Pathophysiology of chemokines and chemokine receptors in dermatological science: A focus on psoriasis and cutaneous T-cell lymphoma

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INTRODUCTION

Chemokines are small cytokines representing a large group of small chemotactic proteins (~8–11 kDa in size) that guide the movement of leukocytes to sites of inflammation. They bind and activate cell-surface chemokine receptors, which belong to a large superfamily of seven-transmembrane-spanning, G-protein-coupled receptors. Chemokines are categorized into four families (C, CC, CXC, and CX3C) according to the spacing of key cysteine residues near the N terminus of the chemokine. Chemokines and their receptors are generally identified by their systematic names, consisting of the family of the chemokine followed by the letter R for receptor or L for ligand, with a number indicating their chronological order of discovery. The CC and CXC families comprise the majority of known chemokines. Redundancies are present in chemokine receptor interactions because certain chemokine receptors bind to multiple chemokines and vice versa. Engagement of chemokine receptors with cognate chemokines can activate several downstream intracellular signaling pathways, including calcium flux as well as phosphoinositide-3 kinase (PI3 K) and mitogen-activated protein kinase activation.

Upon ligation of chemokine receptors, these cell signaling pathways result in diverse cellular processing such as cytoskeleton reorganization, cell locomotion, and prosurvival signaling. Chemokines, as chemoattractant factors, are known for their ability to stimulate directional migration of all classes of leukocytes. Diverse subsets of T cells, such as Th1, Th2, Th17, Treg, and memory T cells, express a regulated set of chemokine receptors that enable them to differentially respond to specific chemokines. In the skin, epidermal keratinocytes are able to express multiple chemokines that can attract certain leukocytes, such as T cells or dendritic cells (DCs), to migrate to the epidermis. In addition to their chemotactic activity, chemokines enhance the ability of rolling and adhesion of leukocytes to endothelial cells by increasing the affinity and avidity of β1 and β2 integrins on leukocytes in vitro and in vivo.

The skin provides a potent physical barrier and possesses a sophisticated immunological defense system. The skin immune system includes keratinocytes (being the most abundant cells in the epidermis), epidermal Langerhans cells (LCs), dermal DCs, T cells, endothelial cells, and fibroblasts. Keratinocytes are able to release several cytokines and chemokines both under baseline and under activated conditions. A delicate balance between pro- and
anti-inflammatory signals is critical in maintaining the normal physiologic functions in the skin. Once disturbed and/or dysregulated, the immune system of the skin may contribute to various diseases because of defective tumor immunosurveillance, uncontrolled malignant T-cell growth, defective pathogen defense, and exaggerated autoimmune reactions. Herein we examine two diseases as examples where the roles for chemokines or their receptors have been demonstrated through human and experimental animal studies. First, mycosis fungoides (MF), a form of CTCL, is characterized by the invasion of epidermis (and dermis) with malignant T cells. Chemokines from keratinocytes, stromal cells, and endothelial cells contribute to the preferential homing, activation, and prosurvival of those malignant T cells. Second, psoriasis, a common dermatological disease that affects 2–3% of the world’s populations and 0.1–0.5% of the Taiwanese populations, causes a significant morbidity in patients and is now known to be associated with comorbidities, including metabolic syndrome, obesity, and ischemic vascular disease. In psoriasis, dermal mixed inflammatory infiltrates and presence of neutrophils in the epidermis along with epidermal hyperproliferation are highly characteristic. Chemokines from various skin cells mediate trafficking of different subsets of inflammatory cells when binding to their corresponding receptors, forming a vicious proinflammatory circle. Selective expression of chemokine receptors in Th17 cells may provide good therapeutic targets in psoriasis.

**Mycosis fungoides**

**Preface**

MF is the most common form of CTCL. Patients with patches and thin plaques usually have an indolent course. However, patients with thick plaques and tumors, often extensive, face a poor clinical prognosis. Sézary syndrome (SS) is a rarer leukemic variant of CTCL (compared to MF) with striking skin findings that include erythroderma as well lymphadenopathy. Malignant SS cells circulating in the bloodstream have cerebriform nuclei and lose normal T-cell surface receptors such as CD7 and CD26. MF is characterized by the invasion of epidermis with malignant T cells. Chemokines from keratinocytes, stromal cells, and endothelial cells contribute to the preferential homing, activation, and, possibly, survival of malignant T cells in both MF and SS. Recent work has indicated that MF and SS arise from distinct populations of memory T cells called skin-resident T cells and central memory T cells, respectively.4

**Role of chemokines and chemokine receptors in neoplasia**

Cancer cells take advantage of their upregulated chemokine receptors to alter their organ-targeting metastatic spread. Mechanistically, chemokine receptors can regulate the ability of cancer cells to arrest on vascular endothelial cells.5 Moreover, chemokine receptor engagement results in the activation of well-characterized prosurvival pathways such as PI3K and Akt (also known as protein kinase B).6 Melanoma cells could utilize CXCR4 and CCR10 to enhance cell survival and to escape killing in the absence of serum deprivation.11,12 Thus, besides the chemotactic functions to enhance metastasis, the prosurvival signals of chemokine receptors in the tumor cells may help these cells evade various forms of death induced by chemotheray or immunotherapy (Figure 1).

**Skin microenvironment and homing of malignant T cells in MF**

In skin, keratinocytes, the major cells in the epidermis, can release multiple chemokines. Those chemokines can attract a wide variety of leukocytes, including T cells, to the epidermis. Chemokines produced by other cells, namely epidermal LCs and dermal DCs bearing yet- unidentified skin antigens, may also play important roles in attracting and activating malignant T cells (Figure 1). Studies have found that DCs synthesize CCR4 ligands, which rapidly promote migration of normal T cells.13,14 A histopathological feature of MF, Pautrier’s microabscesses, represents DC-malignant T-cell conjugates that may result from these DC-derived chemokines. Involvement of DC in CTCL pathobiology has already been extensively reviewed.15

**Individual chemokines that may play a role in CTCL**

In peripheral blood, only ~25% of circulating T cells express CCR4.16 By contrast, MF as well as SS cells have increased CCR4 expressions.16,17 CCL17, a CCR4 ligand, is produced by activated keratinocytes, endothelial cells, and DCs. Interestingly, CCL17 is upregulated in the epidermis and serum of MF patients.18 The increased CCL17 in the skin may result in the preferential homing of MF cells to the skin or aid in the survival of pre-existing skin-resident malignant T cells. Clinically, increased CCL17 in blood may be a useful marker to monitor the disease progression and treatment response in MF.19

Similarly, CCR10, which binds to CCL27 ligand, is only infrequently expressed on peripheral blood T cells, but it is considerably enhanced in cutaneous lymphocyte antigen (CLA+) skin-homing T cells and in CTCL cells.20 Analogous to CCL17 (a CCR4 ligand), CCL27 (a CCR10 ligand) is increased in the serum of MF/SS patients and may serve as a biomarker of disease activity22 and a therapeutic marker after IFN-γ and PUVA therapy.23 CCL27 is constitutively synthesized in basal keratinocytes and is somewhat enhanced under proinflammatory situations. Thus, CCL27 may play a role in T-
cell epidermotropism in MF. Not only CCL27 can regulate cutaneous homing, but it can also regulate nodal homing of T cells by rapidly being released from activated keratinocytes to regional lymph nodes via afferent lymphatics. 

CCR7 is critical for migration of maturing skin DCs and selected T-cell subsets to the cutaneous draining lymph nodes. CCR7 is found to be expressed at high levels in SS cells and may play a role in the tropism of these cells to peripheral lymph nodes, which constitutively synthesize the corresponding CCR7 ligand, CCL21.

Keratinocytes, endothelial cells, and dermal fibroblasts in lesions showed stronger expression of eotaxin-3 than did normalskin. CCR3+ lymphocytes were observed in some cases of advanced CTCL. Both serum eotaxin-3 and eotaxin-1 levels of CTCL patients at advanced stages were significantly higher than those of healthy individuals. The study suggested that interaction of eotaxins and CCR3 may regulate the Th2-dominant tumor environment, which is common in CTCL.

CXCR4 may also be a crucial chemokine in homing of MF and SS cells to skin. Loss of the cell-surface antigen, such as CD7 and CD26, is a characteristic feature in MF and SS. Downregulation of CD26, a dipeptidylpeptidase, is interesting in particular, since CD26 cleaves the critical amino terminus of several chemokines, including CXCL12, and rapidly deactivates this chemokine in terms of its ability to activate through CXCR4. Inactivation of CD26 promoted CXCL12-driven chemotaxis of cell lines derived from SS patients. On the other hand, soluble CD26 was shown to inhibit CXCR4-mediated migration. Thus, loss of CD26 on the SS cells may provide a mechanism for their increased migration and survival in the skin.

**Further mechanistic and applied insights with respect to CCR4 and CCR10 in MF**

CCR4 and CCR10 share similarities in their ability to direct the trafficking of T cells to the skin under inflammatory conditions. Both receptors are selectively expressed by “skin-homing” memory T cells that bear surface carbohydrate ligands to E-selectin, an adhesion protein that is characteristically expressed by inflamed dermal blood vessels. Neutralizing antibodies to CCL27 (the CCR10 ligand) reduced inflammation significantly in a mouse model of contact dermatitis. The role of CCR4 and its ligand CCL17, however, is less clear because optimal inhibition of cutaneous inflammation in CCR4-deficient mice required simultaneous administration of CCL27 antagonists. Recent studies indicated that CCR4 is crucial in the antigen-dependent skin inflammation, as evidenced by the failure to accumulate ovalbumin (OVA)-specific T cells in the skin. The facts that T-cell activation is achieved by the adoptive transfer of CCR4-defected OVA-specific T cells and that CCR4-negative T cells home inefficiently to skin, but normally to the gut, suggested a trafficking defect to the skin as opposed to an intrinsic homing defect in these cells. Besides the in vitro and animal studies, several clinical observational studies suggest that CCR4 is generally very highly expressed among CTCL cells in MF and SS patients (Table 1). Targeting CCR4 and CCR10, the two chemokine receptors that are often expressed by CTCL cells, may be an attractive therapeutic approach to treat CTCL. Since normal circulatory T cells also express those two receptors, it remains unknown whether targeting these two receptors would result in unwanted immunosuppression. Nevertheless, a relatively small portion of the total T-cell population expresses these two receptors. Thus, obliteration of CCR4- and CCR10-positive T-cell populations would not likely result in severe lymphopenia. Small-molecule antagonists of CCR4 and CCR10 (as present in CXCR4) have yet to be developed, but antibodies targeting CCR4 that induce antibody-dependent cellular cytotoxicity have already been reported. The humanized anti-CCR4 antibody has been approved for use in Japan for adult T-cell leukemia/lymphoma (ATLL). Furthermore, bexarotene was reported to inhibit functional activation of CCR4, suggesting a potential mechanism through which bexarotene is effective in CTCL. Analogous to interleukin-2 (IL-2)–diphtheria toxin fusion protein (denileukin diftitox), novel chemokine–toxin fusion proteins may selectively target skin-homing T-cell populations if they utilized chemokines such as CCL17 or CCL27 to direct ligation to cutaneous T cells (Figure 1). Selective binding of the chemokine receptor with a fusion toxin would in endocytosis of the chemokine–toxin and subsequent cell killing. CCL17 molecules fused to the Pseudomonas exotoxin 38 have already been shown to eliminate successfully the lymphoma cells that express CCR4. Therefore, chemokine–toxin fusion proteins may be useful as therapeutic agents in MF and/or SS.

**Table 1 | Role of chemokines and chemokine receptors in the pathophysiology of CTCL**

<table>
<thead>
<tr>
<th>Chemokine receptors</th>
<th>Distribution</th>
<th>Ligands</th>
<th>Distribution</th>
<th>Biological role</th>
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<tbody>
<tr>
<td>CCR2</td>
<td>Macrophages</td>
<td>CCL2</td>
<td>Macrophages</td>
<td>CCL2/CCR2 axis in macrophage is critical in CTCL disease progression</td>
</tr>
<tr>
<td>CCR3</td>
<td>T cells</td>
<td>CCL5, CCL7, CCL8, CCL11</td>
<td>Macrophages and others</td>
<td>CD30+ skin lymphoma expresses CCR3</td>
</tr>
<tr>
<td>CCR4</td>
<td>T cells</td>
<td>CCL17, CCL22</td>
<td>Keratinocytes, DCs, Endothelial cells</td>
<td>CCR4 is important in the homing of T cell to the skin</td>
</tr>
<tr>
<td>CCR7</td>
<td>T cells</td>
<td>CCL21</td>
<td>Lymphatic endothelial cells</td>
<td>CCL2/CCL7 axis in lymphatic endothelial cells is important in the physiological trafficking of T cells to regional lymph nodes</td>
</tr>
<tr>
<td>CCR10</td>
<td>Skin-homing T cells</td>
<td>CCL27</td>
<td>Keratinocytes</td>
<td>CCR7 expression is high in MF and SS cells</td>
</tr>
<tr>
<td>CXCR3</td>
<td>Melanocytes</td>
<td>CCL12</td>
<td>Keratinocytes</td>
<td>CCR7 may facilitate nodal invasion in CTCL and ATLL</td>
</tr>
<tr>
<td>CXCR4</td>
<td>Memory T cells</td>
<td>CCL12</td>
<td>Keratinocytes, Endothelial cell monocytes, Fibroblasts</td>
<td>CCR10 mediates T-cell homing to skin</td>
</tr>
</tbody>
</table>

CTCL – cutaneous T-cell lymphoma; DC – dendritic cell; MF – mycosis fungoides; NK cells – natural killer cells; SS – Sezary syndrome.
**Short summary**

Chemokine receptors are likely to be involved in the selective skin homing that characterizes CTCL. In addition to assisting in the firm arrest of skin-homing T cells on dermal vascular endothelial cells, they provide directional signals for T cells to migrate to specific compartments of the skin, including the epidermis. Even after localizing in skin, chemokine receptors may increase the survival of the malignant T cells through activation of prosurvival pathways such as PI3 K and Akt. The understanding of how chemokine receptors participate in trafficking and survival provides a promising rationale for the use of receptor inhibitors or antiangiogenic receptor antibodies as novel therapeutic agents.

**Psoriasis**

**Clinical manifestations of psoriasis**

Psoriasis can be subdivided into several clinical subtypes: guttate, inverse, palmoplantar, plaque, and erythrodermic psoriasis. Each subtype has its own anatomic predilections, response to therapy, and genetic signatures. Guttate psoriasis presents with small, scaly papules, usually with a preceding streptococcal infection. Inverse psoriasis tends to affect folds of the body, including the axilla, umbilicus, and inguinal creases. Plaque psoriasis is the most common subtype of psoriasis, characterized by red, well-demarcated plaques covered with a silvery scale often related to the extensor aspects of the body skin (Table 2).20,43–63

Histologically, in epidermis, often parakeratosis and occasionally neutrophil accumulation occur in the subcorneal layer, known as subcorneal pustules of Kogoj. The granular layer is often absent, and there are usually striking epidermal acanthosis and a regular elongation of the rete ridges. The suprapapillary plates are thin, making the dilated dermal vessels occasionally grossly visible.

Recent studies have demonstrated that the skin is home to tens of millions of resident effector memory T cells.64 Even under clinical resolution in psoriatic plaques, a genetic signature of psoriasis and its proinflammatory state, a so-called "residual disease genomic profile," remains.65 Palmoplantar psoriasis may thus arise because the hands and feet are constantly traumatized. A better understanding of the individual genetic signatures in the skin microenvironment may provide more precise targets for treatment in the future.

**CCR6 and CCL20 in psoriasis**

Th17 and CCR6 in psoriasis

Recently, a major shift of paradigm has developed in regard to the role of different T-cell subsets in psoriasis. While Th1 cells, producing interferon-gamma (IFN-γ), were previously thought to play the major role in regulating immune reactions in psoriasis, both mouse and human data now indicate that Th1 cells, producing IL-17 and IL-22 cytokines, likely have a greater pathogenic role in regulating skin immunity in psoriasis. IL-23, a major upstream player in the Th17 pathway, is an essential cytokine for Th17 polarization and maintenance. Intradermal IL-23 injection into wild-type (WT) mice results in psoriasis-like inflammatory changes grossly and histologically.66–68 IL-23 is a heterodimeric cytokine that shares its p40 subunit with IL-12 (a Th1 cytokine).69 Ustekinumab (Stelara), a biologic agent targeting the shared p40 component of IL-23, has shown substantial clinical efficacy in psoriasis,70 confirming the role of Th17 cytokines in human psoriasis. Because ustekinumab also blocks IL-12 and IL-17, it is difficult to exclude completely the role of Th1 cells in psoriasis. However, preliminary reports of the efficacy of anti-IL-17A antibodies in human patients with psoriasis validate the role of the Th17 pathway in humans with psoriasis.71,72 Moreover, other human studies suggest that the Th17 signaling pathway is a critical mediator in the development and maintenance of psoriasis.73,74 These studies show that the number of Th17 cells and downstream effector molecules, IL-17A, IL-17F, tumor necrosis factor (TNF)-α, and IL-22 are increased in psoriatic skin lesions.75,76 Roles of different CD4+ T-cell subsets in psoriasis are shown in Figure 2. Circulating Th17 cells in adult human blood express CCR2, CCR4, CCR5, CCR6, and CXCR3.67 Among those, CCR6 has been described as a marker for Th17 cells both in human and in murine T cells.74 Due to the paradigm shift to Th17 in psoriasis, several recent studies have focused on the role of CCR6 in the pathophysiology of psoriasis. CCR6 was initially discovered on both T cells75 and immature DCs.76,77 Recently, several research groups have shown

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### Table 2 Role of chemokines and chemokine receptors in psoriasis.

<table>
<thead>
<tr>
<th>Chemokine receptors</th>
<th>Expression</th>
<th>Ligands</th>
<th>Source</th>
<th>Biological functions</th>
</tr>
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<tbody>
<tr>
<td>CCR2</td>
<td>Monocytes and macrophages</td>
<td>CCL2</td>
<td>Basal KC41,44</td>
<td>Chemotaxis of monocytes, macrophages, and Th1 cells43 Th1 and Th17 trafficking45–47</td>
</tr>
<tr>
<td>CCR4</td>
<td>Epidermal T cells</td>
<td>CCL17 (TARC)</td>
<td>KC45</td>
<td>Chemotaxis of Th1 cells, monocytes, and DCs47,48</td>
</tr>
<tr>
<td></td>
<td>Dermal CD3 + T cells</td>
<td>CCL22 (MDC)</td>
<td>Suprabasal KC40,52</td>
<td>Chemotaxis of eosinophils</td>
</tr>
<tr>
<td></td>
<td>PBMCs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCR5</td>
<td>Epidermal CD3 + T cells</td>
<td>CCL3 (MIP1x)</td>
<td>Epidermis46–51</td>
<td>Chemotaxis of Th1 cells, monocytes, and DCs47,48</td>
</tr>
<tr>
<td>Macrophages</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCR6</td>
<td>Epidermal T cells</td>
<td>CCL5 (RANTES)</td>
<td>Basal KC43,48</td>
<td>Th17 trafficking52</td>
</tr>
<tr>
<td>PBMCs</td>
<td>CCL20 (MIP3α, LARC)</td>
<td>Suprabasal KC40,52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCR10</td>
<td>Many leukocytes</td>
<td>CCL27 (CTACK)</td>
<td>Basal KC40,53,54</td>
<td>CLA+CD4+ or CLA+CD8+ cell chemotaxis20</td>
</tr>
<tr>
<td>CCR1</td>
<td>Epidermis</td>
<td>CCL8 (IL-8)</td>
<td>Suprabasal KC43,55,56</td>
<td>Chemotaxis of PMN and T cells KC hyperproliferation57,58</td>
</tr>
<tr>
<td>CXCR2</td>
<td>Suprabasal KC</td>
<td>CCL1 (GROα)</td>
<td>Suprabasal KC43,55,56</td>
<td>Chemotaxis of PMN and T cells KC hyperproliferation57,58</td>
</tr>
<tr>
<td>CXCR3</td>
<td>Dermal CD3 + T cells</td>
<td>CCL8 (IL-8)</td>
<td>CCL9 (Mig)</td>
<td>Th1 and pDC trafficking45,59</td>
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<tr>
<td>Macrophages</td>
<td></td>
<td></td>
<td>KC Macrophages</td>
<td></td>
</tr>
<tr>
<td>CXCR6</td>
<td>Basal KC</td>
<td>CCL10 (IP10)</td>
<td>EC45,54,59,61</td>
<td>Psoriatic skin (unknown)50</td>
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<tr>
<td>pDC</td>
<td>CCL11 (ITAC)</td>
<td></td>
<td></td>
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<tr>
<td>CCR3R1</td>
<td>None reported</td>
<td>CCL16</td>
<td>Basal KC EC46</td>
<td>Leukocyte chemotaxis and KC hyperproliferation</td>
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<tr>
<td>EC</td>
<td>CCL31 (Fractalkine)</td>
<td></td>
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</table>

GLA = cutaneous lymphocyte antigen; CTACK = cutaneous T-cell-attracting chemokine; DC = dendritic cell; EC = endothelial cell; GRO = Growth regulated oncogene; IL = interleukin; ITAC = Interferon inducible T-cell alpha chemoattractant; KC = keratinocyte; LARC = liver activation regulated chemokine; MDC = Human macrophage-derived chemokine; MIP = macrophage inflammatory proteins; pDC = plasmoid dendritic cell; PBMC = peripheral blood mononuclear cells; PMN = polymorphonuclear leukocytes; RANTES = regulated and normal T cell expressed and secreted; TARC = Thymus and activation regulated chemokine.
that CCR6 plays an important role in the Th17 signaling pathway and in the pathogenesis of psoriasis (as described below). CCR6 was initially shown to mediate adhesion and arrest of T cells to endothelial cells under physiologic shear stress. Moreover, current models suggest that IL-23 from DCs maintain dermal CCR6-expressing Th17 cells. CCR6 appears to be essential for the development of a psoriasiform phenotype in mice since IL-23 injection in skin of WT mouse, but not in that of CCR6 knockout mice, results in psoriasis-like skin lesions. CCR6 may be a provisional target in psoriasis. Of note, anti-CCR6 antibody reduced the severity of collagen-induced arthritis, a model for rheumatoid arthritis. While no small-molecule inhibitors of CCL20 or CCR6 have yet been described, new in silico techniques that have successfully identified drug-like CXCR4/CXCL12 antagonists may soon allow the rational design of CCR6/CCL20 antagonists.

CCL20 and psoriasis

CCL20 is the only known chemokine ligand for CCR6; however, human β-defensin 2 (hBD2) also induces chemotaxis of leukocytes via CCR6. CCL20 is constitutively expressed at low levels in epidermal keratinocytes and dermal endothelial cells. Its expression is strongly enhanced by proinflammatory cytokines, including TNF-α, IL-1α, IL-17, and IFN-γ in psoriatic skin lesions. CCL20 is robustly expressed throughout the epidermis and may be crucial in recruiting CCR6-expressing T cells into inflamed epidermis from underlined dermis, whereas CCL20 expressed by dermal endothelial cells may serve to arrest CCR6-positive leukocytes from the blood stream. Furthermore, production of CCL20, which is enhanced by CCR6 + Th17 cells producing IL-17, positively reinforces the recruitment of more CCR6 + Th17 cells (Figure 3).

Other chemokines that may possibly be involved in psoriasis

Neutrophils and CXCL8

CXCL8, a neutrophil chemoattractant (chemokine), is notably increased in psoriatic skin by quantitative polymerase chain reaction (qPCR).

T cells and CCR10

Analogous to that occurs in MF, more than 90% of the T cells in psoriatic skin expresses CCR10, a receptor for the chemokine ligand CCL27 that is constitutively expressed in the epidermis. TNF-α upregulates CCL27 expression in keratinocytes both in mice and in humans, and therefore recruits more effector memory T cells to the skin.

DCs and CCR6

In addition to T cells, LCs also express CCR6 and are strongly migrate toward CCL20. Komine et al showed that the number of CD1a+CD11c+Langerin+ DCs in lesional skin was increased compared with those in uninvolved skin. CD11c+ mature DCs harvested from the dermis of psoriatic skin lesions generate IL-23, a key factor that maintains Th17 differentiation. Another subset of dermal DCs, TNF/iNOS-producing DCs, plays a role in the development of psoriasis through production of IL-20. Besides DCs, dermal macrophages show increased expression of CCR2, CCR5, and CXCL9 in psoriatic skin lesions. CCR6 may not be present on mature macrophages; however, it may be involved in the development of macrophage lineage. Of note, in Rag1-deficient mice, which lack both T and B cells, IL-23 injection in the first 5–6 days of treatment (but not after that) resulted in a psoriasiform skin phenotype along with production of IL-22 and IL-17A, suggesting that T cells are not essential in the initial responses to IL-23.

Therefore, LCs, DCs, and macrophages may also be able to induce psoriasis-like features initially in the absence of T cells, although it appears that expression of T cells is required to maintain expression of IL-17A and IL-22 after initial induction of psoriasiform dermatitis.

Role of γδ T cells in psoriasis

While there appears to be a convincing role for conventional γδ T cells in psoriasis, the role of unconventional T cells, including γδ T cells...
cells, in psoriasis has only recently been explored. New clinical studies show that γδ T cells are increased in numbers in psoriatic skin lesions.93,94 Interestingly, peripheral γδ T cells express high levels of IL-23 receptor, and they are activated by IL-1β and IL-23 to produce IL-17 and IL-22.95 Furthermore, a new study describes a motile population of dermal γδ T cells that express low-intermediate levels of CCR6, CXCR6, and IL-17.96 Using the IL-23 skin injection psoriasis mouse model,56,68,97 Mabuchi et al98 showed that IL-22, IL-17A, and IL-23 receptor were highly upregulated in a population of CCR6+ T cell receptor (TCR) γδ- T cells that accumulated in skin with marked infiltration of the epidermis. Large numbers of CCR6+ cells were detected at or above the level of the epidermal basement membrane 5 days after repeated IL-23 injections, in parallel with increased GALT cells in the epidermis. TCR δ-deficient mice (lacking γδT cells) had diminished ear swelling and impaired expression of IL-22 and IL-17A in the epidermis following IL-23 injection, suggesting that γδT cells play a critical role in IL-23-mediated psoriasis or other Th17-mediated autoimmune disease.99

Role of β-defensin 2 in psoriasis
In addition to CCL20, hBD2 also signals through CCR6.85 Defensins are small (3.5–4.5 kDa in size) antimicrobial peptides that are primarily expressed by epithelial cells in the skin, kidney, and trachea—bronchial lining. Defensins exhibit a broad spectrum of antimicrobial activity against Gram-positive and Gram-negative bacteria, fungi, and viruses. The defensin hBD2 is highly expressed in the epidermis of psoriatic skin.100 Increased copy numbers of β-defensin gene are associated with susceptibility to psoriasis in Dutch and German populations,101 and serum levels of hBD2 may be a useful marker for disease activity in psoriasis.100 Increased hBD2 production in psoriasis may act in concert with CCL20 to attract requisite populations of CCR6+ cells, including Th17 cells.

CXCR3 in dermal CD3+ lymphocytes
CXCR3 is upregulated on dermal CD3+ lymphocytes. The corresponding ligands CXCL9, CXCL10, and CXCL11 (also known as Mig, IP10, and IFN-β, respectively) are increased in psoriatic skin lesions.45,59 CXCR3 is involved in transendothelial migration of T cells and T-cell trafficking to psoriatic epidermis.45

CCR5 in epidermal T cells and dermal macrophages
CCL5, or RANTES, one of the ligands for CCR5, is highly expressed in psoriatic skin lesions.49,51 Calcipotriol, an active vitamin D3 analogue, can inhibit CCL5 production in cultured normal epidermal keratinocytes.49 Furthermore, CCR5 expression was considerably higher in both epidermal T cells and dermal macrophages in lesional psoriatic skin compared to that measured in nonlesional skin.48 Although these results suggested a potential role for CCR5 and CCL5 in the inflammatory cascade of psoriasis, the CCR5 inhibitor SCH51125 yielded neither clinical benefit nor significant differences in CCR5 expression during psoriasis clinical trials.48

Therapeutic targets of chemokines and chemokine receptors in psoriasis

CXCR3 small-molecule antagonist T487
The CXCR3 small-molecule antagonist T487 was found to relieve symptoms and hinder the progression of rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, and psoriasis.102 Although a phase II trial of T487 in psoriasis was performed in 2003,103 its use in psoriasis has not been reported since that time.

CXCL8 neutralized monoclonal antibody ABX-IL8
CXCL8 (also known as IL-8), a common ligand for CXCR1 and CXCR2, represents a potent chemoattractant for neutrophils. It likely plays a role in recruitment of neutrophils to the epidermis and cornified layer, leading to Munro abscesses, a characteristic feature in psoriasis. ABX-IL8 is a fully neutralized monoclonal antibody against CXCL8 that was evaluated in a phase II clinical trial for psoriasis. However, ABX-IL8 was not effective in reducing PASI scores.102 While the reason for the lack of clinical effect is unclear, this might have resulted from the presence of other redundant neutrophil-attracting CXCR1/CXCR2 ligands such as CXCL1, CXCL2, CXCL3, CXCL5, and CXCL6.100

Short summary
Multiple chemokines and chemokine receptors maybe involved in the development and progression of psoriasis. The redundancy of the chemokine system makes therapies targeting single chemokine receptor challenging. However, in mouse models of psoriasis, therapeutic agents inhibiting the CCR6 pathway have demonstrated efficacy. Moreover, the mice lacking CCR6 are remarkably resistant to induction of psoriatic phenotype following IL-23 injection. Both CCL20 and hBD2 may recruit CCR6-expressing cells into inflamed epidermis. Given the possibility that these two peptides redundantly recruit inflammatory cells via CCR6, targeting CCR6 itself rather than its ligands, CCL20 or hBD2, with a monoclonal antibody or small molecule would seem to be a better targeting strategy in psoriasis.

Conclusion
Chemokines and chemokine receptors have long been recognized for their chemotactic activities with respect to many leukocytes, including Th1 cells, Th17 cells, macrophages, DCs, neutrophils, etc. Many of those chemokines and chemokine receptors are present in psoriatic skin and contribute to dermal inflammation and, perhaps indirectly, to epidermal keratinocyte hyperplasia in psoriasis. Preferential expression of CCR6 in Th17 cells makes CCR6 a rational therapeutic target in psoriasis. In neoplastic CTCL, malignant T cells proliferate, accumulate, and "home" to the skin—processes that likely result from increased expression of chemokine receptors such as CCR4 and CCR10 in neoplastic T cells. Not only interactions of chemokines and chemokine receptors direct trafficking in those neoplastic cells, but those cells may also take advantage of the chemokine pathways to provide prosurvival signals and evade apoptosis by various assaults. The recent approval of an anti-CCR4 antibody for ATLL in Japan that has efficacy in CTCL provides definitive evidence that targeting chemokine receptors in neoplastic diseases can have clinical utility. Further attempts are warranted to identify CCR6 (and possibly other chemokine receptor) antagonists that may be useful in psoriasis and other autoimmune skin diseases.

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