

### Skin homing of Langerhans cell precursors: Adhesion, chemotaxis, and migration

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Langerhans cells (LCs) are epidermal antigen-presenting dendritic cells. They contain unique granules, known as Birbeck granules, which are substructures of the endosomal recycling compartment. LCs migrate from the epidermis to the regional lymph nodes for presentation of antigenic peptides to T cells. There LCs either initiate a primary immune response or induce antigen-specific tolerance. The replenishment of the LC pool in the epidermis is the topic of this review. Chemokines produced by epidermal keratinocytes and by dermal fibroblasts guide the arrest of LC precursors on endothelial cells of dermal venules, followed by their transmigration through endothelium and dermis toward the epidermis. One necessary prerequisite for this is the coordinated expression of adhesion receptors and counterreceptors on LC precursors and on endothelial and dermal cells. LC precursors attach to and degrade basement membrane proteins to penetrate the dermal matrix and the basement membrane of the dermal-epidermal junction. LC migration depends on the activity of matrix metalloproteinases, which are proteolytic endopeptidases cleaving matrix components. Matrix metalloproteinases also execute an important role in modulating inflammatory and immune responses by processing chemokines, which turns them into dual players for the immigration of LC precursors into the epidermis. (*J Allergy Clin Immunol* 2006;117:163-8.)

**Key words:** Langerhans cell, adhesion, migration, chemotaxis, matrix metalloproteinases

Dendritic cells (DCs) are key regulators of immune responses capable of promoting or suppressing T-cell responses. Langerhans cells (LCs) are bone marrow-derived DCs that are typically localized in the basal and suprabasal layers of the epidermis and along mucosal surfaces. These cells represent a critical outpost of the immune system at the interface to the external environment. LCs and DCs are characterized by the expression

#### Abbreviations used

|         |                                                          |
|---------|----------------------------------------------------------|
| BRAK:   | Breast- and kidney-expressed chemokine                   |
| CCL:    | CC chemokine ligand                                      |
| CCR:    | CC chemokine receptor                                    |
| CD34DC: | CD34 <sup>+</sup> stem cell-derived dendritic cell       |
| CXCL:   | CXC chemokine ligand                                     |
| DC:     | Dendritic cell                                           |
| ICAM:   | Intercellular adhesion molecule                          |
| JAM:    | Junctional adhesion molecule                             |
| LC:     | Langerhans cell                                          |
| LFA:    | Lymphocyte function-associated antigen                   |
| MADDAM: | Metalloprotease and disintegrin dendritic antigen marker |
| MCP:    | Monocyte chemoattractant protein                         |
| MIP:    | Macrophage inflammatory protein                          |
| MMP:    | Matrix-degrading metalloproteinase                       |
| PECAM:  | Platelet-endothelial cell adhesion molecule              |
| RAP1:   | Guanosine triphosphatase-activating protein 1            |
| SDF:    | Stromal-derived factor                                   |
| TARC:   | Thymus and activation-regulated chemokine                |

of CD1a molecules. The unique marker for LCs, langerin, is the major constituent of Birbeck granules, which are special phagosomes present in LCs.

DCs bridge innate and adaptive immunity and participate in both responses. On capture of pathogens, DCs release inflammatory cytokines and chemokines, attracting other immune cells to the infection site. Through the  $\beta_2$ -integrin Mac-1, activated neutrophils, which are the major players of the innate immune system, bind to the DC-specific C-type lectin DC-specific intercellular adhesion molecule (ICAM) 3—grabbing nonintegrin on immature DCs, thereby inducing DC maturation.<sup>1</sup> Mature LCs migrate into draining lymph nodes. In T-cell compartments of lymph nodes, they activate T cells and trigger an antigen-specific immune response. Cutaneous DCs play a key role in the pathogenesis of atopic dermatitis. Activated by keratinocyte-derived thymic stromal lymphopoietin, they polarize naive CD4 T cells toward pro-allergic cytokine-producing T<sub>H</sub>2 cells. Transgenic mice overexpressing thymic stromal lymphopoietin in the epidermis spontaneously exhibit clinical hallmarks of atopic dermatitis.<sup>2</sup>

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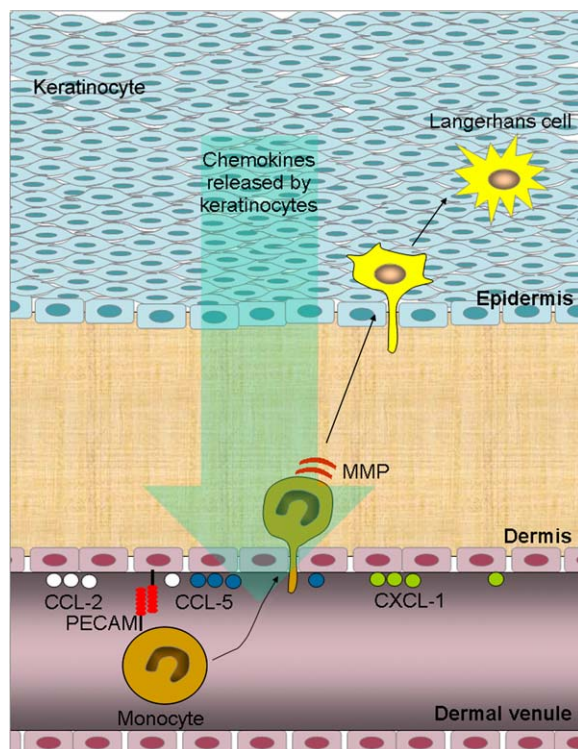


FIG 1. Skin homing of LC precursors.

Little information exists about the signals controlling immigration of LC precursor cells from the blood into the epidermis. Fig 1 shows our concept for skin homing of LC precursors. On trauma or inflammation in the epidermis, keratinocytes produce chemokines, which results in firm adhesion of LC precursors to endothelial cells of dermal venules. Adhesion and subsequent migration across the endothelial barrier rely on special adhesion molecules of both LC precursor cells and endothelial cells. By assistance of matrix metalloproteinases, LC precursors intersect the dermis and the dermal-epidermal junction. Subsequently, LCs migrate toward the epidermis guided by a chemokine gradient and simultaneously differentiate to resident epidermal LCs. Our review discusses the equipment of potential LC precursors with adhesion molecules, chemokine receptors, and matrix metalloproteinases required for immigration into the epidermis and the production of the corresponding chemokines by endothelial cells, epidermal keratinocytes, resident LCs, and dermal fibroblasts.

### LC PRECURSOR CELL SUBSETS

It is assumed that LCs have no single origin. Local conditions within the epidermis direct the development of LCs. As recently reviewed by Moser et al,<sup>3</sup> studies of chimeric mice suggest that under normal noninflammatory conditions, LCs are replaced entirely from a local precursor pool, which could be derived from dermal CD14<sup>+</sup> cells. Furthermore, no LCs of recipient origin were

observed in transplanted human hands over a period of 4.5 years.<sup>4</sup> These results strongly suggest that under steady-state conditions, the replacement of human epidermal LCs from bone marrow–derived precursors occurs very slowly, if at all. In contrast, inflammation induces replacement of emigrated LCs, largely through a bone marrow–derived precursor.

Monocytes, MHC class II<sup>+</sup> CD11c<sup>+</sup> cells, and CD34<sup>+</sup> cell–derived CD1a<sup>+</sup> cells might give rise to development of LCs.<sup>5</sup> In an *in vitro* study it was demonstrated that CD14<sup>+</sup>CD34<sup>+</sup> PBMCs migrate across the endothelium and initiate development of immunostimulatory DCs.<sup>6</sup> Although the presence of Birbeck granules could not be demonstrated for DCs derived *in vitro* from CD14<sup>+</sup>CD34<sup>+</sup> precursor cells, these cells fulfill the criteria for *bona fide* DCs and could give rise to LCs.

Moreover, it was reported that the rare CD16<sup>+</sup> monocyte subtype (5% to 10% of peripheral blood monocytes), which is dramatically increased under inflammatory conditions, differentiates into LCs.<sup>5</sup> In an *in vitro* model of transendothelial trafficking, CD16<sup>+</sup> monocytes preferentially differentiate into DCs. Interaction with endothelial cells might be sufficient for differentiation of monocytes to DCs.<sup>5</sup>

### EFFECT OF ADHESION MOLECULES ON THE MIGRATION OF LC PRECURSORS

On their route from blood vessels, LC precursors pass the vascular endothelium and traffic across dermal tissue barriers before they reach the keratinocyte layers forming the epidermis. Cell-cell contacts mediated by adhesion molecules enable and control trafficking of LC precursors. DCs express ICAMs, lymphocyte function–associated antigen 1 (LFA-1), vascular cell adhesion molecule, and platelet endothelial–cell adhesion molecule 1 (PECAM-1). In addition, DCs are able to interact with endothelial and epithelial cells through integrins, cadherins, and selectins.<sup>7</sup> Syndecans (CD138) enable DCs to bind growth factors and extracellular matrix molecules.

Leukocyte extravasation from vascular endothelium begins with the selectin-dependent tethering, rolling, and arrest of leukocytes on endothelial cells, which involves integrins. Thereafter, during diapedesis, leukocytes migrate across the endothelial layer lining the blood vessels.<sup>8</sup> Locomotion of monocytes on endothelium, whereby the monocyte moves from a site of firm adhesion to the nearest junction to begin diapedesis, is a critical step during extravasation. This process requires interaction of the integrins CD11a/CD18 and CD11b/CD18 with ICAM-1 and ICAM-2.<sup>9</sup>

In addition, as a counterpart for ICAM-2 on endothelial cells, the human DC-specific adhesion receptor DC-specific ICAM-3–grabbing nonintegrin (CD209) was identified,<sup>5</sup> which is responsible for DC rolling and transendothelial migration. Migration of CD14<sup>+</sup>CD34<sup>+</sup> precursor cells depends on PECAM-1.

During the rapid process of diapedesis, the leukocyte extends itself by a pseudopod across the endothelial

border. Leukocyte diapedesis is sequentially regulated by 2 distinct molecules: PECAM-1 and CD99. Blockage of PECAM-1 arrests monocytes at the apical surface of endothelial cells, whereas inhibition of CD99 blocks monocytes from passing the junction.<sup>5</sup> During transendothelial migration, recycling PECAM from a membrane compartment close to the cell borders of endothelial cells is targeted to segments of the junction, across which monocytes are migrating.<sup>5</sup> Distinct and separate Ig domains of PECAM are involved in mediating diapedesis and in passage through the extracellular matrix.<sup>5</sup> In a recent report, the DNAX accessory molecule 1 (CD226) present on monocytes has been shown to regulate extravasation through its interaction with poliovirus receptor (CD155) expressed at the endothelial junctions of normal endothelial cells.<sup>10</sup> In addition to the above-mentioned adhesion molecules, a new family of junctional adhesion molecules (JAMs) has been identified.<sup>11</sup> In human vascular endothelial cells, JAM-A localizes in close proximity to tight junctions. JAM-A is not restricted to cells that form junctions but is also expressed on circulating human monocytes, neutrophils, lymphocytes, and platelets.<sup>8</sup> Transmigration and recruitment of monocytes requires functional JAM-A binding to its ligand, LFA-1. JAM-B on endothelial cells binds its ligand, JAM-C, on T cells, natural killer cells, and DCs. Moreover, JAM-C is abundantly expressed on the basolateral intestinal epithelia and localizes to desmosomes but not to tight junctions. JAM-C binds specifically to CD11b/CD18 on leukocytes.<sup>12</sup>

Penetration of DC precursors from the blood vessels into peripheral tissues is promoted by activated endothelial cells because DC adhesion and transmigration across an endothelial cell barrier were markedly increased after exposing endothelial cells to hypoxia, oxidized low-density lipoprotein, or TNF- $\alpha$ .<sup>13</sup> This result supports the importance of local chemokines associated to endothelial venules for leukocyte trafficking across endothelia.

## CHEMOATTRACTANTS FOR MONOCYTES

Monocytes extravasate from endothelial venules in response to a chemokine gradient caused by inflammatory processes. However, the molecular mechanism controlling the slow homeostatic traffic of DCs is not clear. The breast- and kidney-expressed chemokine (BIAK; CXC chemokine ligand [CXCL] 14), which binds highly selectively to blood monocytes but to which immature or mature DCs do not respond,<sup>5</sup> could be involved in trafficking of LC precursors. BIAK expression is highest in basal keratinocytes in the epidermis and in scattered cells within the dermis. These scattered BIAK-positive dermal cells are often in conjunction with CD68<sup>+</sup> macrophages. Constitutive expression in skin suggests a homeostatic rather than an inflammatory role for BIAK. Also, macrophage inflammatory protein 3 (MIP-3 $\alpha$ /CC chemokine ligand [CCL] 20) produced by keratinocytes supports local DC differentiation through steady-state recruitment of DC precursors from peripheral blood.<sup>3</sup>

The inflammatory factors responsible for adhesion and transmigration of LC precursors and their target structures on endothelial cells and on migrating cells are largely unknown. Monocyte chemoattractant protein 1 (MCP-1/CCL2) triggers migration of monocyte subsets,<sup>14</sup> which might induce their differentiation into LCs. In contrast to other monocytes, CD16<sup>+</sup> monocytes express high levels of the chemokine receptors CX3CR1 and CXCR4 but low amounts of CC chemokine receptor (CCR) 2 and CD62L. In response to fractalkine (CX3CL1) and stromal-derived factor 1 (SDF-1)/CXCL12, but not to MCP-1/CCL2,<sup>5</sup> as other monocytes, CD16<sup>+</sup> monocytes gain efficient transendothelial migration capacity.

MCP-1 triggers migration of monocyte subsets, which might induce their differentiation into LCs. Furthermore, MCP-1 and IL-8 (CXCL8) can both induce migrating monocytes to adhere firmly to E-selectin expressed on endothelial cells.<sup>5</sup> IL-8-mediated binding of monocytes to E-selectin on the vascular membrane of endothelium requires  $\beta_2$ -integrin and no  $\alpha_4$ -integrin, which is also found on monocytes. Neither  $\beta_2$ -integrin nor  $\alpha_4$ -integrin induces MCP-1-mediated firm adhesion. The ability of chemokines to trigger monocyte adhesion to E-selectin-expressing vascular endothelium is independent from their capability to induce calcium influx.

## CHEMOATTRACTANTS FOR DCs

Distinct chemokine receptors govern DC migration from the blood to inflamed tissues. Subpopulations of LC precursors and information to their chemotactic responsiveness are shown in Fig 2.<sup>5,14-16</sup> for chemokines produced by epidermal keratinocytes, LCs, and dermal fibroblasts. Apparently, the LC precursor can migrate to the epidermis in the virtual absence of inflammation-related stimuli. Immature DCs, generated *in vitro* from monocytes, express a unique repertoire of chemokine receptors (CCR1, CCR2, and CCR5). Both immature DCs and LCs express CCR6 and respond to MIP-3 $\alpha$ /CCL20.<sup>15</sup> Monocytes and DCs migrate in response to MCP-1/CCL2, MCP-2/CCL8, MCP-3/CCL7, MCP-5/CCL12, MIP-1 $\alpha$ /CCL3, MIP-1 $\beta$ /CCL4, RANTES/CCL5, complement 5a, and the strong chemoattractant formyl-methionyl-leucyl-phenylalanine.<sup>15</sup> Monocytes and DCs also migrate in response to the macrophage-derived chemokine/CCL22.

Changes in the chemokine receptor profile and the selective expression of several chemokines in distinct microenvironments determine precursor cell migration by controlling precursor-stromal cell interactions. Studies with chemokine gene-deficient mice have shown that often chemokines act redundantly so that the deficiency in one chemokine is overcome by other chemokines.<sup>3</sup>

Migration of immature DCs toward inflammatory chemokines is induced on processing of the extracellular nicotinamide-adenine-dinucleotide by the adenosine diphosphate-ribose cyclase CD38, producing adenosine diphosphate ribose and cyclic adenosine diphosphate ribose.<sup>17</sup>

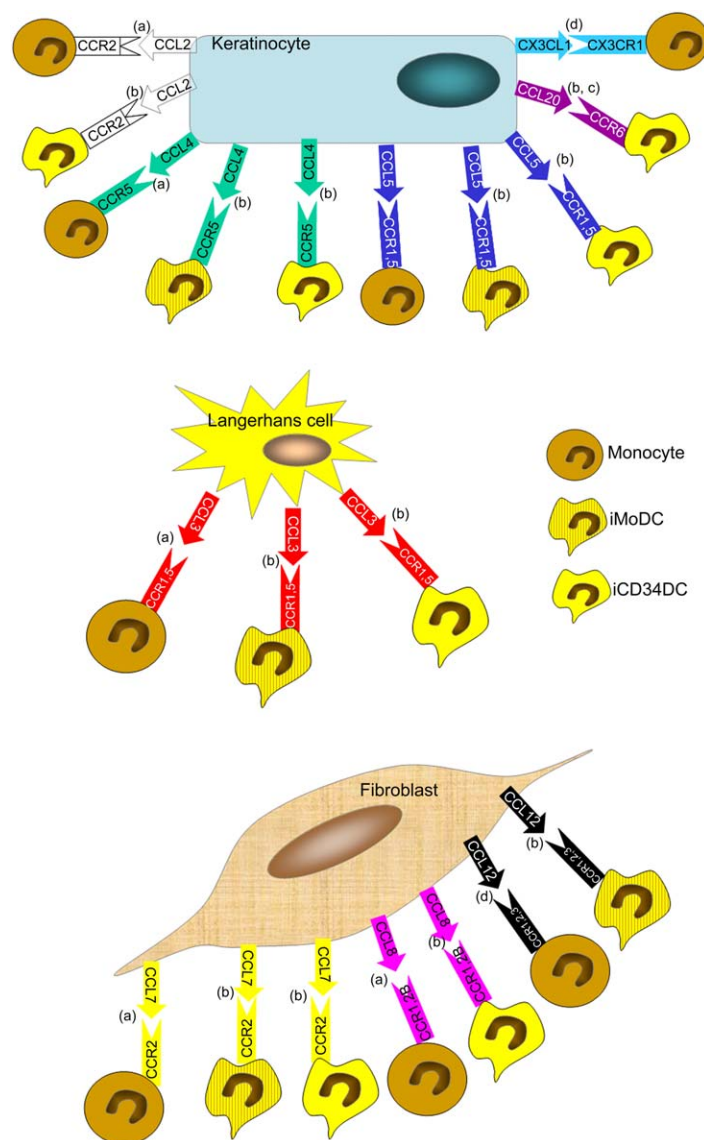


**FIG 2.** Chemokine responsiveness of DC subsets. Epidermal keratinocytes, LCs, and dermal fibroblasts produce chemokines, which monocytes, immature DCs (iMoDC), and immature CD34<sup>+</sup> stem cell-derived DCs (iCD34) recognize through specific receptors and toward which they migrate. (a), Muller (2001)<sup>14</sup>; (b), Sozzani et al (2000)<sup>15</sup>; (c), Ono et al (2003)<sup>16</sup>; (d), Imhof and Aurrond-Lions (2004).<sup>5</sup>

## CHEMOKINES PRODUCED BY KERATINOCYTES

Which chemokines are produced by keratinocytes under steady-state conditions and which are produced under inflammatory conditions? Keratinocytes produce large quantities of IL-1 and TNF- $\alpha$  in response to trauma, UV radiation, or cytokines.<sup>18</sup> TGF- $\beta$ , a cytokine indispensable for immigration of LC precursors in the epidermis, is constitutively produced by keratinocytes. The epidermis of TGF- $\beta$  knockout mice is devoid of LCs.<sup>19</sup> Immigration of LC precursors into the epidermis induces keratinocytes to secrete MCP-1/CCL2, which constitutively recruits DCs and LCs to the skin.<sup>15</sup> MCP-1/CCL2

production is increased under inflammatory conditions in psoriatic skin.<sup>18,20</sup> *In vitro*<sup>21</sup> MCP-1 production is enhanced by IFN- $\gamma$ . Moreover, MCP-1 and RANTES/CCL5 trigger arrest of rolling monocytes on endothelial cells.<sup>22</sup> RANTES is constitutively expressed in the skin of patients with atopic dermatitis.<sup>18</sup> RANTES production by keratinocytes is enhanced by IFN- $\gamma$  and TNF- $\alpha$ . TNF- $\alpha$  also induces MIP-3 $\alpha$ /CCL20 secretion by keratinocytes,<sup>23</sup> which is also found in lesional skin of patients with atopic dermatitis.<sup>20</sup> Moreover, MIP-3 $\alpha$  plasma levels from atopic patients are enhanced. Constitutively, keratinocytes secrete cutaneous T cell-attracting chemokine/CCL27<sup>16</sup> and thymus and activation regulated chemokine (TARC)/CCL17.<sup>24</sup> Cutaneous T cell-attracting chemokine

binds specifically to CCR10, which is expressed by epidermal LCs.<sup>16</sup> TARC binds to CCR4 and CCR8 expressed by monocytes.<sup>16</sup>

## CHEMOKINE-TO-RECEPTOR BINDING INDUCED INTRACELLULAR SIGNALING

Chemokine receptors are G protein–coupled receptors, with a characteristic hydrophobic sequence that passes the cellular membrane 7 times. Pertussis toxin, a G protein–signaling inhibitor, inhibits leukocyte adhesion to the endothelium. Through distinct signaling pathways, chemokines trigger integrin affinity and mobility changes. Chemokine-induced signal transduction events have been recently reviewed.<sup>5</sup> Chemokine-induced activation of guanosine triphosphatase-activating protein 1 (RAP1), a guanosine triphosphatase of the RAS family, plays a vital role in the signal transduction pathway, which activates leukocyte integrins and induces cell migration and trans-endothelial extravasation. Exodus 2/CCL21 and SDF-1/CXCL12 activate RAP1 to its guanosine triphosphate-bound active form. RAP1 subsequently activates LFA-1 and very late antigen 4. On binding of a chemokine to its cognate G protein–coupled receptor, RAP1 is activated through cyclic AMP, and the exchange protein is directly activated by cyclic AMP. Activated RAP1 forms a complex with the regulator for cell adhesion and polarization enriched in lymphoid tissues, whereupon this complex binds to the  $\alpha$  subunit of LFA-1 ( $\alpha_L\beta_2$  integrin). Simultaneously, activation of talin by calpain occurs, and activated talin binds to the  $\beta$  subunit of LFA-1. Binding of talin and RAP1 induces an allosteric change in LFA-1, creating a binding site for ICAM-1. This process leads to an increased affinity. Induction of Rho A activity (RAS homologue gene family, member A) downstream of the chemokine receptor is required at the same time for an affinity switch. An alternative signaling pathway involves the activation of phosphatidylinositol 3 kinase, which in turn mediates activation of atypical protein kinase C  $\zeta$ . Protein kinase C  $\zeta$  signaling increases integrin avidity by facilitating its lateral mobility. Binding of protein tyrosine kinase 2 $\beta$  to the integrin clusters induces a polarity complex in the anterior part of the cell, which is a prerequisite for polarized adhesion and transmigration.

## MATRIX METALLOPROTEINASES

LC precursors attach to and degrade basement membrane proteins to cross the basement membrane of the dermal-epidermal junction. Matrix-degrading metalloproteinases (MMPs) which are proteolytic enzymes, are key enzymes in the extracellular matrix turnover and mediators of cell migration. Twenty-three MMPs are known to date, but only gelatin-binding MMP-2 and MMP-9 and simple hemopexin domain–containing MMP-3<sup>25</sup> have

been demonstrated on the surface of immature, mature, or both dermal and epidermal DCs and LCs from the skin. Treatment of CD34<sup>+</sup> stem cell–derived dendritic cells (CD34DCs) with TNF- $\alpha$  induced membrane-associated MMP-2 and MMP-9 expression on their cell surface, which preceded the migration of LC precursors through an artificial basement membrane (Matrigel; Becton Dickinson, Heidelberg, Germany).<sup>26</sup> Withdrawal of TNF- $\alpha$  from day 5 during differentiation of CD34DCs abrogated the spontaneous synthesis of MMP. Moreover, MMP-13 production is upregulated on DC activation.<sup>27</sup>

MMPs are mainly known for their extracellular matrix-degrading activity. However, they can also modulate inflammation through proteolytic activation or inactivation of cytokines, chemokines, and growth factors. N-terminal processing of SDF-1/CXCL12 by MMP-2 and MMP-9 results in loss of binding to its cognate receptor, CCR4.<sup>28</sup> Also, the N-terminal 4 amino acid residues of MCP-3/CCL7 are cleaved by MMP-2, which results in loss of receptor activation.<sup>29</sup> In contrast, MMP-9–mediated cleavage of the proinflammatory chemokine IL-8/CXCL8 results in a 10-fold more potent chemokine, providing an important positive feedback loop for chemotaxis. This suggests that MMPs are both effectors and regulators of inflammatory responses.

Furthermore, it has been shown that MMPs activate TGF- $\beta$  and thereby promote attraction of LC precursors.<sup>29</sup> MMP-9 functions through proteolytic activation of IL-1 $\beta$  and IL-8.<sup>29</sup> In MMP-9<sup>−/−</sup> mice, the inflammatory transmigration of DCs into the airway lumen is impaired, whereas DC traffic from the airway epithelium to the draining lymph nodes remains unaffected. In addition, TARC/CCL17 production by purified lung DCs falls short in MMP-9<sup>−/−</sup> mice.<sup>30</sup> In an *in vivo* study, Kobayashi et al<sup>31</sup> showed that MMP-9 is involved in LC migration and maturation. An MMP-9–specific mAb inhibits hapten-induced LC emigration. In murine models emigration of LCs from skin explants is reduced by MMP-2–specific mAb.<sup>25</sup> Emigration of LCs from skin explants is also reduced by MMP-9–specific mAb, as well as in explants from MMP-9<sup>−/−</sup> mice. In a model system of contact hypersensitivity, MMP-9<sup>−/−</sup> mice fail to produce IL-10 at the site of inflammation and showed a prolonged contact hypersensitivity response. The response of MMP-3<sup>−/−</sup> mice to contact irritants is strongly impaired.<sup>29</sup>

In addition to the classical MMPs mentioned earlier, monocyte-derived DCs and CD34DCs express the metalloprotease and disintegrin dendritic antigen marker (MADDAM).<sup>32</sup> Two members of the a disintegrin and metalloprotease family, MADDAM and decysin, are expressed weakly in freshly isolated monocytes. In DCs decysin is only expressed after maturation induced by LPS but not by CD40 ligand or TNF. In contrast, MADDAM is expressed in immature DCs and more strongly in mature DCs. Therefore MADDAM, but not decysin, is a suitable marker for human monocyte-derived DCs. Moreover, Rosenzweig et al<sup>33</sup> described CD13/N-aminopeptidase, a zinc metalloprotease, being expressed in CD34DCs and playing a role in the growth of DC precursors.

## CONCLUSION

In response to trauma or inflammation, LC precursors circulating in the peripheral blood are attracted to the epidermis by chemokines produced by epidermal keratinocytes. MCP-1/CCL2 and RANTES/CCL5 trigger arrest of rolling monocytes on endothelial cells and thus initiate their transmigration across the endothelial-dermal barrier. During transmigration, monocytes and endothelial cells interact with adhesion molecules, such as PECAM and CD99. Further migration of LC precursors toward the epidermis is guided by gradients of several inflammatory chemokines. Some of these chemokines need to be activated by MMP-2 and MMP-9 from the LC precursors, which cleave inactive precursor forms of the chemokines. In addition, metalloproteinase activity is required for proteolysis of proteins constituting the extracellular matrix, which has to be crossed by LC precursors on their route to the epidermis. Thus matrix metalloproteinases fulfill a double role during the immigration of LC precursors into the epidermis.

As antigen-presenting cells in the epidermis, LCs control T cell-mediated allergen-specific immune responses. Allergens can penetrate the epidermis, mucosal barriers, or both and thus induce eczema in patients with atopic disorders. The local cytokine milieu in the epidermis influences the LC-regulated T-cell response against the encountered allergen toward silent elimination, allergy, or tolerance. The recent progress made in understanding the mechanisms by which LCs populate the skin opens new therapeutic strategies for the modulation of immune responses in atopic diseases. Through manipulation of LC development and biology *in vitro* or *in vivo*, new strategies for the treatment of allergic diseases could evolve.

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