

Dendritic cell migration

with

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Dendritic cells (DC) are potent antigen presenting cells with a unique ability in inducing T and B cell responses. Immature DC are localized in peripheral tissues where they exert a sentinel function for incoming antigens (1). Within an inflammatory context DC enter afferent lymphatics and travel to local lymph nodes where they present antigens, in the context of co-stimulatory molecules, to direct T cell response (1,2).

There is evidence that steady-state migration of DC to lymph nodes also occurs in normal conditions and may serve to tolerate T cells against self and non-dangerous antigens (3). In addition, DC participate in the regulation of the inflammatory reaction with the production of oxygen radicals (4), chemokines (2,5,6) and cytokines, including angiogenic factors, which may participate in the resolution of the inflammatory process (7).

What is known about dendritic cell migration?

Silvano Sozzani: DC migration is a complex process that involves the production of chemotactic factors, the activation of adhesion molecules and the interaction of the cells with physical obstacles, such as basement membranes and collagen meshwork (8). Furthermore, it must be considered that DC are a heterogeneous population that possess unique homing properties (8,9). Myeloid blood CD11c⁺ DC migrate in response to a wide variety of inflammatory chemotactic agonists produced at the sites of infection and immune reaction. On the other hand, CD123⁺ plasmacytoid DC are normally absent from peripheral tissues and migrate from the blood

into lymph nodes through high endothelial venules (10). Recruitment of plasmacytoid DC to non-lymphoid tissues is observed in some pathological conditions, such as autoimmune diseases (i.e. lupus erythematosus disease, psoriasis and rheumatoid arthritis), allergic diseases (i.e. contact dermatitis and nasal mucosa polyps) and in certain tumors (i.e. ovarian carcinoma, neck squamous cell carcinoma and melanoma) (8,11) but the molecular basis for this response are largely unknown. It is likely, that the regulated expression of functional chemotactic receptors represents one of the main factors that regulate the distribution of DC subsets *in vivo*.

Why is the correct tissue localization important?

Silvano Sozzani: The proper localization of immature DC to peripheral tissues is pivotal for the prompt capture of antigens at the site of infection. Similarly, the migration of maturing DC and the proper localization into secondary lymphoid organs is a critical event for optimal immune response. These considerations are based on a series of experimental evidences obtained in conditions in which

DC migration was altered. For instance, mice lacking CCR7, the lymph node homing chemotactic receptor, or its ligands (i.e. CCL19 and CCL21), show an altered architecture of the lymph nodes and a defect in specific immunity (12,13). Similarly, mice lacking the gamma isoform of phosphoinositide-3 kinase (PI3K γ), an enzyme located downstream seven-transmembrane chemotactic receptors that plays

a non redundant role in cell migration (14), show an impaired DC migration and defects in contact hypersensitivity reactions (15). In general alterations that hamper DC migration, like those observed in *Jam-A*^{-/-} or *MMP-9*^{-/-} mice cause a defect in specific immunity (8). Conversely, when

migration of DC is facilitated, such as in mice that lack SPARC (Secreted protein, acidic and rich in cysteine), a calcium-binding matricellular glycoprotein that binds extracellular matrix components, antigen specific immune responses are increased (16).

Are chemokines involved in dendritic cell migration?

Silvano Sozzani: Migration is a multistep process that involves the adhesion with endothelial cells and the activation of chemotactic receptors. In the past ten years, our group, and others, have clearly shown the central role of chemokines in directing DC migration (17,18). Chemokines are small-secreted chemotactic cytokines that regulate the migration of leukocytes under steady state and inflammatory conditions (19). Immature DC express a unique repertoire of inflammatory chemokine receptors (i.e. CCR1, CCR2, CCR5, CCR6) that bind "inflammatory" chemokines, such as CCL5, CCL2, CCL3, CCL4 and CCL20. A dramatic change in the pattern of chemokine receptors is promoted by DC activation. This change is responsible for the migration of DC from the periphery to regional lymph nodes. The signals that promote this process include a variety of inflammatory cytokines, such as IL-1 and TNF, as well as many microbial products, such as the activators of Toll-like pattern recognition receptors (TLRs) and some endogenous molecules, like CD40L, expressed by

activated T cells. Activation of DC is associated with the down-regulation of chemokine inflammatory receptors and the expression of CCR7, the receptor for CCL19 and CCL21, two chemokines that are expressed at the luminal side of high endothelial venules and in the T cell rich areas of secondary lymphoid organs, like tonsils, spleen and lymph nodes. CCR7 expression by DC is also required for the entry of DC into lymphatic vessels at peripheral sites both in steady state and inflammatory conditions. During inflammation, the entry of DC into lymphatic vessels is boosted by the up-regulation of CCL21 on lymphatic endothelial cells. Therefore, inflammatory stimuli not only promote the recruitment of immature DC into tissues but also initiate their maturation process and boost the recruitment of maturing DC into lymphatics (20). The migration pathway that leads DC from periphery to secondary lymphoid organs also involves the expression of CCR8 by migrating DC and the expression of its ligand, namely CCL1, in the lymph node subcapsular sinus (21).

What is the role of non-chemokine chemotactic factors?

Silvano Sozzani: Recent work has documented that a number of chemotactic agonists, different from chemokines, play a relevant role in DC subset recruitment (6,17,22-24). These chemotactic stimuli include receptors for bacterial components, for bioactive lipids and for signals of "tissue danger"; all these agonists are produced within minutes at the site of inflammation and represent an early signal for the recruitment of DC, or their precursors, which precedes chemokine action.

Early work performed by this group described that myeloid immature DC express functional receptors for formylated peptides (fMLP) and chemotactic components of the complement cascade (i.e. C5a) (17). More recently, it was shown that DC also express FPRL2, another member of the formyl chemotactic peptide receptor family. FPRL2 binds F2L, an endogenous high affinity ligand that derives from the cleavage of the N-terminus of the intracellular heme-binding protein

(HBP). It is conceivable that F2L, released by proteolysis of HBP by dying cells, serves to recruit DC at the site of tissue destruction (24). Human and mouse DC express functional receptors for platelet activating factor (PAF) (22) and recent results have suggested that PAF acts as a retention factor for DC in peripheral tissues and in pathological conditions like in atherosclerotic plaques (25). Chemerin, a new chemotactic protein that belongs to the cathelicidine family, was shown to induce the migration of both myeloid and plasmacytoid DC through the interaction with ChemR23 (6,23). Since chemerin is produced during some pathological conditions characterized by plasmacytoid DC accumulation, such as ovarian carcinoma, lupus erythematosus and rheumatoid arthritis, it is likely that this protein plays

a role in the recruitment of these cells into pathological tissues (6). Other proteins that belong to the cathelicidine family, such as the α - and β -defensins, are chemotactic for immature DC. The chemotactic activity of β -defensins is mediated by the interaction with CCR6, the receptor for CCL20, whereas the receptor used by α -defensins is still unknown (26). Some chemokine receptors can be engaged by non-chemokine ligands as in the case of Histidyl-(HisRS) and asparaginyl-(AsnRS) tRNA synthetases, two cytoplasmic proteins involved in protein synthesis, that function as autoantigens in myositis, and induce the migration of immature DC through the binding to CCR5 (27). Therefore, self-antigens may promote autoimmunity through the direct recruitment of antigen presenting cells at the site of tissue injury.

In which way DC migration is regulated?

Silvano Sozzani: Migration of DC is regulated at multiple levels; a first strategy is represented by the regulated production of chemotactic signals and the regulation of chemokine receptor expression during DC activation (8). However, multiple experimental evidences have shown that chemokine receptor expression is not predictive of DC migration since multiple factors, including prostaglandins, leukotrienes, sphingosine 1-phosphate, extracellular nucleotides and some membrane proteins (e.g. CD38) play an important role in the regulation of chemokine receptor function (8,9,28).

● Conclusions

DC represent a heterogeneous population of bone marrow-derived cells that are both powerful initiators and modulators of immune responses. DC play a crucial role in the activation

of adaptive immunity and in the generation of tolerance against non-dangerous signals. To accomplish their functional program DC need to migrate to both non-lymphoid and lymphoid tissues, and this migration needs to be carefully regulated. Pathological conditions that are characterized by an altered migration of DC result either in immune deficiencies or in autoimmunity. For these reasons, DC migration is a tightly regulated process, controlled at multiple levels. A detailed understanding of the rules that govern migration might allow the design of new therapeutic strategies to control DC function in all those pathological conditions characterized by an excessive activation of DC, as in autoimmune reactions and chronic inflammation, or by their insufficient activation, as observed in tumor patients.

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