue, circulating DC precursors roll, adhere to the endothelium and extravasate just as lymphocytes do. Human DC progenitor populations express cutaneous lymphocyte-associated antigen (CLA, an E-selectin ligand) on their surfaces and are able to roll in the post-capillary venules of non-inflamed mouse skin in an E- and P-selectin-dependent fashion (Robert et al., 1999). Also, iDC are able to transmigrate across the resting endothelium *in vitro*, whereas mDC are not (Wethmar et al., 2006), demonstrating different interaction abilities between iDC and mDC. Resting endothelial cells express high levels of intercellular adhesion molecule-2 (ICAM-2), while iDC express DC-SIGN. The interaction between ICAM-2/DC-SIGN allows the rolling and transmigration of human DC (Geijtenbeek et al., 2000), indicating that expression of DC-SIGN regulates iDC migration from blood into peripheral tissues. In contrast, mDC migrate from peripheral tissues to the SLO through the afferent lymph vessels. The latter is highly dependent on CCR7 expression by DC (Forster et al., 1999; Ohl et al., 2004). Below, we will discuss the mechanism involved in upregulating CCR7 in maturing DC with the subsequent migration towards SLO from peripheral tissue.

DC migration to and from the skin

There are different subtypes of DC present in the skin. Among them, LC are the most well characterized. LC are present above the basal layer of the epidermis and they are anchored to neighboring keratinocytes (KC) through E-cadherin homotypic interactions (Banchereau and Steinman, 1998). Under steady-state conditions, LC turnover is slow. However, under inflammatory conditions, in which a high number of resident LC leave the skin, replacement is increased (Merad et al., 2002). Therefore, under inflammatory conditions, the emigrated LC population is replaced by bone marrow-derived precursor cells (Koch et al., 2006). These precursor cells travel throughout the bloodstream, adhere to the skin endothelium, cross the dermal tissue barriers and finally reach the epidermis where, under the influence of KC, they differentiate into LC. KC produce cytokines, such as TGF-ß, which has been shown to be crucial for LC differentiation, as observed in the epidermis of either TGF-ß-deficient mice or Langerin-cre TGF-ßRII mice, which lack LC (Borkowski et al., 1996, 1997; Kaplan et al., 2007). In addition, KC produce CCL20/MIP-3α, a chemokine that promotes the recruitment of LC precursors to the epidermis (Moser et al., 2004). Both DC precursors and LC express the CCL20 receptor CCR6 and migrate in response to this chemokine (Sozzani et al., 2000). Furthermore, KC can produce CCL17 (Morales et al., 1999; Vestergaard et al., 2004) whose receptor CCR4 is expressed on skin-homing lymphocytes and monocytes, respectively (Ono et al.,

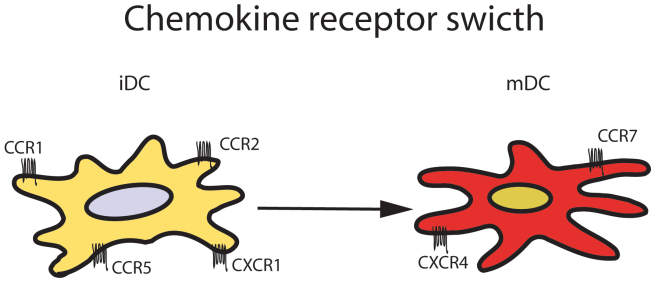

Fig. 1: Chemokine receptor switch between immature (iDC) and mature DC (mDC). iDC express high levels of the chemokine receptors CCR1, CCR2, CCR5 and CXCR1 and therefore they respond to inflammatory chemokines. When iDC are exposed to different maturation stimuli (e.g., LPS, CD40L) they downregulate the inflammatory chemokine receptors and upregulate CCR7 and CXCR4, thus gaining responsiveness to CCL19, CCL21 and CXCL12, chemokines present in the LN.

2003), suggesting a pivotal role for this chemokine/chemokine receptor pair on DC precursor immigration and/or DC homeostasis in the skin.

Skin-associated DC migrate to the draining lymph node via a CCR7-dependent mechanism

Upon maturation, skin-associated DC, such as LC and dermal DC, leave the peripheral tissue and migrate towards SLO where they present antigen to naïve T cells (Steinman et al., 1997). In this regard, the chemokine receptor CCR7 is essential for the migration of skin-associated DC to LN under both inflammatory and steady state conditions, as demonstrated in CCR7 deficient mice (Forster et al., 1999, Ohl et al., 2004) and in *plt/plt* mutant mice, which lack CCL21 expression and only partially express CCL19 (Gunn et al., 1999).

Positive and negative signals control LC migration from the skin to LN. TNF-α and IL-1ß are required to induce LC departure from the epidermis. Systemic administration of neutralizing antibodies specific for either cytokine resulted in significant inhibition of contact allergen-induced LC migration (Cumberbatch et al., 1997). Therefore, a "LC departure" mechanism from the skin has been proposed in which, once allergens are sensed, LC produce IL-1ß which acts on adjacent KC inducing them to produce TNF-α, which then acts as a second migratory signal for LC (Griffiths et al., 2005) (Fig. 2). LC and KC are firmly associated by E-cadherin/E-cadherin homotypic junctions. Binding of TNF-αRII, IL-1RI and IL-1RII on LC by their ligands TNF-α and IL-1ß, respectively, affect the interaction between LC and KC by diminishing the expression of E-cadherin (Schwarzenberger and Udey, 1996), allowing their disentanglement from surrounding KC and stimulating actin-dependent movement (Winzler et al., 1997). In addition, these cytokines inhibit the expression of CCR6 on LC, which makes them unresponsive to KC-produced CCL20 and also induces the expression of α6ß1 integrin, which allows interactions between LC and the extracellular matrix. Therefore, TNF-α and IL-1ß are two necessary signals for inducing LC emigration from the skin (Fig. 2).

Lipids, such as prostaglandins and leukotrienes (LT), positively affect LC migration to the LN via a CCR7-dependent mechanism (Robbiani et al., 2000, Kabashima et al., 2003). Mice deficient in the leukotriene C_4 (LTC_4) transporter multi-drug resistance-associated protein 1 (MRP1) show a strong reduction in the mobilization and trafficking of LC from the epidermis into the afferent lymphatic vessels (Robbiani et al., 2000). Also, *Ptger4*$^{-/-}$ mice, which lack the PGE2 receptor EP_4, show a significant reduction of LC accumulation in the draining LN upon antigen exposure, an observation further confirmed by using the EP_4 antagonist AE3-208 (Kabashima et al., 2003). Furthermore, upon exposure to EP_4 agonists, DC enhance their expression of CCR7 and migrate more efficiently *in vitro* towards the CCR7-ligands CCL19 and CCL21 (Scandella et al., 2002; Kabashima et al., 2003). Interestingly, human MoDC stimulated with TNF-α and IL-1ß do not express CCR7 and their migration in vitro towards either CCL19 or CCL21 is marginal. However, when PGE2 is supplemented, CCR7 mRNA is increased about 40 fold with a consequent increase in migration towards CCL19 and CCL21 (Scandella et al., 2002). Notably, both TNF-α and IL-1ß are potent inducers of cyclooxygenase (COX)-2 (Feng et al., 1995), which participates in PGE2 synthesis. It is therefore likely that cytokines induce COX-2 expression by either keratinocytes or DC themselves to produce PGE2, which induces CCR7 expression on DC in a paracrine and/or autocrine manner (Fig. 2).

On the other hand, LC migration is negatively controlled by anti-inflammatory cytokines, such as IL-10 (Wang et al., 1999) and IL-4, the latter by interfering with the expression of TNF-αRII on LC (Takayama et al., 1999). Another negative regulator of LC migration is prostaglandin D2 (PGD2) (Angeli et al., 2001). In fact, TNF-α-mediated mobilization of LC from the epidermis and accumulation in LN is strongly impaired by PGD2, an effect mediated by the activation of nuclear receptor peroxisome proliferator-activated receptor gamma (PPARγ) (Angeli et al., 2003). The latter is consistent with the inhibition of CCR7 mRNA expression observed

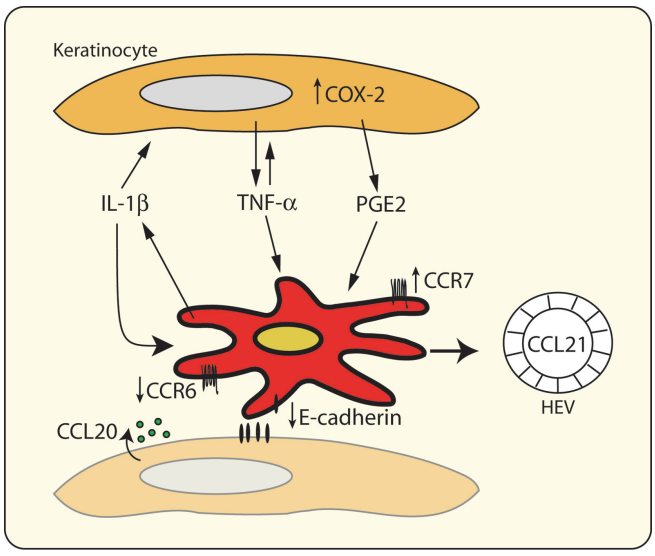

Fig. 2. Molecular events on LC migration from the skin. Precursor of LC express CCR6 and are recruited to the skin by keratinocyte (KC)-secreted chemokine CCL20. In addition, LC anchorage to keratinocytes is mediated by E-cadherin homotypic interactions. Under inflammatory conditions, LC produce and secrete IL-1b which acts on KC to induce TNF-α. Both IL-1ß and TNF-α affect the interaction between KC and LC by diminishing the expression of E-cadherin, stimulating actin-dependent movement and inhibiting CCR6 expression on LC. At the same time, these cytokines induce the expression of cyclooxygenase (COX)-2 on KC. COX-2 is involved in PGE2 synthesis, which acts on DC to induce CCR7 expression/function and LN tropism. In the LN, DC can locate close to HEV, which also express CCL21.

in human MoDC when PPARγ is activated (Nencioni et al., 2002). Analogously, activation of PPARγ inhibits the migration of lung DC to the thoracic LN (Angeli et al., 2003), suggesting that this inhibitory mechanism is conserved among different tissues. Interestingly, PGD2 also binds to the membrane D prostanoid receptor 1 (DP1) (Hammad et al., 2003), suggesting that PGD2 may exert its inhibitory effect on DC migration through two different signaling pathways, PPARγ and DP1 receptors. However, LC migration is rescued upon incubation with PPARγ antagonists, suggesting that the inhibitory effect of PGD2 is mostly DP1-independent (Angeli et al., 2003).

DC migration in the gut

Gut-associated DC are found in both organized gut-associated lymphoid tissues (GALT), such as mesenteric lymph nodes (MLN) and Peyer's patches (PP), and also in the tissue layer between the epithelium and the muscularis mucosa, which is called the lamina propria (LP). DC are abundant in the small intestine where, similar to their counterparts in the skin, they act as sentinels for incoming antigens. However, little is known about how intestinal DC and/or their precursors reach the gut mucosa.

Role of CCR9 and α4ß7 in homing to the small intestine

Mucosal addressin cell adhesion molecule-1 (MAdCAM-1), which is expressed on the endothelium of the high endothelial venules (HEV) in GALT and also on the postcapillary venules of the gut lamina propria, mediates the adhesion of lymphocytes expressing the integrin α4ß7 (Berlin et al., 1993). In fact, mice lacking ß7 integrins exhibit a severe reduction in the number of T and B lymphocytes in the intestine (Wagner et al., 1996). Consistent with this observation, blocking either MAdCAM-1 or α4ß7 significantly inhibits lymphocyte homing to the small intestine (Hamann et al., 1994), confirming the key role of these molecules in gut-tropism. Also, during inflammatory conditions, MAdCAM-1 expression is increased in LP venules (Briskin et al., 1997). Indeed, in a mouse model of T cell-mediated colitis, blocking ß7 and MAdCAM-1 reduces the recruitment of T cells to the inflamed colon and also the severity of colitis (Picarella et al., 1997).

Another important gut-homing molecule is the thymus-expressed chemokine, TECK (CCL25), which is expressed both in thymus and in the small intestine. Its receptor CCR9 is expressed on CD4 and CD8 T cells that migrate to the small intestine (Zabel et al., 1999). Moreover, CCR9 is selectively induced and/or maintained on CD4 and CD8 T cells activated in GALT but not in PLN. Consistent with an important role of this receptor in lymphocyte migration to the small intestine, CCL25 neutralization strongly inhibits the recruitment of recently activated T cells to the small bowel (Svensson et al., 2002; Stenstad et al., 2006), effect that is recapitulated in CCL25-deficient mice (Wurbel et al., 2007). Furthermore, CCR9-deficient effector CD8 T cells are severely impaired to migrate to the small bowel (Johansson-Lindbom et al., 2003) and CCR9-deficient mice have reduced numbers of IgA-ASC in the small intestine LP (Pabst et al., 2004). Therefore, both CCL25/CCR9 and MAdCAM-1/α4ß7 interaction are needed for the efficient homing of lymphocytes and ASC to the small intestine. However, little is known about whether or not they also contribute to DC gut-colonization.

Role of CCR9 in DC migration to the intestine

How do DC and/or their precursors migrate to mucosal tissues, such as the intestine? It was recently shown that mice lacking CCR9 have lower numbers of pDC in the intestinal LP and PP, while in MLN pDC numbers were comparable to those found in wild type mice (Wendland et al., 2007). Indeed, pDC express high levels of CCR9, while integrins ß2 (CD18) and α4ß7 are expressed at high and intermediate levels, respectively (Wendland et al., 2007). Interestingly, the majority of pDC isolated from the BM express high levels of CCR9, while CXCR4 is only weakly expressed, suggesting that BM-derived $CCR9^+$ pDC could directly colonize the gut. Consistent with a role of CCR9 in pDC homing to the gut, CCR9-deficient pDC were impaired in their capacity to migrate to the small intestine under both steady-state and inflammatory conditions (Wendland et al., 2007). These data suggest that CCR9 plays an important role in pDC migration to the gut. However, it remains unclear whether pDC precursors are also able to migrate to the gut in a CCR9-dependent manner, thus contributing to intestinal pDC colonization. Of note, pDC seem to be a sessile DC subset in the gut, as suggested by their conspicuous absence in the intestinal-draining lymph, at least in rats (Yrlid, Cerovic et al., 2006). However, pDC can secrete TNF-α and type-I interferons upon TLR-stimulation, affecting in this way the activation and migration of other DC subsets in the gut mucosa (Yrlid et al., 2006).

Of interest, it has been shown that blood monocytes can also give rise to some DC subsets found in intestine-draining lymph (Yrlid et al., 2006), suggesting that some gut-associated DC may derive from blood-borne monocytes. Related to this, it has been suggested that PSGL-1 is required for monocyte adhesion on ileum venules, at least under inflammatory conditions (Inoue et al., 2005). Also, monocytes can migrate from the blood to PLN (Palframan et al., 2001) and it is possible that a similar mechanism operates in PP, although PP do not seem to contribute significantly to the pool of DC found in the intestinal-draining lymph (Bimczok et al., 2005).

Spleen-derived $CD11b^+$ DC do not express CCR9 and they respond only marginally to CCL25 (Wendland et al., 2007), suggesting that $CD11b^+$ DC (or their precursors) use a mechanism different from CCR9 for

gut colonization. Also, as discussed below, the vitamin A-metabolite retinoic acid is known to induce CCR9 and α4ß7on T and B cells. This raises the question of whether the same mechanism may induce CCR9 (and α4ß7) on pDC. Also, it is unknown whether pDC homing is also dependent on α4ß7 integrin. In addition, it has been shown that LC can differentiate locally in the epidermis from self-renewing precursors (Merad et al., 2002), raising the possibility that an analogous self-renewing precursor may also exist in the gut to give rise to some intestinal DC subsets. Finally, it has been suggested that, under certain conditions, DC may migrate directly from the skin to PP (Belyakov et al., 2004; Enioutina et al., 2007). However, the adhesion receptors involved and physiological relevance of this putative mechanism of DC migration are currently unknown.

Microenvironmental location of DC in PP and LP

In mice, at least four different PP-DC subsets have been reported (Iwasaki and Kelsall, 2000; Contractor et al., 2007). $CD11b^+$ ("myeloid") DC are preferentially located in the subepithelial dome (SED) of PP, where they function to capture antigen transported by M cells. In contrast, $CD8\alpha^+$ ("lymphoid") DC are located in the T cell-rich interfollicular region, where they can prime naïve T cells. Finally, DC that are double negative ($CD11b^-CD8\alpha^-$) and $B220^+$ pDC are located in both regions of PP (Iwasaki and Kelsall, 2000, Contractor et al., 2007). CCL20 mRNA is highly expressed in the follicle-associated epithelium (FAE) and the CCL20 receptor CCR6 is expressed on $CD11b^+$ DC in the SED of PP (Iwasaki and Kelsall, 2000), suggesting that this chemokine/chemokine receptor pair may play an important role in DC location within PP (Fig. 3). Consistent with this possibility, mice expressing GFP under the control of the CCR6 promoter reveal that this receptor is only expressed by $CD11b^+CD8\alpha^-$ DC. Moreover, $CCR6^+$ DC are mostly found in PP (Kucharzik et al., 2002; Salazar-Gonzalez et al., 2006), whereas no CCR6 expression is visualized in the entire small bowel LP either under steady-state or inflammatory conditions (Salazar-Gonzalez et al., 2006). It was also shown that mice lacking CCR6 lacked $CD11b^+$ DC in PP SED (Cook et al., 2000; Varona et al., 2001), which correlated with an impaired humoral response to orally administered antigen, whereas immune response to subcutaneously administered antigen was normal (Cook et al., 2000). However, another study showed that $CD11b^+$ DC are not significantly reduced in PP SED of CCR6-deficient mice (Zhao et al., 2003), suggesting that the correct positioning of $CD11b^+$ DC in PP may not necessarily require CCR6. In addition to CCL20, the chemokine CCL9 is highly expressed in the FAE of mouse PP and its receptor CCR1 is also expressed on CD11b+ DC (Zhao et al., 2003). Indeed, experiments blocking CCL9 show a significant decrease of $CD11b^+$ cell numbers in PP SED, suggesting a role for this chemokine in $CD11b^+$ DC recruitment to the PP SED. Two CCL9 chemokine receptors have been described, CCR1 and CCR5. However, both CCR1- and CCR5-deficient mice have normal $CD11b^+$ DC numbers in PP SED (Zhao et al., 2003), implying that either they are redundant or that another receptor is involved in CCL9-mediated myeloid DC recruitment.

Infection with *S. typhimurium* induces a quick

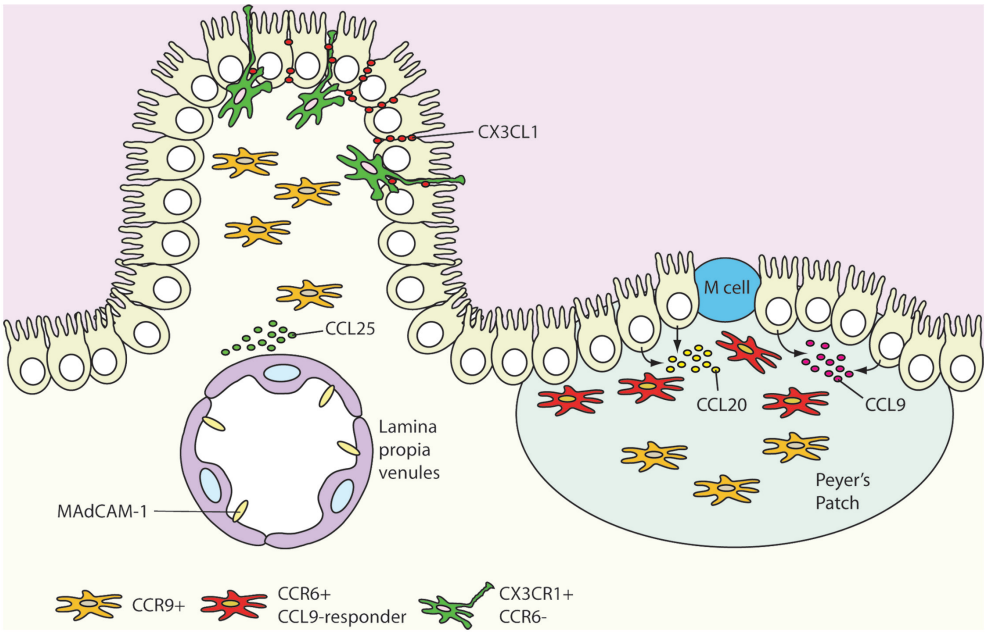

Fig. 3. Chemokine-dependent DC homeostasis in the small intestine. Plasmacytoid DC (depicted in yellow) express CCR9 and respond to CCL25 which is present in the small intestine. CCR9 is important for pDC location in both LP and PP. $CCR6^+CD11b^+$ DC (depicted in red) are absent in the LP, but highly represented in PP where the CCR6-ligand CCL20 is expressed by the follicle-associated epithelium (FAE). CCL9 is also produced by the FAE and this chemokine is important for the location of $CD11b^+$ DC in the PP subepithelial dome (SED). Another DC population that expresses $CX3CR1^+$ is found throughout the entire LP (depicted in green). The CX3CR1-ligand CX3CL1 (fractalkine) is highly expressed by intestinal epithelial cells and this chemokine seems to be involved in the extension of intraepithelial dendrites by DC to sample antigens located in the gut lumen.

recruitment of CCR6$^+$ DC towards the FAE of PP (Salazar-Gonzalez et al., 2006). In a later stage of infection, CCR6$^+$ DC can be detected in the SED, the FAE and interfollicular regions of PP. In contrast, DC from CCR6-deficient mice are not recruited after challenge with *S. typhimurium* (Salazar-Gonzalez et al., 2006). The latter is translated into a functional defect, since Salmonella-specific T cell activation and expansion is reduced following S. typhimurium infection in CCR6-deficient mice as compared to wild type mice (Salazar-Gonzalez et al., 2006), suggesting that CCR6 is required for infection-mediated recruitment of DC to PP SED in order to prime an efficient T cell response. Therefore, it can be speculated that both CCL9 and CCL20 are important for maintaining DC homeostasis in PP: During steady-state non-inflammatory conditions, CCL9 would be the main chemoattractant, since CCR6-deficient mice have the same number of CD11b$^+$ DC as wild type mice whereas CCL9 blockade induces a strong decrease in CD11b$^+$ DC numbers in PP SED. In contrast, under inflammatory conditions, CCR6 would be crucial for the quick recruitment of CD11b$^+$ DC to the PP FAE and SED in order to initiate an adaptive immune response. However, whether CCR6$^+$ and CCL9-responder DC belong to the same DC subpopulation remains to be determined. Also, it needs to be determined whether blocking CCL9 does or does not affect T cell responses against pathogens.

Another DC subset, which expresses CX3CR1 but not CCR6, populates the entire LP of the intestine and is also found in PP SED (Salazar-Gonzalez et al., 2006) (Fig. 3). The CX3CR1 ligand CX_3CL1 (fractalkine) is highly expressed by intestinal epithelial cells (IEC) in the terminal ileum. In wild type animals, DC extend dendrites across the IEC for sampling antigens in the intestinal lumen (Niess et al., 2005), whereas CX3CR1-deficient mice lack intraepithelial dendrites and show enhanced susceptibility to *S. typhimurium* infection (Niess et al., 2005), suggesting that CX3CR1 is involved in the capacity of LP-DC to extend dendrites through IEC in order to sample intestinal bacteria and initiate protective immune responses. Nonetheless, CX3CR1-deficient DC are still present in the LP, indicating that the recruitment of these cells to this compartment is independent of CX_3CR1.

Lymphocyte homing imprinting

Activated T cells acquire the capacity to migrate to non-lymphoid tissues. In addition, some T cell subsets exhibit remarkable migratory selectivity for specific non-lymphoid tissues, such as the gut and the skin (McWilliams et al., 1977; Guy-Grand et al., 1978; McDermott and Bienenstock, 1979; Kantele et al., 1999). Skin-homing relies on the expression of E- and P-selectin ligands (E-lig and P-lig, respectively) (Picker et al., 1991; Fuhlbrigge et al., 1997) and the chemokine receptors CCR4, and/or CCR10 (Campbell et al., 1999, 2007; Morales et al., 1999; Soler et al., 2003). On the other hand, gut-tropism is dependent on the expression of the intestinal homing receptors CCR9 and α4ß7 (Berlin et al., 1993; Wagner et al., 1996; Agace, 2006; Mora and von Andrian, 2006).

It is well documented that the tissue where the antigen is encountered influences the trafficking pattern that lymphocytes acquire. For example, pathogens entering through the skin preferentially induce lymphocytes with skin-homing receptors (Koelle et al., 2002, 2005; Kantele et al., 2003; Gonzalez et al., 2005), whereas oral vaccination induces high levels of the gut-homing integrin α4ß7 on effector/memory T cells (Rott et al., 1997; Kantele et al., 1999; Lundin et al., 2002; Rojas et al., 2003) and B cells (Quiding-Jarbrink et al., 1997; Kantele et al., 1997, 1999, 2005; Youngman et al., 2002; Gonzalez et al., 2003). In fact, CD4 T cells activated in GALT rapidly upregulate α4ß7 and CCR9 as compared to those activated in skin-draining PLN. Conversely, E-Lig and P-Lig are preferentially induced in skin-draining PLN (Campbell and Butcher, 2002).

DC imprint tissue-specific homing on lymphocytes

During the quest for specific elements in the lymphoid microenvironment that are responsible for imprinting lymphocytes with tissue-specific homing, several groups have provided evidence that DC from lymphoid organs are sufficient to confer tissue-specific homing capacity to lymphocytes ex vivo. Indeed, DC isolated from GALT (PP or MLN), but not from PLN or spleen, imprint high levels of α4ß7, CCR9 and gut-migratory capacity on activated T cells (Stagg et al., 2002; Johansson-Lindbom et al., 2003; Mora et al., 2003, 2005; Dudda et al., 2005). Of note, LFA-1, ß1 integrins, αEß7 and PSGL-1, as well as cytokine production and cytolitic activity, are induced at comparable levels on T cells activated with DC from different SLO, showing that the DC imprinting affects only gut-homing receptors, but not other adhesion molecules or effector function on T cells (Mora et al., 2003, Johansson-Lindbom et al., 2003, Mora et al., 2005, Dudda et al., 2005). Gut-tropism induced by GALT-DC is not restricted to T cells, since both murine and human B cells upregulate α4ß7 and CCR9 when activated by GALT-DC (Mora et al., 2006). Moreover, recent reports have shown that MLN-DC and LP-DC, in the presence of TGF-ß, induce naïve T cells to become bona fide foxp3$^+$ regulatory T cells (T_{REG}), which, in addition, express high levels of α4ß7 and CCR9 (Coombes et al., 2007; Mucida et al., 2007; Sun et al., 2007). Interestingly, both induction of foxp3$^+$ T_{REG} and gut-homing receptors by MLN-DC are dependent on the vitamin A-metabolite retinoic acid (discussed below).

In PP, different DC subsets are able to induce gut-homing T cells (Mora et al., 2005). However, it has been shown that, in MLN, a subpopulation of αE/CD103$^+$ DC induces CCR9 on activated T cells more efficiently than CD103$^-$ DC (Johansson-Lindbom et al., 2005). Moreover, CD103$^+$ DC can also induce foxp3$^+$ T_{REG},

even in the absence of exogenous TGF-ß, an effect that is enhanced by adding exogenous TGF-ß1 and abrogated if TGF-ß is blocked in the culture (Coombes et al., 2007; Denning et al., 2007; Sun et al., 2007). It remains to be determined under which conditions GALT-DC promote either tolerogenic gut-homing T_{REG} or protective gut-homing effector T cells *in vivo*.

On the other hand, DC from skin-draining lymph nodes (PLN-DC) induce higher levels of E- and P-Lig on CD8 T cells as compared with PP-DC (Dudda et al., 2005; Mora et al., 2005). Moreover, PLN-DC induce mRNA for fucosyltransferase-VII (FucT-VII), which is an essential enzyme for synthesizing E-Lig and P-Lig (Maly et al., 1996; Mora et al., 2005). Although the skin-homing chemokine receptor CCR4 is expressed on activated CD8 T cells regardless of the activating DC, CCR10 was not induced under any of the in vitro activating conditions tested (Mora et al., 2005).

Molecular mechanisms imprinting gut- and skin-homing lymphocytes

Why do GALT-DC have the ability to induce gut-tropism while PLN-DC do not? It has been described that vitamin A-deficient rats exhibit impaired migration of lymphoblasts to the intestinal mucosa and a marked decrease in the number of IgA-ASC and CD4 T cells in the ileum (McDermott et al., 1982; Bjersing et al., 2002). However, the molecular basis for these observations was provided only recently in a seminal paper by Iwata and colleagues, in which it was demonstrated that vitamin A-deficient mice have significantly fewer effector/memory T cells in the gut mucosa, whereas their numbers were not decreased in other tissues (Iwata et al., 2004). Moreover, naïve CD4 T cells and B cells stimulated *in vitro* in the presence of the vitamin A-metabolite retinoic acid (RA) upregulated both α4ß7 and CCR9 and homed efficiently to the small intestine (Iwata et al., 2004; Mora et al., 2006). Consistent with this, synthetic agonists of the RA-nuclear receptors of the RAR family also induced gut-tropism on T cells (Iwata et al., 2004). Of note, GALT-DC, unlike PLN-DC, express high levels of retinal dehydrogenase (RALDH) enzymes, which are essential for the biosynthesis of RA (Iwata et al., 2004). In addition, as mentioned above, RA-induced T_{REG} also express α4ß7 and CCR9 and home to the gut (Benson et al., 2007). Moreover, RAR-antagonists block the capacity of GALT-DC to induce α4ß7 and CCR9 on T and B cells as well as the induction of T_{REG}, indicating that RA is essential for the imprinting of both gut-homing and T_{REG} by GALT-DC (Iwata et al., 2004; Mora et al., 2006; Mucida et al., 2007; Sun et al., 2007). Interestingly, RA also suppresses the expression of the skin-homing receptors E-lig, P-Lig, CCR4 and FucT-VII on T cells (Iwata et al., 2004), suggesting that RA inhibits the default acquisition of skin-tropism by activated T cells (Fig. 4).

Another vitamin metabolite, $1,25(OH)_2D_3$, which is the most physiologically active form of vitamin D_3, has been recently shown to induce the skin-associated chemokine receptor CCR10 on human T cells (Fig. 4) (Sigmundsdottir et al., 2007). IL-12 supplementation was needed for optimal CCR10 induction by $1,25(OH)_2D_3$ (Sigmundsdottir et al., 2007). Interestingly, $1,25(OH)_2D_3$ also suppressed α4ß7 and CCR9 expression, presumably because the vitamin D receptor VDR/RXR competes for RXR, which is also an essential nuclear partner for the RA-receptor RAR (Sigmundsdottir et al., 2007). Of note, human monocyte-derived DC (MoDC) express CYP27B1 (1-hydroxylase)

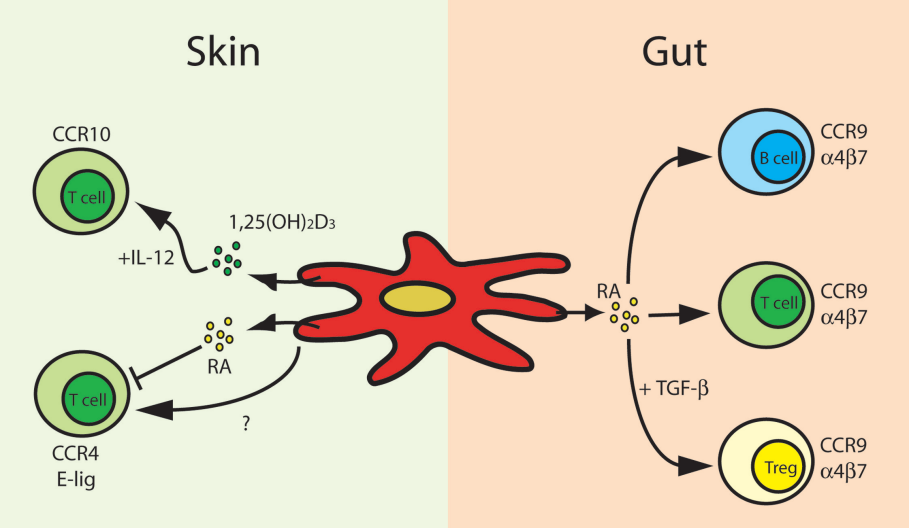

Fig. 4. Control of tissue-specific lymphocyte homing by DC. Gut-associated DC (from GALT or LP) induce the expression of α4ß7 and CCR9 on naïve T and B cells upon activation, an effect that is mediated by the secretion of retinoic acid (RA) by DC. Notably, RA in the presence of TGF-ß induce the differentiation of foxp3+ Treg that also express CCR9 and α4ß7. In contrast, RA inhibits the generation of T cells expressing the skin-homing receptors E-lig, P-Lig and CCR4. Peripheral DC (including skin-draining DC) do not secrete RA and induce skin-homing receptors on T cells, i.e., E-Lig (including CLA), P-Lig and CCR4. The induction of these skin-homing receptors may represent a default pathway in the absence of RA. CCR10, another skin-associated chemokine receptor, is not induced by default. Interestingly, skin-draining DC synthesize the vitamin D3-metabolite $1,25(OH)_2D_3$, which acts on human (but not murine) naïve T cells to induce the expression of CCR10. However, whether the latter represent a mechanism to induce CCR10 on skin-homing T cells in vivo is presently unclear.

and CYP27A1 (25-hydroxylase), which are the main enzymes involved in the synthesis of $1,25(OH)_2D_3$ from vitamin D_3 (Sigmundsdottir et al., 2007). Consistent with this, MoDC, as well as mature cutaneous DC isolated from sheep, converted vitamin D_3 to $1,25(OH)_2D_3$ (Sigmundsdottir et al., 2007), thus linking cutaneous DC with the ability to induce CCR10 on T cells. It should be considered, however, that other skin-homing receptors, such as CLA (E-Lig) and CCR4, are not induced by $1,25(OH)_2D_3$ on T cells (CLA is actually downregulated) (Sigmundsdottir et al., 2007). Therefore, in contrast to RA in the gut, $1,25(OH)_2D_3$ is apparently not sufficient to induce skin-homing T cells. In fact, CCR10 induction may actually occur after T cells have homed to the skin in order to direct T cells towards the epidermis, which is rich in the CCR10-ligand CCL27/CTACK (Homey et al., 2000). Also, $1,25(OH)_2D_3$ does not induce CCR10 on murine T cells (Sigmundsdottir et al., 2007), suggesting that the molecular mechanisms inducing this receptor may vary across species.

Therapeutic implications

Gut-associated inflammatory diseases, such as inflammatory bowel disease (IBD), are characterized by extensive lymphocyte infiltration. MAdCAM-1 expression is upregulated during exacerbation of IBD (Briskin et al., 1997), thus promoting the recruitment of α4ß7-expressing T cells to the gut. Also, blocking α4ß7 prevents the development of intestinal graft versus host disease (GVHD) in allogenic-transplanted mice (Petrovic et al., 2004) and GALT are important for initiating GVHD by inducing gut-tropic effector T cell responses (Murai et al., 2003). Of note, anti-human α4 antibody (natalizumab), which blocks α4ß7 and α4ß1 integrins, is effective in treating patients with ulcerative colitis (Ghosh et al., 2003). However, it has also been associated with progressive multifocal leukoencephalopathy (PML), a lethal viral opportunistic infection (Berger and Koralnik, 2005). Since α4ß1 is important for T cell homing to the central nervous system (CNS) (Yednock et al., 1992), it is possible that α4 blockade also interferes with T cell immuno-surveillance in that compartment resulting in predisposition to opportunistic viral diseases such as PML (Langer-Gould and Steinman, 2006). Therefore, alternative strategies are needed to inhibit leukocyte migration in IBD. In this regard, blocking α4ß7 should not interfere with the CNS immunosurveillance mechanism and a recent clinical trial suggests that it may be a good alternative for treating gut-inflammatory diseases (Feagan et al., 2005). Another possibility would be to generate gut-homing. Indeed, recent work suggests that this can be accomplished by activating ex vivo naïve T cells in the presence of TGF-ß and RA (Coombes et al., 2007; Denning et al., 2007; Mucida et al., 2007; Sun et al., 2007).

DC are poorly represented in some tumors such as renal cell carcinoma (Troy et al., 1998), suggesting the existence of a escape mechanism in which the tumor impairs DC recruitment. Therefore, improving the recruitment of DC or their precursors to the site of tumor growth may be an effective strategy for eliciting anti-tumor immunity. Mice inoculated with melanoma engineered to secrete GM-CSF reject the tumors and show increased accumulation of mature DC at the tumor site, as well as in LN, in a dose-dependent fashion (Armstrong et al., 1996; Stoppacciaro et al., 1997). Also, MCP-3, a potent DC-chemoattractant, is important for the immunological rejection of mastocystoma cells, which is associated with the accumulation of peritumoral DC (Fioretti et al., 1998). DC are also found in human carcinoma and peritumoral DC infiltration has been correlated with improved patient survival (Nomori et al., 1986). Of note, it has been demonstrated that the route of administration of DC loaded with tumor-associated antigens determines the distribution of tumor-specific T cells and favors the pattern of regional tumor control (Mullins et al., 2003; Sheasley-O'Neill et al., 2007). Particularly, subcutaneous DC immunization protects mice from subcutaneous and lung tumors, whereas intravenous immunization protects mice only from lung tumors (Mullins et al., 2003). Hence, immunotherapeutic strategies aimed at increasing DC recruitment to the tumor site, as well as promoting DC migration to tumor-draining LN, could have a significant therapeutic impact.

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