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Dendritic Cells and Contact Dermatitis

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Abstract Contact dermatitis is a biological response to simple chemicals in the skin. Although it is well known that allergic contact dermatitis is mediated by the immune system, it is still uncertain whether it is a kind of protective response or it is simply an unnecessary response. We have demonstrated the following: (1) haptens activate Langerhans cells in the initiation phase of murine allergic contact dermatitis in vivo, (2) haptens activate human monocyte-derived dendritic cells in vitro, (3) the activation of dendritic cells by haptens is primarily mediated by the activation of p38 mitogen-activated protein kinase (MAPK), and (4) the activation of p38 MAPK is mediated by stimulation related to an imbalance of intracellular redox. Based on these observations, we will discuss the biological significance of contact dermatitis. In addition, we will review some up-to-date findings on Langerhans cell biology.

Keywords Contact dermatitis · Dendritic cells · Langerhans cells · p38 Mitogen-activated protein kinase · Redox balance · Knock-in mice

Pathophysiology Allergic Contact Dermatitis

Contact dermatitis is classified into irritant and allergic dermatitis based on its mechanisms to induce the inflammation of the skin (Fig. 1). Irritant contact dermatitis is an inflammatory reaction caused by the simple toxicity of chemicals or by the stress response induced by them. On the other hand, antigen-specific adaptive immune responses to simple chemicals, i.e., haptens, play an essential role to induce allergic contact hypersensitivity (ACH).

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ACH Involves the Following Six Steps

Sensitization Phase

First Step: Antigen Invasion and Activation of Langerhans Cells Immediately after haptens enter the skin, epidermal Langerhans cells (LC) take them up and become activated with the augmentation of their expression of various co-stimulatory molecules, such as CD54, CD80, and CD86, and the increased production of proinflammatory cytokines, such as IL-1α, TNF-α, and IL-12 [1].

Second Step: Migration of LC to the Regional Lymph Nodes The activated LC express CCR7 and migrate to regional lymph nodes (LN) via afferent lymphatic vessels. Secondary lymphoid-tissue chemokine (SLC)/6Ckine and EBI-1-ligand chemokine (ELC)/MIP-β, which are the ligand for CCR7, are expressed in lymph nodes and mediates the chemotaxis of LC [1–5]. On the other hand, LC down-regulate the expression of E-cadherin, resulting in their decreased affinity to surrounding keratinocytes [6]. Moreover, LC produce matrix metalloproteinases, MMP9 and MMP2, which promote their migration through basement membrane [7–9].

Third Step: Antigen presentation to Naive T cells at the LN Once LC migrate to the draining LN, LC stimulate naive T cells and induce hapten-specific T cells [10, 11]. They can stimulate both CD4 and CD8 T cells, and

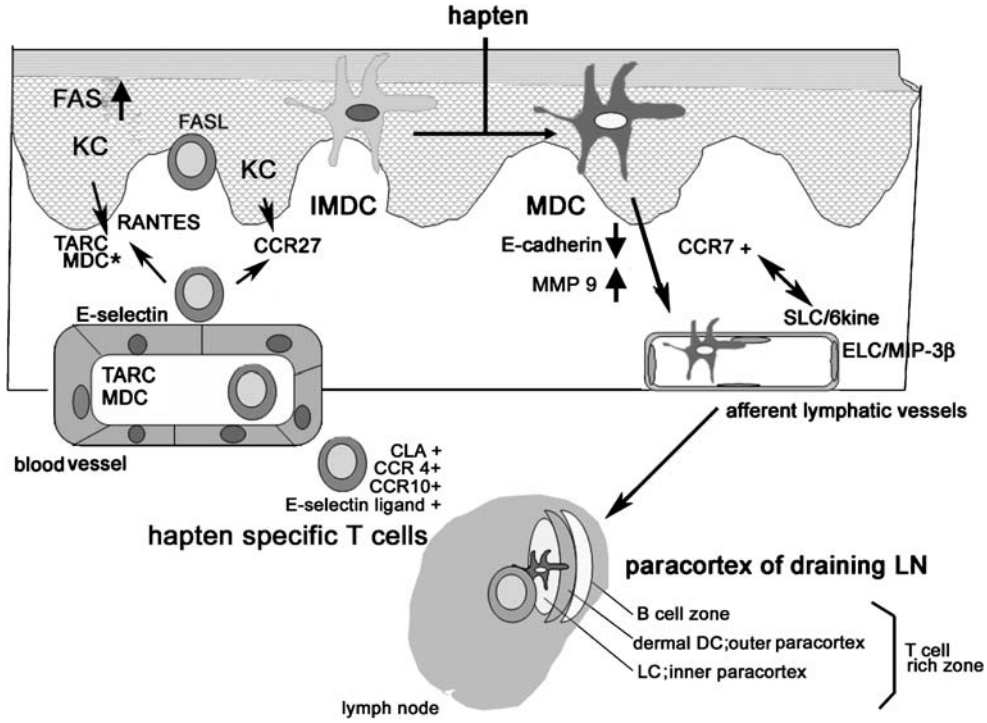


Fig. 1 Mechanisms of ACH. *IMDC* Immature dendritic cell, *MDC* mature dendritic cell, *LN* lymph node, *KC* keratinocyte, *FASL* FAS ligand, *TARC* thymus and activation-regulated chemokine, *MDC** macrophage-derived chemokine, *CLA* cutaneous lymphocyte antigen, *CCR* CC chemokine receptor, *MMP* matrix metalloproteinases, *SLC* secondary lymphoid-tissue chemokine, *ELC* EBI-1-ligand chemokine, *MIP-3β* macrophage inflammatory protein-3β

moreover, they may determine the Th1/Th2 differentiation or Tc1/Tc2 differentiation [12–14]. Although not all the mechanisms that determine the Th1/Th2 polarization are understood, the regulation of IL-12 production is one of the main mechanisms [15].

Elicitation Phase

Fourth Step: Migration of T Cells to the Skin After Sensitization After naive T cells are stimulated by DC, they express chemokine receptors, CCR4, and respond to its ligand, TARC (thymus and activation-regulated chemokine) and MDC (macrophage-derived chemokine) [16]. Both the interaction between CCR4 and TARC and that between E-selectin ligand expressed by stimulated T cells and E-selectin on endothelial cells are essential to their skin homing [16]. Additionally, the skin infiltrating lymphocytes in the lesional skin of ACH, psoriasis, or atopic dermatitis express CCR10, whereas basal keratinocytes produce its ligand, CCL27. The CCL27–CCR10 interactions also play a pivotal role in T-cell-mediated skin inflammation [17].

Fifth Step: Cross-Talk Between LC, T Cells and Keratinocytes at the Skin During the elicitation of ACH, leukocyte recruitment is under the control of chemokines released in a sequential and coordinated manner from resident skin constituents [18]. Keratinocytes are activated by hapten and release TNF-α and IL-1α. Afterwards, MCP-1 from keratinocytes seem to drive the influx of T cells. Activated endothelial cells can also contribute to attract leukocytes by expressing adhesion molecules and chemokines [16, 19, 20]. Infiltrating DC are themselves a source of chemokines. The activated hapten-specific T cells that are recruited into the skin lead to the production of IFN-γ, TNF-α, and IL-4, which stimulate keratinocytes to produce IP-10, Mig, and I-TAC, the ligands for CXCR3. They also produce RANTES, I-309, IL-8, and MDC [18]. The inflammatory infiltrates in ACH are composed of CD4+ and CD8+ T cells, monocytes, and DC. Several papers have suggested that CD8+ T cells are effector cells, whereas CD4+ T cells are endowed with regulatory mechanisms [21–24].

Sixth Step: Induction of Inflammation by T Cells T cells infiltrating the skin up-regulate Fas on keratinocytes and render them susceptible to apoptosis via their production of IFN-γ. On the other hand, T cells express Fas ligand (FasL) and induce apoptosis of keratinocytes [25].

The Activation of DC by Haptens

Among these six steps, we have focused on the first step and investigated the activation mechanisms of DC including LC by haptens. Recently, it has become elucidated that DC recognize various microorganisms using the family of Toll-like receptors (TLR) [26] whose signals induce DC maturation sufficiently for the activation of naive T cells. However, we still lack the information how DC discriminate haptens from innocuous chemicals and stimulate naive T cells specific to haptens.

DC Response to Haptens In Vivo and In Vitro

We reported that murine LC up-regulate their expression of class II major histocompatibility complex antigen and antigen-presenting function after hapten painting to the skin, whereas chemicals that simply irritate the skin rather than sensitize animals cannot induce this phenomenon [27] (Fig. 2). Afterwards, we demonstrated that the application of haptens to murine skin was accompanied by the upregulation of several costimulatory molecules on LC, i.e., CD40, CD54, CD80, and CD86 [28]. Subsequently, Enk and Katz [29] demonstrated the crucial role played by the IL-1β secreted by LC themselves in their increased expression of class II major histocompatibility complex antigen after exposure to hapten application. In addition to these in vivo studies, using human monocyte-derived DC (MoDC), we [30] demonstrated in vitro that purified MoDC respond to haptens such as $NiCl_2$ and 2,4-dinitrochlorobenzene (DNCB), but not to irritants such as benzalkonium chloride (BC) or sodium lauryl sulfate (SLS), by significantly augmenting their expression of CD54, CD86, and HLA-DR and by increasing their production of proinflammatory cytokines.

Furthermore, using Langerhans cell-like DC induced from peripheral blood monocytes in the presence of transforming growth factor-β1, GM-CSF, and IL-4 (monocyte-derived LC) according to a procedure reported by Geissmann et al. [31], we showed that in vitro treatment with haptens can induce the phenotypic and functional changes in monocyte-derived LC seen in epidermal LC during the initiation phase of contact hypersensitivity reaction in vivo [32], e.g., the downregulation of E-cadherin [33] and cutaneous lymphocyte antigen [34], the induction of matrix metalloproteinase-9 expression [7], and the augmentation of some of β1-integrins [35, 36], CD44 and some of its variants [37], as well as the expression of CCR7 messenger RNA (mRNA) that enable LC to respond to MIP-3β [2, 38, 39].

What Signal Pathways Does Hapten Activate to Induce DC Maturation?

These observations raised the next question how different haptens can stimulate MoDC to acquire a mature phenotype. Kuhn et al. [40] demonstrated that strong haptens could induce the formation of phosphotyrosine in MoDC in vitro, suggesting that tyrosine phosphorylation plays an important part in the activation of MoDC by haptens. Meanwhile, Ardeshna et al. [41] have reported the precise mechanisms for the survival and maturation of MoDC stimulated by LPS. According to their report, both p38 mitogen-activated protein kinase (MAPK) and nuclear factor (NF)-κB signal transduction pathways are responsible for the up-regulation of CD80, CD83, and CD86 induced by LPS, whereas phosphoinositol 3-kinase is important in maintaining their survival. Therefore, it is conceivable that haptens also stimulate p38 MAPK, NF-κB, or phosphoinositol 3-kinase (Fig. 3).

In fact, using MoDC, Arrighi et al. [42] have reported that 2,4-dinitrofluorobenzene and $NiSO_4$ induce p38 MAPK phosphorylation and that the augmentation of CD80 and CD83 induced by $NiSO_4$ is partially suppressed by p38 MAPK inhibitor. The MAPKs are an important group of serine/threonine signaling kinases that, by modulating the phosphorylation and, hence, the activation status of transcription factors, link transmembrane signaling with gene induction events in the nucleus. There are at least three genetically distinct MAPK pathways in mammals, including the extracellular signal-regulated kinases (ERK), the c-jun N-terminal kinases (JNK), and the p38 MAPK. These kinases are activated by phosphorylation on both threonine and tyrosine residues in a regulatory TXY loop present in all

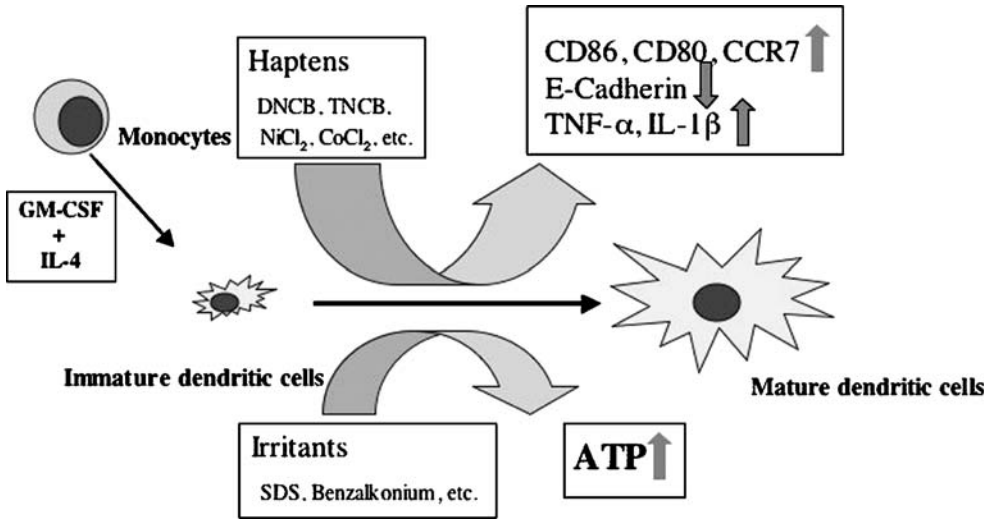


Fig. 2 DC response to haptens in vitro. *DNCB* 2,4-dinitrochlorobenzene, *TNCB* trinitrochlorobenzene, *SDS* sodium dodecyl sulfate [27–30, 57]

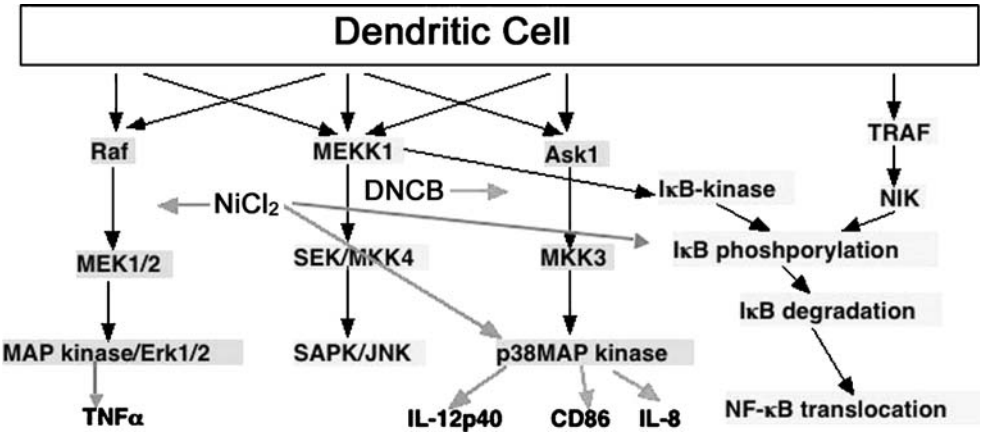


Fig. 3 Signal transduction pathways to induce DC maturation by distinct haptens. *MEKK* MAP/ERK kinase kinase, *ERK* p44/42 extracellular signal-regulated kinases, *SEK* SAPK/ERK kinase, *SAPK/ JNK* stress-activated protein kinase/c-jun N-terminal kinases, *ASK1* apoptosis signal-regulating kinase 1, *TRAF* tnf receptor-associated factor, *NIK* NF-κB inducing kinase, *p38MAPK* p38 mitogen-activated protein kinase [41–45]

MAPKs. This phosphorylation is performed by distinct upstream dual-specificity MAPK kinases (MAPKK). Activated MAPKs then phosphorylate their respective substrates on serine or threonine residues [43–45].

We also examined the activation of three distinct MAPK pathways such as ERK, JNK, and p38 MAPK, and NF-κB on human MoDC by two representative haptens with different chemical structures, i.e., DNCB and $NiCl_2$. We found that DNCB and $NiCl_2$ stimulated MoDC via different signal transduction pathways. Namely, DNCB preferentially stimulated p38 MAPK, whereas $NiCl_2$ activated ERK and NF-κB in addition to p38 MAPK [46].

What are the Upstream Events of MAPK Activation?

Next, we focused on the mechanism of p38 MAPK activation by haptens. In general, the oxidized/reduced glutathione (GSSG/2GSH) couple provides a very large pool of reducing equivalents and is considered to be a cellular redox buffer [47]. Recently, it has been demonstrated that a cellular redox imbalance could be induced by reactive oxygen species (ROS) or by thiol oxidants such as diamide without generating ROS [48] and that the redox imbalance detected as changes in the intracellular GSH/GSSG ratio modulates MAPK and various transcription factors related to growth, differentiation, and death [47, 49].

Among MAPKs, p38 MAPK has been demonstrated to be phosphorylated by oxidizing conditions via apoptosis signal-regulating kinase 1 modulation [50]. Therefore, we examined the relationship between the GSH/GSSG ratio and phosphorylation of p38 MAPK in human MoDC stimulated with various haptens having different chemical structures. We found that all the haptens at a sublethal concentration reduced the GSH/GSSG ratio in MoDC and that this was accompanied by the phosphorylation of p38 MAPK.

In some experiments, we used an antioxidant, *N*-acetyl-L-cysteine (NAC), which increases the intracellular concentration of GSH [51], to further investigate the relationship between the redox and the activation of p38 MAPK and that between the redox and the activation of MoDC, such as the augmentation of CD86 expression. The treatment with NAC, which suppressed the reduction of the GSH/GSSG ratio in MoDC, abrogated both the phosphorylation of p38 MAPK and the augmentation of CD86 expression by MoDC. These data support the role of the redox imbalance in stimulating DC maturation by haptens (Fig. 4).

Other Mechanisms Involved in Activation and/or Migration of DC by Haptens

Hyaluronan Hyaluronan (HA) [52] is a ubiquitous extracellular matrix (ECM) component, present at high concentrations in the skin. HA is synthesized primarily by dermal fibroblasts and by epidermal KC. In normal skin, HA exists as a high-molecular-weight (600,000–1,000,000) nonsulfated glycosaminoglycan (GAG) composed of repeating units of D-glucuronic acid-*N*-acetyl-D-glucosamine (HMW-HA) [53]. HMW-HA is cleaved at the sites of inflammation. Small HA fragments induce the maturation of human monocyte-derived DC that produce the cytokines IL-1β, TNF-α, and IL-12. During inflammation, the interaction of DC with small HA fragments may induce DC maturation [52, 53].

ATP Extracellular ATP mediates numerous biological activities by interacting with plasma membrane P2 purinergic receptors. DC also express several P2 purinergic receptors. Several researchers have reported the expression sets of purinergic receptors in DC [54–56]. Chemically injured keratinocytes release ATP [52]. In the presence of extracellular ATP, DC transiently increase their endocytotic activity. Subsequently, DC up-regulate CD86, CD54, and MHC-II, secrete IL-12, and exhibit an improved stimulatory capacity for allogeneic T cells. ATP can synergize with TNF-α in the activation of DC, which may play a role in the afferent phase of ACH [57]. Indeed ATPγS, a hydrolysis-resistant P2 agonist, is reported to enhance ACH to dinitrofluorobenzine (DNFB) in mice as an endogenous adjuvant [58].

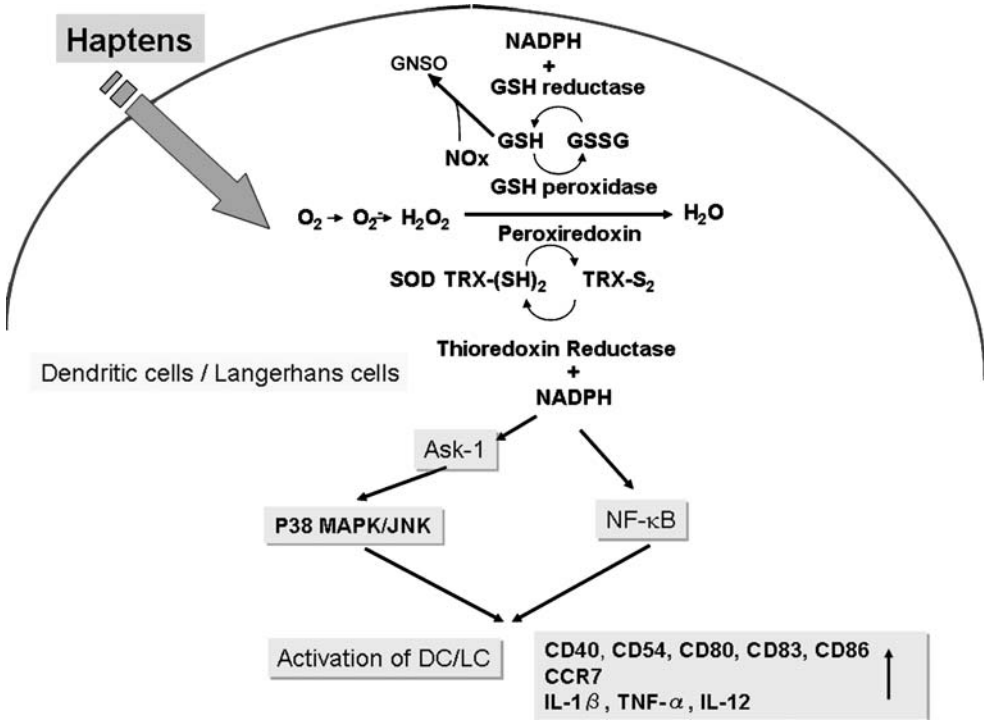


Fig. 4 Role of the redox imbalance in stimulating DC maturation by haptens. *SOD* Superoxide dismutase, *TRX* thioredoxin [47–51]

Prostaglandin Prostaglandin E2 is produced in skin exposed to haptens. The migration of murine LC is dependent on PGE2-EP4, which is one of the four PGE2 receptor subtypes. PGE2-EP4 signaling promotes the expression of co-stimulatory molecules and ability to stimulate T cells by DC [59]. CHS to DNFB was significantly reduced in EP4 deficient mice [59]. In contrast to murine DC, human MoDC require a signal mediated by EP2 or EP4 either alone or in combination [60].

Etiologic Consideration of ACH

In conclusion, we hypothesize that at least one of the biological role of ACD is a defense reaction to the xenobiotics that have potential to insult the redox balance.

Topics in Langerhans Cell Biology

Although LC, the prototypic DC of the skin, have long been considered to derive from bone marrow, they require GM-CSF for their differentiation and play a crucial role in the initiation of ACH. Recent studies using genetically engineered mice have raised questions about this central dogma.

The Direct Precursors of LC

It is well known that LC are bone marrow (BM)-derived epidermal DC. Recently, however, Merad et al. [61] have demonstrated that LC are maintained locally under steady-state conditions, although inflammatory changes in the skin result in their replacement by blood-borne LC progenitors. Furthermore, using CSF-1 receptor-deficient mice, they demonstrated that CSF-1R is critical in the maintenance of LC in steady state and the reconstitution of the LC pool in inflamed skin [62]. In human, we also demonstrated that, in a serum-free culture condition including stem cell factor, Flt3 ligand, TNF-α, and TGF-β1 without GM-CSF, macrophage colony-stimulating factor (CSF-1) could induce CD1a+ Birbeck granule+ Langerin+ E-cadherin+ factor-like XIIIa Langerhans cells from hematopoietic progenitor cells of human cord blood [63].

Larregina et al. [64] identified and characterized a population of LC precursors in human skin. These immediate precursors expressed CD14, langerin, and functional CCR6, while Gr-1hi monocytes are the direct LC precursors in mice [62]. Schaerli et al. [65] demonstrated that CD14+ DC precursors, either derived from CD34+ hematopoietic progenitor cells or isolated from blood, were attracted by the chemokine CXCL14, which is constitutively produced in healthy skin and other epithelial tissues. Their model assigns unprecedented roles to CXCL14 and epidermal tissue as attractant and niche of differentiation, respectively, in the renewal of LC under steady-state conditions.

Finally, LC differentiation from progenitors is absolutely dependent on TGF-β1 in vitro as well as in vivo. Heinz et al. [66] have reported that both PU.1 and Id2 are induced by TGF-β1 in human CD34+ monocyte/LC (M/LC)

progenitor cells and that Id2 suppressed monocyte differentiation while PU.1 strongly promotes LC differentiation.

CHS in the Mice Lacking LC

Surprisingly, LCs are not essential for CHS responses according to three different studies, in which LC were selectively removed in the genetically engineered mice. Kissenpfennig et al. [67, 68] and Bennett et al. [68] made knock-in mice that expressed diphtheria toxin receptors under the control of the langerin gene. When the toxin is administered to the designed mice, LC disappear completely from the epidermis. Although Kissenpfennig et al. [67, 68] reported that CHS responses were not affected in LC-deficient, Bennett et al. [68] reported that they were decreased.

On the other hand, Kaplan et al. [69] generated BAC transgenic mice in which the regulatory elements from human Langerin were used to drive expression of diphtheria toxin. In these mice, epidermal LC are constitutively absent but these mice are otherwise normal [69]. Interestingly, the CHS in these mice was rather amplified, suggesting that LC not only were dispensable for CHS, but they served to regulate the response.

LC and Dermal DC

Kissenpfennig et al. [67] developed knock-in mice expressing enhanced green fluorescent protein (EGFP) under the control of the *langerin* (*CD207*) gene and succeeded in clearly discriminating LC and dermal DC in the draining lymph nodes. After epicutaneous application of a fluorescent dye, tetramethylrhodamine-5-(and-6)-isothiocyanate (TRITC), the first TRITC-laden DC observed in the draining lymph node were dermal-derived DC (TRITC+, EGFP-) as early as 24 h after skin painting and peaking 2 days, whereas immigrating LC-derived DC (TRITC+, EGFP+) were more slowly peaking 4 days after skin painting. Interestingly, it was revealed that these two DC subsets migrate to distinct areas of the paracortex of draining LN [67]. Namely, within T-cell-rich zone, dermal DC localize to the outer paracortex, adjacent to the B-cell follicles, whereas LC localize to the inner paracortex. In CHS reaction, LC are found to be blunt and slow moving, whereas dermal DC encounter T cells more rapidly in lymph nodes in anatomically distinct areas.

Concluding Remarks

Recently, the role of LC is reconsidered in infectious immunity. LC do not contribute to protect against specific pathogens. Allan et al. [70] showed that infection of murine epidermis by herpes simplex virus did not result in the priming of virus-specific cytotoxic lymphocytes by LC. Rather, the priming response required a distinct CD8 alpha+ DC subset. Similarly, Ritter et al. [71] demonstrated that CD8 alpha (–) Langerin (–) DC but not LC are the basis of the protective immune response to intracellular *Leishmania major* parasites in vivo. These studies, as well as the recent studies using genetically engineered mice, question the central dogma of the role of LC in the contact hypersensitivity.

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