

Dendritic Cell Migration to Peripheral Lymph Nodes

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Abstract Dendritic cells are potent antigen-presenting cells endowed with the unique ability to prime T-cell responses. To present foreign antigens to naïve T cells, dendritic cells must migrate from inflamed or injured peripheral tissues to the closest draining lymph nodes through afferent lymphatic vessels. In addition, conventional dendritic cells, plasmacytoid dendritic cells and monocytes enter lymph nodes from blood crossing high endothelial venules. The selective migration of dendritic cells and their residence in non lymphoid as well as in lymphoid organs are tightly regulated events, whose molecular control is being unraveled rapidly. In this chapter, we review key aspects of what is known about dendritic cell traffic to peripheral nodes from tissues, in particular skin, and from blood. A better understanding of the regulation of dendritic cell migration for optimal priming of T-cell responses is essential for future advances in manipulating dendritic cell traffic as a means to improve immune responses in clinical settings.

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1 Introduction

Dendritic cells (DCs) are unique antigen presenting cells owing to their capacity to acquire and process antigens, and their potential to express high levels of co-stimulatory molecules that trigger naïve T-cell activation (Banchereau and Steinman 1998). In addition, DCs induce immune responses by driving T-cell memory differentiation and polarization. Indeed, DCs transmit a distinct set of information to T cells, based on their state of differentiation or maturation, and these instructions determine different outcomes that range from Th1, Th2, Th17 effectors to memory and regulatory T-cell responses (Lanzavecchia and Sallusto 2001).

A crucial attribute of DCs at various differentiation stages is their mobility, which allows them to be present in the right place at the right time for regulation of immunity (Austyn et al. 1988). DC precursors migrate from bone marrow to all bodily tissues where they reside in an immature state to exert a sentinel function for incoming antigens, and they readily relocate to secondary lymphoid organs, particularly lymph nodes (LNs), to ensure an efficient encounter with naïve and with central memory T cells (T_{CM}) (Banchereau et al. 2000; Steinman et al. 2003). Chemokines are mediators of cell migration during steady state immune surveillance and inflammation. Chemokines bind to G protein-coupled receptors that trigger intracellular signaling pathways involved in cell movement and activation (Moser et al. 2004). Chemokines and chemokine receptors play a determinant role in the trafficking of DCs to LNs through afferent lymphatic vessels (Gunn et al. 1999; Martín-Fontecha et al. 2003; Ohl et al. 2004) and from blood (Diacovo et al. 2005; Yoneyama et al. 2004) and, thus, have become relevant targets for immune intervention (Proudfoot 2002).

The current model describes a linear route between antigen uptake in the periphery and T-cell priming in the LNs. This model is based primarily on observations of the migration of Langerhans cells (LCs) following administration of skin-sensitizing agents (Macatonia et al. 1987), carcinogens, or upon infection (Dandie et al. 1994; Merad et al. 2000). By applying sensitizers admixed with haptens and fluorescent molecules in the skin, it was possible to detect antigen-carrying DCs in draining LNs, where they initiate adaptive immune response (Ruedl et al. 2001; Stoitzner et al. 2003). Models of *Leishmania major* infection have shown that LCs take up *L. major* upon subcutaneous or intradermal infection and subsequently migrate to LNs to induce T-cell priming (Moll et al. 1993). Infection with other pathogens also induce a strong migration of DCs and their precursors from the blood stream, increasing antigen presentation capabilities in LNs. Thus, monocytes (Palframan et al. 2001), conventional DCs (Martin et al. 2002) and plasmacytoid DCs (PDCs) (Diacovo et al. 2005; Yoneyama et al. 2004) can gain access to peripheral LNs via high endothelial venules (HEVs) with subsequent impact on T cell-mediated responses.

Here, we will review what is known about the mechanisms that govern DC migration to subcutaneous LNs and the main regulation check points in the context of triggering T cell-mediated immune responses. A comprehensive view on how

mucosal DCs integrate signals from the epithelial cells and other stromal cells, and migrate to mucosa-draining LNs to mount regulatory and stimulatory immune responses can be found in a recent review (Iwasaki 2007).

2 From Skin to Draining Lymph Nodes

The skin is the body's largest exposed interface with the environment and has evolved as a barrier to shield external pathogens from entering the body. DCs are strategically present near superficial surfaces like the skin to initiate immune defense responses when pathogens succeed in breaching peripheral barriers. Well-known examples of skin resident DCs are LCs, a subset of immature DCs settled in the epidermis, and dermal DCs (dDCs) in the dermis (Caux et al. 2000). On their way from the epidermis, LCs must cross the basement membrane and move through connective tissue until they reach a lymph vessel, which they enter to travel further to the draining LNs. The pathway through the collagenous connective tissue is the same for dDCs. Proteinases are, therefore, important for DC migration, particularly when these cells must pass relatively solid tissues such as basement membranes. Matrix metalloproteinases (MMPs) constitute a family of proteinases (including collagenases) that participate in cell migration (Salmi and Jalkanen 2005). MMPs may be expressed on the surface of cells, thus allowing for precise, localized proteolysis that creates a path for migrating cells (Murphy and Gavrilovic 1999). MMP-9 is expressed by epidermal LCs, up-regulated by inflammatory cytokines (TNF- α , IL-1 β) (Saren et al. 1996) and it has been shown to be released following topical application of skin sensitizers (Kobayashi 1997). Further confirmation on the role of MMPs comes from experiments, where the migration of both LCs and dDCs was prevented by broad spectrum MMP inhibitors (BB-3103), by antibodies to MMP-9 and MMP-2, and by the natural tissue inhibitors of metalloproteinases (TIMP), TIMP-1 and TIMP-2 (Ratzinger et al. 2002). In vivo evidence of the importance of extracellular matrix-DC interaction for migration stems from mice deficient for the secreted protein, acidic and rich in cysteine (SPARC). SPARC is a calcium-binding matricellular glycoprotein that binds a range of extracellular matrix components (Bradshaw et al. 2002). LCs and dDCs in SPARC-deficient and SPARC-sufficient mice show striking differences in terms of mobility to draining LNs (Sangaletti et al. 2005). Although similar numbers of LCs populate the ear skin of SPARC^{-/-} and SPARC^{+/+} mice, more LCs are found in the LNs draining antigen-sensitized ears of SPARC^{-/-} mice and significantly more LCs migrate from null-mice-derived ear skin explants. Importantly, the increased DC migration had a profound influence on contact-induced, delayed type-hypersensitivity and naïve T-cell priming.

Enzymatic digestion of surrounding tissues is thus a critical step in the initiation of the complex process of DC relocation to LNs. However, DCs may be situated far away (millimeters) from the closest skin lymphatic vessel and targeting into lymph flow may be facilitated by additional guidance provided by chemokines. Based on the chemokine receptor expression profile of DCs, as well as on chemokines found

to be expressed in the inflamed skin, it has been proposed that CCL22 (Campbell et al. 1999), CCL17 (Katou et al. 2001), CCL20 (Dieu-Nosjean et al. 2000), CXCL9, CXCL10, and CXCL11 (Flier et al. 2001) play an important role in recruiting bone marrow-derived immature DCs to these sites. Most of the receptors recognizing these chemokines are expressed on immature DCs, while mature DCs express chemokine receptors CCR7 and CXCR4, (Sallusto et al. 1998) indicating a role for CCL19, CCL21 and possibly CXCL12 in driving DC exit from sites of inflammation and migration to T-cell zones of draining LNs.

Most *in vivo* studies of DC migration are based either on models that induce some degree of inflammation of the skin (Thomas et al. 1980) or in settings in which bone marrow-derived DCs (BMDCs) are activated *in vitro* with inflammatory stimuli before *in vivo* transfer (Martín-Fontecha et al. 2003). These experimental conditions are known to trigger the maturation of skin LCs, dDCs and BMDCs. Nevertheless, tissue-derived DCs are also found in the draining LNs in the absence of an inflammatory event, suggesting a continuous migration of DCs, a process described as steady-state migration (Merad et al. 2002). A recent report has provided strong evidence that CCR7 is involved in the steady-state migration of skin DCs (Ohl et al. 2004), indicating that maturation and migration can be independently regulated events. In support of this idea, Geissman and colleagues found that LCs present in T-cell areas of skin-draining LNs of dermatopathic lymphadenitis patients were largely immature (Geissmann et al. 2002). Furthermore, *in vitro*-generated LCs maintained their immature phenotype when cultured in the presence of TGF- β 1 and TNF- α , in spite of acquisition of CCR7 expression and responsiveness to LN homing chemokines.

Adoptive transfer experiments of *in vitro* generated CCR7-deficient BMDCs to normal CCR7-sufficient hosts (Martín-Fontecha et al. 2003) it have shown that upon inflammation, DCs need to express CCR7 to migrate efficiently to LNs. Transfer of CCR7-deficient BMDCs resulted in the recovery of less than one-tenth the number of DCs from draining LNs compared with transfer of CCR7⁺ DCs. Further, FITC-bearing skin-derived, CD11c⁺ MHCII^{high} cells are absent in the draining LN after skin sensitization of CCR7-deficient mice (Ohl et al. 2004). Together, these data provide strong evidence to suggest that CCR7 is involved in recruiting LCs as well as other skin-derived DC into skin-draining LN under inflammatory conditions.

The genes encoding the CCR7 ligands CCL19 and CCL21 have been duplicated and modified during evolution such that there is now more than one gene encoding for each chemokine. In mice, there are two known functional genes that encode CCL21: CCL21Leu protein is expressed in the periphery by lymphatic vessels, while CCL21Ser is expressed in LNs, including lymphatic vessels in subcapsular sinus. It is not clear, however, which of these CCL21 gene products is expressed in skin lymphatic vessels. In contrast, functional CCL19 expression is restricted to mature DCs and to stromal cells in LNs. In a naturally occurring mouse mutant, the *plt/plt* (paucity of lymph-node T cells) mouse, some of the genes that encode CCL19 and the CCL21Ser variant are absent (Luther et al. 2000; Vassileva et al. 1999), while CCL21Leu is preserved. Consistent with a role for CCR7 ligands in DC trafficking, a number of laboratories have reported impaired DC migration to LNs in

plt/plt mice after FITC painting (Gunn et al. 1999), lipopolysaccharide administration (Yoshino et al. 2003) or injection of microspheres (Qu et al. 2004). Although appealing, the hypothesis that lymphatic-vessel expression of CCR7 ligands guides DCs towards these vessels for subsequent entry has not yet been formally proven. When DCs become activated for maturation and migration, they begin to secrete CCL19 (Sallusto et al. 1999). Hence, it is possible that DCs, in addition to following chemokine gradients to move, might use autocrine CCR7-dependent mechanisms to migrate towards lymphatics and LNs. A recent study proposed that CCR8 and its cognate ligand CCL1 are also involved in the emigration of mouse monocyte-derived DC from the skin. Considering the anatomical expression of CCL1 in the subcapsule of LNs, it is possible that, in addition to CCR7/CCL21/Leu interactions, the CCL1/CCR8 pair may function downstream the entry of DCs into the lymphatic vessel by regulating the exit from the afferent terminals towards the subcapsular sinus of LNs.

The relevance of intracytoplasmic events, including chemotactic receptor signaling, on DC migration has been clearly documented in mice, lacking the gamma isoform of phosphoinositide-3 kinase (PI3K γ). PI3K γ is located downstream of seven trans-membrane chemotactic receptors, and plays a non redundant role in cell responses to chemotactic agonists. DCs from PI3K γ deficient mice show a profound migration defect both in vivo and in vitro settings in response to chemokines, and this defect is associated with a defective ability to mount antigen specific T-cell responses (Del Prete et al. 2004). Cytoskeletal rearrangements in LCs are also critical for determining LC ability to dislodge and transmigrate. For example, epidermal LCs deficient in the Wiskott–Aldrich syndrome protein (WASp) show impaired migration to LNs following contact sensitization (de Noronha et al. 2005). Importantly, the observed impaired migration of in vitro generated WASp deficient DCs when transferred into wild type C57BL/6 mice was associated with a reduced capacity to prime CD4 and CD8 T cells in vivo (Bouma et al. 2007).

Consistent with a requirement for molecular interactions between DCs and the skin lymphatic endothelium, some data point to a role for intercellular adhesion molecule 1 (ICAM-1) expressed by a peripheral cell type, namely lymphatic endothelial cells, in mediating the migration of DCs to LNs (Ma et al. 1994; Xu et al. 2001). Also JAM-1 (junctional adhesion molecule 1), an adhesion molecule expressed by DCs and by the lymphatic endothelium, affects DC mobility since the absence of JAM-1 expression in DCs facilitates their migration to LNs (Cera et al. 2004).

3 From Blood to Lymph Nodes

It has become widely accepted that the trafficking of naïve T and B cells from blood stream into peripheral LNs is controlled by a sequence of at least three distinct adhesion and signaling events (Butcher and Picker 1996; Springer 1994; von Andrian and Mackay 2000). A slow rolling step along the vessel follows an initial tethering

that allows leukocytes to bind to endothelial cells. Chemotactic stimuli from the endothelium engage and trigger specific chemokine receptors on the surface of the rolling lymphocyte, a step that, in turn, induces intracellular signals leading to conformational changes on endothelium integrins. This results in firm adhesion, which enables cells to emigrate through the vessel wall (von Andrian and Mempel 2003).

Intravital microscopy (IVM) has been instrumental in defining the molecular mechanisms behind adhesion cascades that mediate T-cell homing to LNs (Stein et al. 2000; Warnock et al. 1998). Tethering and rolling are mediated by L-selectin (CD62L); the endothelial L-selectin ligand is PNAd, an O-linked carbohydrate moiety, the main components of which are recognized by the monoclonal antibody MECA-79 (Streeter et al. 1988). Stick of naïve and central memory T cells to HEVs is mediated by the CCL21 chemokine which is constitutively expressed by HEVs and binds to CCR7 (Gunn et al. 1999). The second CCR7 agonist, CCL19, is expressed by the lymphatic endothelium and interstitial cells in LNs, but not by HEVs. Nonetheless, perivascular CCL19 can be transported to the luminal surface of HEVs and induce integrin activation on rolling T cells (Baekkevold et al. 2001). The relative contribution of CCL19 versus CCL21 in T-cell homing has remained elusive, but some clues will likely be provided in the near future as a result of the recent development of CCL19 deficient but CCL21 sufficient mice (Link et al. 2007). Firm arrest of sticking T cells is mediated by the integrin leukocyte function-associated antigen 1 (LFA-1), which interacts with ICAM-1 and ICAM-2 on HEVs (Hamann et al. 1988).

Currently available data support the concept that the extravasation of DCs into peripheral LNs follows the same rules as those described for naïve T and B cells, with a major role for selectins, chemokine receptors and integrins. The mechanisms for conventional DC precursor recruitment during inflammatory responses was addressed by Ardavin and colleagues (Martin et al. 2002) in a model of infection with the mouse mammary tumor virus MMTV. The authors reported a strong increase of blood-borne CD8 DCs in peripheral LNs following subcutaneous administration of MMTV. This dramatic increase was prevented in mice that were injected with anti-L-selectin antibodies, suggesting that DC precursor recruitment occur via HEVs. Furthermore, conventional, blood borne-DCs have also been found in resting LNs (Ruedl et al. 2000), indicating that, in the steady state a continuous migration of circulating DC precursors may occur, although the molecular requirements for entry in these conditions remain to be established.

PDC represent a rare subset of DCs present in blood and in secondary lymphoid organs (Colonna et al. 2004), that have the extraordinary capacity to produce high amounts of type I interferons following viral infections (Cella et al. 1999). PDCs express several adhesion molecules and chemokine receptors on their surface that could promote interactions with HEVs and support their migration from the blood into peripheral LNs. Indeed, L-selectin is constitutively expressed on these cells, and may play a role in PDC migration to secondary lymphoid organs, as the number of PDCs in non inflamed LNs of L-selectin-deficient mice is reduced compared to controls (Nakano et al. 2001). However, in vivo experiments have shown that blockade of L-selectin inhibits mobilization of PDC precursors in the circulation,

but not their migration across HEVs (Yoneyama et al. 2004). Concerning the role of particular chemokine receptors in this process, it was initially proposed to be solely dependent on CXCR3 (Yoneyama et al. 2004). However, other chemokine receptors, such as CCR5, known to regulate PDC trafficking into sites of inflammation (Penna et al. 2001) may also regulate PDC migration to inflamed LNs. Diacovo and colleagues used IVM to study the behavior of murine PDCs in the microvasculature of subiliac LNs in the absence or presence of an inflammatory stimulus. The results of this study provided the first direct evidence that PDCs can emigrate from the blood into peripheral LNs by interacting with HEVs through a coordinated multi-step process. The authors showed that PDCs rolled on HEVs of resting LNs but little transmigration was observed. They also demonstrated that entry into activated LNs was dependent upon the expression of E-selectin on LNs and, in contrast to previous studies (Yoneyama et al. 2004), of CCR5 on PDCs. Discrepancies may relate to the use of different adjuvants that may deliver different signals to draining LNs and the expression of a different set of chemokines on HEVs.

4 Dendritic Cell Localization Within Lymph Nodes

The visualization of DC behavior within LNs through the use of two photon microscopy has advanced our understanding of DC function in the context of triggering T-cell responses (Celli et al. 2007). Nonetheless, this powerful technique has not allowed the identification of the precise route followed by DCs to migrate from the subcapsular sinus to the T-cell zone of the LN cortex. Although mouse LNs are thought to be simple with regard to lymphatic-vessel entry, a great complexity of interstitial lymphatic-vessel structure in mouse LNs has been appreciated and gained much interest in recent years (Gretz et al. 1997; Sixt et al. 2005). Whether migrating DCs use such structures connecting the subcapsular sinus to perivenular spaces around HEVs in order to relocate into deeper areas of the LNs is presently unknown.

Initial studies indicated that DCs migrating from nearby tissues primarily relocate to areas next to HEVs for efficient encounter with naïve T cells. The immune system may have developed this strategy to optimize encounter of rare antigen-specific T cells and DCs presenting the relevant antigen. Indeed, by using confocal microscopy, Bajenoff and colleagues (Bajenoff et al. 2003) showed, that DCs that have picked up antigens within the skin are preferentially located in the vicinity of HEVs, and that most antigen-specific T cells passing the HEVs are selectively trapped by the relevant DCs (Bajenoff et al. 2003). A more detailed picture in the interstitial localization of different subsets of tissue-derived DCs within LNs comes from recent work by B. Malissen's group (Kissenpfennig et al. 2005). In order to track and discriminate LCs from dermal DCs *in vivo*, this group developed knockin mice expressing enhanced green fluorescent protein (EGFP) under the control of the langerin (CD207) gene. The study showed that most EGFP⁺ LCs were sessile under steady-state conditions, whereas skin inflammation induced LC motility and emigration to LNs. After epicutaneous painting, dDCs and LCs were not evenly

intermingled in the paracortex of draining LNs. They occupied distinct, contiguous areas within this T cell-rich zone suggesting the existence of a previously unrecognized microanatomy of the paracortex of LNs. Whether these distinct locations confer LC-derived DCs and dDCs the ability to encounter distinct T-cell subsets remains to be established.

Refined studies using two-photon microscopy have also revealed that DC micromotility within LNs is a critical step for efficient T-cell priming (Bousso and Robey 2003; Celli et al. 2007). By using transgenic mice in which all DCs expressed enhanced yellow fluorescent protein (EYFP) controlled by the CD11c promoter, Lindquist and colleagues studied the behavior of endogenous and adoptively transferred DCs (Lindquist et al. 2004). Most endogenous DCs in the network were involved in continuous probing movements toward T cells, but did not change position and thus seem to be sessile. The dynamics of DC migration into the LNs from peripheral tissue were studied by intradermal injection of DCs marked with green fluorescent protein. It was shown that injected DCs moved faster than resident DCs, and were found mainly at the boundary between the T and B cell zone. Subsequently, these cells became progressively dispersed into the resident network and lost motility by 2–3 days after transfer. The authors proposed a model whereby the initial motility of DCs mainly serves the function of dispersing the cells in the network rather than in promoting encounters with T cells.

A recent study by Bajenoff et al. (2006) has provided evidence that the fibroblastic reticular cell network essentially defines and supports the apparent random walk movement of naive T cells within the LN paracortex. Importantly, CCR7 ligands immobilized on fibroblastic reticular cells or extracellular matrix surfaces, rather than soluble chemokines, mediate the observed CCR7-dependent induction of intranodal T-cell motility (Worbs et al. 2007). Whether similar mechanisms are used by DCs, and whether the contribution of CCL21 and CCL19 on guiding DCs in T-cell areas is redundant, is not clear at present.

5 Regulation of Dendritic Cell Migration to Lymph Nodes

DC migration *in vivo* is a tightly regulated process controlled at different levels. Primarily, much attention has been paid to the production of chemokines and the expression of relevant chemokine receptors, yet modulation of certain selectins on HEVs and structural changes on stimulated LNs may also affect DC migration. A dramatic change in the repertoire of chemokine receptors is promoted by Toll-like receptor (TLR)-mediated stimulation of DCs (Sallusto et al. 1998), including the up-regulation of CCR7. Exogenous administration of the TLR-4 agonist LPS promotes *in vivo* mobilization of DCs from the periphery within a few hours (De Smedt et al. 1996; Ruedl et al. 2000), and mice treated with neutralizing antibodies to IL-1 or TNF show an impaired migration of DCs (De Smedt et al. 1996). Activation of DCs is also associated with down-regulation of inflammatory chemokine receptors to facilitate unidirectional migration towards draining LNs and release from the inflammatory site.

Although the expression of CCR7 is necessary for the migration of tissue resident DC to draining LNs, it is not sufficient, as this chemokine receptor can be expressed in a biologically inactive state resulting in failure to undergo chemotaxis towards CCR7 ligands (Scandella et al. 2002) or requiring a high concentration of CCR7 ligands (Robbani et al. 2000). Signals found at sites of inflammation, including the lipid mediators leukotrienes and prostaglandin E2 (Robbani et al. 2000; Scandella et al. 2002), and the ADP-ribosyl cyclase CD38 (Partida-Sanchez et al. 2004), sensitize CCR7 to CCL19 and CCL21 (Scandella et al. 2004).

P- and E-selectins are transiently expressed in non lymphoid tissues following stimulation with a variety of inflammatory stimuli (Ley 2003). P- and E-selectin ligands are fucosylated oligosaccharides expressed by several proteins such as P-selectin glycoprotein ligand-1 (PSGL-1) that enable a rapid traffic of effector T cells to injured tissues to control pathogen spread (Agace 2006). Adoptive transfer of fluorescently-labeled wild type PDCs into E-selectin-sufficient or into E-selectin-deficient mice showed that transmigration of PDCs to LNs was E-selectin-dependent (Diacovo et al. 2005), suggesting that acutely stimulated LNs undergo changes in HEVs that result in recruitment of PDCs.

DC migration can also be regulated indirectly. For instance, lymphatic vessel structure within LNs is not static, and lymphatic vessel expansion directly correlates with alterations in the magnitude of DC accumulation in LNs (Angeli et al. 2006). Indeed, Angeli and colleagues reported that B cell-derived signals produced in activated draining LNs, i.e. VEGF-A, increased the migration of skin DCs. Thus, mobilization of DCs to LNs can be regulated by signals initiated within LNs themselves. In line with the idea of an indirect check point control we found that inflammatory stimuli present in the skin influence DC migration not only by modulating the expression of CCR7 by DCs, but also through up-regulation of CCL21 which is induced by TNF and IL-1 β (Fig. 1) (Martín-Fontecha et al. 2003).

One alternative recruitment pathway for increased migration of monocytes to peripheral LNs via HEVs involves the transport of inflammatory chemokines from skin to draining LNs. Palframan and colleagues showed that inhibition of monocyte chemoattractant protein-1 (MCP-1, CCL2) blocked this inflammation-induced monocyte homing to LNs (Palframan et al. 2001). They reported that CCL2 mRNA in inflamed skin was over 100-fold upregulated and paralleled by CCL2 protein levels, whereas in draining LNs CCL2 mRNA induction was much weaker and occurred only after a pronounced rise in CCL2 protein expression, suggesting that CCL2 in draining LNs was primarily derived from inflamed skin. In CCL2-deficient mice, intracutaneously injected CCL2 accumulated rapidly in the draining LNs, where it enhanced monocyte recruitment. IVM showed that skin-derived CCL2 was transported via the lymph to the luminal surface of HEVs, where it triggered integrin-dependent arrest of rolling monocytes. These findings demonstrate that inflamed peripheral tissues project their local chemokine profile to HEVs in draining LNs, and thereby exerting *remote control* over the composition of leukocyte populations that home to these organs from the blood.

Pathogens, in their quest for survival, have evolved several ways to escape immunity eventually by subverting DC function, especially through the manipulation

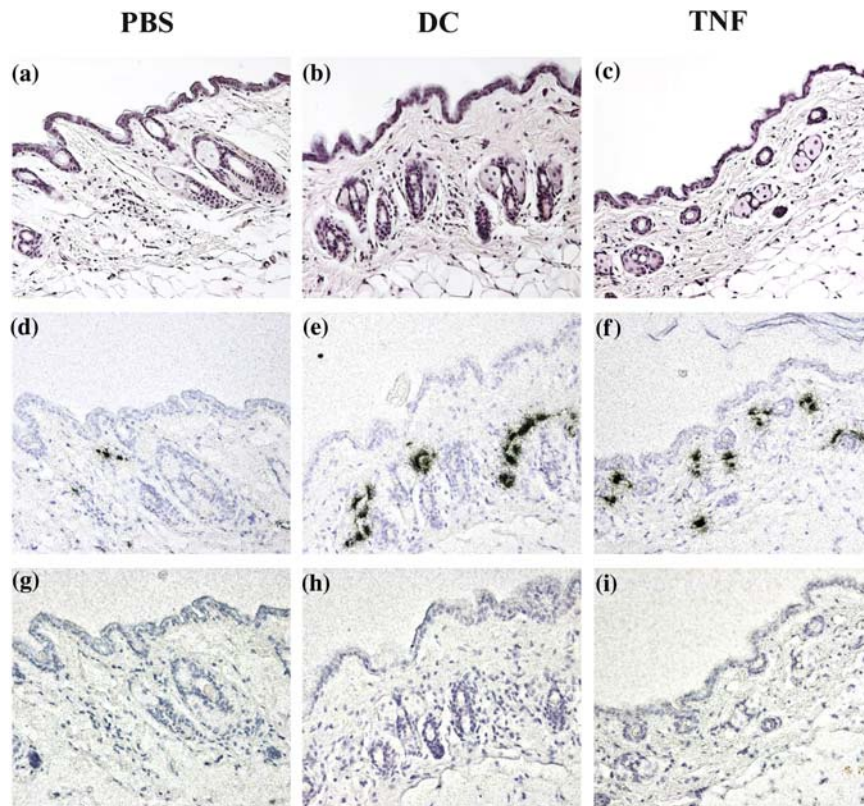


Fig. 1 CCL21 is up-regulated on lymphatic endothelial cells after injection of mature DCS or TNF. Mice were injected intradermally with PBS, 10^5 syngeneic dcs, or 10 ng TNF. 8 h later, skin samples were collected and embedded in paraffin. Serial sections were stained with hematoxylin and eosin (a)–(c), or hybridized with antisense (d)–(f) or sense (inset) 35 S-labeled CCL21 riboprobe or stained with a polyclonal antibody to mouse CCL21 (g)–(i). X20. This figure is reproduced with the kind permission of the *Journal of Experimental Medicine*. (Martín-Fontecha et al. 2003, Copyright 2003. Rockefeller University Press)

of pathogen-recognition receptors (PRRs), and also by modulating DC migration. A number of studies have indeed appreciated that many viruses, including MMTV (Martin et al. 2002), Rauscher leukaemia virus (RLV) (Gabrilovich et al. 1994), simian immunodeficiency virus (SIV) (Barratt-Boyes et al. 2002), human cytomegalovirus (HCMV) (Moutaftsi et al. 2004) and herpes simplex virus (Prechtel et al. 2005) have found ways to inhibit DC migration to draining LNs. Although the mechanisms for such control is not clear, adhesion molecules like ICAM-1 and CD44 (Gabrilovich et al. 1994) and chemokines (Moutaftsi et al. 2004; Prechtel et al. 2005) may be targets for viral control of DC mobilization.

6 Dendritic Cells-Based Vaccines Against Cancer

Recent advances have been made in understanding DC biology, in the context of prevention and therapy of immune disorders (Steinman and Banchereau 2007). In particular, ex vivo generated cancer vaccines based on DCs are currently applied in the clinic (Banchereau and Palucka 2005). DC migration must be taken into consideration in order to improve strategies to deliver such immunological tools into sites of T-cell priming for induction of an antitumour immune response (Tacken et al. 2007). Indeed, mouse studies show that DC migration directly correlates with the extent of T-cell proliferation and effector cell differentiation (Martín-Fontecha et al. 2003). Therefore, efforts to enhance the delivery of ex vivo generated DCs into LNs of cancer patients might prove to be beneficial. Several clinical trials have been carried out or are in progress to determine the efficacy of therapeutic vaccines that use ex vivo-matured DCs as the main component.

The discovery that DCs can be generated from monocytes in the presence of granulocyte-macrophage colony-stimulating factor and interleukin-4 boosted the clinical application of monocyte-derived DCs (moDCs) (Sallusto and Lanzavecchia 1994). Recently completed patient trials, applying ¹¹¹-indium labeled moDC as cancer vaccines, revealed that although immature moDCs migrate much less than mature moDCs in vivo, in general less than 5% of intradermally administered mature moDCs reach the draining LNs (De Vries et al. 2003). Data from mouse models employing ex vivo generated BMDCs labeled with either ¹¹¹-indium or carboxyfluorescein diacetate succinimidyl ester (CFSE) and BMDCs endogenously expressing green fluorescent protein revealed, that DC migration from the intradermal injection site is in the same efficiency range (Eggert et al. 2003; Martín-Fontecha et al. 2003).

In addition to the intradermal injection of DCs, alternative routes of administration have been explored in both mice and humans. In mice, intravenous injection of DCs resulted in the accumulation of DCs in the spleen, as expected (Eggert et al. 1999). Nevertheless, a few but detectable DCs can be found in peripheral LNs in mice following i.v. injection (Cavanagh et al. 2005). Also, we have observed that following i.v. injection of high numbers of OVA-loaded LPS-matured DCs, antigen-specific DO11.10 CD4 T cells were primed in peripheral LNs (Fig. 2; AMF, unpublished observation). To exclude that CD4 T cells were primed in spleen and emigrated to peripheral LNs, we also analyzed the activation of CD4 T cells in mice that were splenectomized (spleen-X) before transfer of DCs i.v. Figure 3 (AMF, unpublished observation) shows a similar CFSE profile in CD4 T cells in LNs whether antigen-loaded DCs were transferred in spleen-X mice or control mice, suggesting that CD4 T cells were primed in LNs. Although we cannot formally rule out that mature DCs injected i.v. migrated to LNs from afferent lymphatics, the fact that the CFSE profile is essentially the same in the LNs of spleen-X mice and control mice suggest that, under certain circumstances, DCs may gain access to peripheral LNs across HEVs and prime T cells. As CD62L is not expressed by ex vivo generated DCs (Robert et al. 2003), the molecular requirements governing DC extravasation from blood remain unknown. In human trials, DC migration following intravenous injection has so far not been monitored. Alternative strategies that are currently

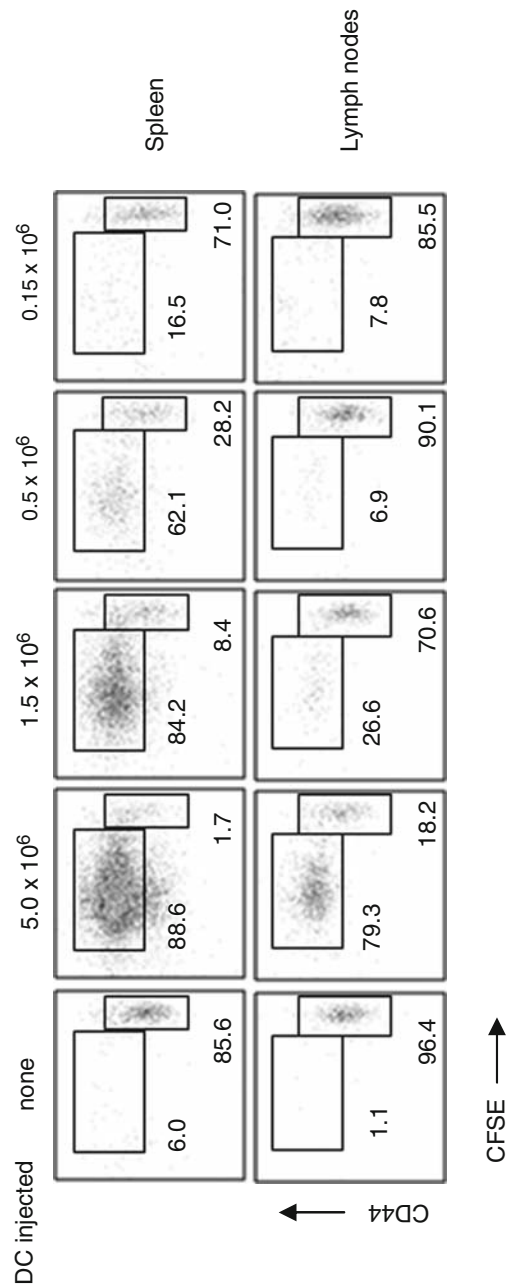


Fig. 2 Antigen carrying DC injected i.v. prime CD4 T cells in subcutaneous lymph nodes. 3×10^6 naïve rag2^{-/-} DO11.10 CD4 T cells were labeled with CFSE and adoptively transferred into syngeneic BALB/c mice. Mice were primed by increasing numbers of OVA₃₂₃₋₃₃₉-pulsed LPS-matured DCS injected i.v. Shown are the expression of CD44 and the CFSE profiles of CD4⁺/KJ1.26⁺ cells in spleen and subcutaneous lymph nodes three days after priming. Numbers represent the percentage within the indicated gates

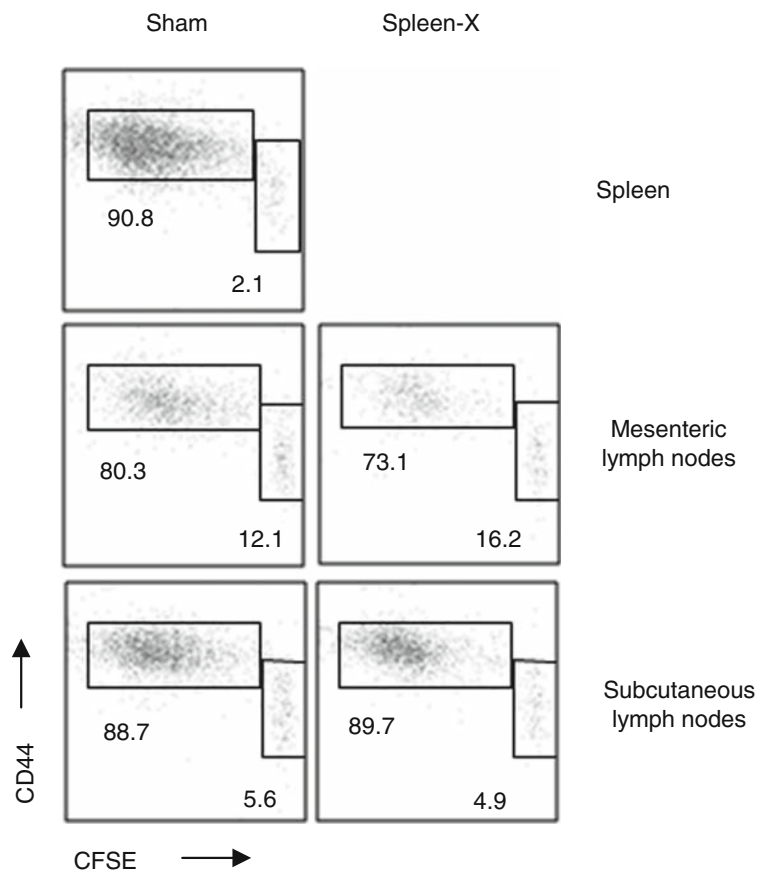


Fig. 3 CD4 T cells are primed in subcutaneous lymph nodes in splenectomized mice. 3×10^6 naïve rag2^{-/-} DO11.10 CD4 T cells were labeled with CFSE and adoptively transferred into syngeneic BALB/c mice. Mice were splenectomized (Spleen-X) or sham operated and primed by an i.v. injection of 5×10^6 OVA₃₂₃₋₃₃₉-pulsed LPS-matured DCS. Shown are the expression of CD44 and the CFSE profiles of CD4⁺/KJ1.26⁺ cells in spleen and subcutaneous lymph nodes three days after priming. Numbers represent the percentage within the indicated gates

employed to facilitate DC migration following intradermal injection include pretreatment of the vaccine injection site with inflammatory cytokines such as TNF- α (Martín-Fontecha et al. 2003). Similarly, pretreatment with TLR ligands is used to induce an inflammatory environment to improve DC migration (Nair et al. 2003).

An alternative approach that circumvents the skin migration problem involves the direct injection of DCs into the LNs (Jonuleit et al. 2001; Nestle et al. 1998). Although intranodal injection may destroy the architecture of the injected node, migration to subsequent nodes has been observed and follows the physiological path through lymph vessels. Therefore, intranodal versus intradermal administration of peptide-loaded DC vaccines remains to be explored in much more detail, including the quality of the induced T-cell response.

Several studies in which DC vaccination of cancer patients has been explored demonstrate that DC vaccines are safe, and clearly indicate that maturation of DCs is mandatory to induce an effective immune response. One of the concerns relating to ex vivo generated DCs is, how to ensure effective migration to the T-cell areas in the LN. In this context, enhancement of migration of ex vivo generated DC vaccines by *pre-conditioning* peripheral tissue like the skin with either inflammatory cytokines or TLR agonists is worth pursuing (Martín-Fontecha et al. 2003). Preclinical studies also suggest that multiple routes of vaccination are preferable to induce systemic immunity.

In summary a deeper knowledge of the molecular interactions underpinning DC migration may enable us to better understand regulation of immune responses and to better use DCs in the clinical setting.

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