Chemokine Receptors in T-Cell-Mediated Diseases of the Skin

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The chemokine/chemokine receptor network is an integral element of the complex system of homeostasis and immunosurveillance. Initially studied because of their role in coordinating tissue-specific migration and activation of leucocytes, chemokines have been implicated in the pathogenesis of various malignancies and diseases with strong inflammatory components. We discuss recent findings suggesting a critical involvement of chemokine receptor interactions in the immunopathogenesis of classical inflammatory skin disorders such as psoriasis and atopic dermatitis, as well as neoplastic diseases with a T-cell origin, such as mycosis fungoides. A deeper understanding of the underlying contribution of the chemokine network in the disease processes is key for the development of selective targeted immunotherapeutics that may meet the delicate balance between efficacy and safety.

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INTRODUCTION

In the past two decades, chemokine receptors have emerged as important determinants for the directed trafficking of T cells and their function in primary, effector, and memory immune responses (Sallusto *et al.*, 2000). Although their role in leukocyte activation and differentiation is well established, it is becoming increasingly clear that chemokine receptor/ligand interactions participate in several other key biological processes such as apoptosis, tumorigenesis, and antimicrobial activity (Zlotnik *et al.*, 1999; Rossi and Zlotnik, 2000).

A comprehensive discussion of the biology of chemokines has been the focus of several recent publications (Luster, 1998; Rossi and Zlotnik, 2000; Charo and Ransohoff, 2006; Bromley *et al.*, 2008) and is beyond the scope of this review.

Instead, we aim to highlight the areas of chemokine biology with particular impact on the immunopathogenesis of classical T-cell-mediated skin diseases, such as psoriasis, atopic dermatitis (AD), and mycosis fungoides (MF), and discuss possible implications in the development of novel targeted therapies. The structural organization of the skin allowing directional migration of leucocytes within the two defined compartments of the epidermis and dermis, as well as its convenient accessibility, identifies the skin as an ideal model for *in vivo* studies on chemokine involvement in the pathogenesis of defined skin disorders.

THE CHEMOKINE SYSTEM

Chemokines are small (8–11 kDa), secreted proteins that are predominantly involved in regulating leukocyte chemoattraction (Luster, 1998). The approximately 50 identified members of the chemokine superfamily are systematically subcategorized on the basis of the position and number of conserved cysteine motifs in one out of four related families: C, CC, CXC, and CX_3C chemokines (Rossi and Zlotnik, 2000). On the basis of their constitutive or inducible production under homeostatic or inflammatory conditions, chemokines can be further classified into inflammatory or homeostatic chemokines.

Chemokines interact with members of the large family of seven-transmembrane G-protein-coupled receptors (Charo and Ransohoff, 2006). The C-terminal intracellular domain of the receptor is involved in receptor signaling and internalization, whereas the extracelluar acidic amino-terminal portion mediates ligand binding. To date, approximately 18 different chemokine receptors have been molecularly defined (Mantovani *et al.*, 2006).

Notably, there is considerable redundancy in the chemokine network, with chemokines binding to more than one receptor and vice versa.

DIFFERENTIAL CHEMOKINE RECEPTOR EXPRESSION ON T-CELL SUBSETS

Chemokine receptors have emerged as important determinants for the pheno-

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Abbreviations: AD, atopic dermatitis; APC, antigen-presenting cell; CD, cluster of differentiation; CLA, cutaneous lymphocyte-associated antigen; CTCL, cutaneous T-cell lymphoma; DC, dendritic cell; MF, mycosis fungoides; LC, Langerhans cells; SS, Sézary syndrome; T-cell, T lymphocyte; TNF-α, tumor necrosis factor-alpha; Treg, regulatory T lymphocyte

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typical and functional characterization of distinct T-cell subsets. The significance of a deeper insight into the role of the chemokine/chemokine receptor network in the immunopathogenesis of T-cell-mediated skin diseases arises essentially from the observation that distinct subsets of pathogenic effector leucocytes are preferentially recruited in different T-cell-mediated skin diseases, three of which will be discussed as examples in this review.

Different subsets of T-helper cells can develop from naive CD4+ T cells and may be characterized by a discrete pattern of cytokine production. Although IFN-γ-producing Th1 cells are thought to primarily promote cell-mediated immune responses, Th2 cells, which secrete IL-4, IL-5, and IL-13, are mostly involved in humoral immunity, including allergic reactions. IL-17 and IL-22 have been described as the hallmark cytokines of Th17 cells, a newly described T-helper subset with considerable involvement in several inflammatory and autoimmune diseases (Hirota *et al.*, 2007; Pene *et al.*, 2008).

In cutaneous T-cell lymphoma (CTCL), the malignant cell is thought to typically derive from a Th2-polarized origin. In AD, Th2 cells are predominantly implicated in the early phase of the disease. In contrast, chronic lesions of AD are characterized by an accumulation of skin-homing T cells with a Th1 phenotype (Grewe *et al.*, 1998). By contrast, the inflammatory infiltrate in psoriasis is predominantly composed of Th1-polarized lymphocytes of a memory phenotype as well as neutrophils, macrophages, and increased numbers of dendritic cells (DCs) (Prens *et al.*, 1995). In addition, Th17 cells have recently been implicated in the pathogenesis of psoriasis and other autoimmune inflammatory diseases (Lowes *et al.*, 2007; Steinman, 2007; Zaba *et al.*, 2007).

Over the past decade, the close association of chemokine receptor expression with the functional properties, differentiation, and maturation status of T-cell subsets has been convincingly documented. Th1 cells have been reported to selectively express CXCR3 and CCR5 (Loetscher *et al.*, 1998; Sallusto *et al.*, 1998a) and show migration in response to CCL3-5 and CXCR9-11. By contrast, Th2 cells have been found to preferentially express CCR4 (Bonecchi *et al.*, 1998; Sallusto *et al.*, 1998a), CCR8, and, to a lesser extent, CCR3 (Sallusto *et al.*, 1997), and can be selectively recruited by the respective chemokines (CCL17, CCL22, CCL1, and CCL11). CCR6 has recently been described as a marker for human and murine Th17 cells, identifying the vast majority of IL-17-producing T cells in human peripheral blood (Acosta-Rodriguez *et al.*, 2007; Annunziato *et al.*, 2007; Singh *et al.*, 2008).

CCR4 has been found to be abundantly expressed on many systemic peripheral blood memory T cells, which consequently respond to its ligands, the chemokines, CCL17 and CCL22 (Campbell *et al.*, 1999). Interestingly, these cells include essentially all T cells with a skin-homing CLA+ phenotype, regardless of their Th1 or Th2 polarization (Andrew *et al.*, 2001).

Further studies examining the T-cell chemokine receptor expression *in vivo* indicate that the patterns and regulation of chemokine receptor expression *in vivo* are more complex than those suggested by present *in vitro* models of Th1 *versus* Th2 cell generation. Kim *et al.* (2001) reported that *in vivo*-activated Th1 and Th2 cells display a remarkable heterogeneity with regard to their chemokine receptor expression. Similarly, the IL-17-secreting subset of T-helper cells, as well as the population of antigen-specific Foxp3+ regulatory T cells, seems to be heterogeneous with regard to chemokine receptor expression. T regulatory cells (Treg) and Th17 cells share chemokine receptors with other T-cell lineages and might differentiate to have distinct chemokine receptor expression profiles depending on the microenvironment in which they are activated (Acosta-Rodriguez *et al.*, 2007; Bromley *et al.*, 2008). Although the observed heterogeneity and flexible programing of chemokine receptor expression might be an advantageous feature for the migratory potential to diverse tissues *in vivo*, these studies call the physiological relevance of several *in vitro* observations into question.

TRADITIONAL FUNCTIONS AND NEW ASSIGNMENTS

Chemokine interactions have been intensely studied for their significant importance in the controlled regulation of immune cell trafficking and activation. Recent studies indicate that chemokines may have additional roles and exert further key biological functions, with possible implications for the immunopathogenesis of T-cell-mediated skin diseases.

Chemokine-mediated T-cell trafficking to the skin

Molecular mechanisms controlling the multistep process of directed migration and tissue positioning are an area of intense research. In response to antigen encounter in secondary lymphoid organs, activated T cells not only acquire effector functions but also achieve the capacity to efficiently migrate to extralymphatic tissues, such as the skin. The tissue-selective recruitment of naive and memory T lymphocytes can largely be explained by the joint expression of chemokine receptors and adhesion molecules such as selectins and integrins (Butcher and Picker, 1996).

Chemokine receptor engagement is thought to facilitate transmigration by permitting the firm adhesion of rolling lymphocytes to the luminal vascular endothelium in an integrin-independent manner (Campbell *et al.*, 1998; Campbell and Butcher, 2000; Fitzhugh *et al.*, 2000). Subsequently, chemokine gradients in the skin may guide receptor-bearing subsets of T cells to distinct sites within the tissue compartment (Hwang, 2001).

In humans, the expression of cutaneous lymphocyte antigen (CLA) defines a subset of skin-homing T cells with specific carbohydrate-mediated binding to E-selectin, an adhesion molecule highly expressed by endothelial cells under inflammatory conditions (Berg *et al.*, 1991; Springer, 1994; Fuhlbrigge *et al.*, 1997).

Although CLA+ T lymphocytes represent only 10–15% of circulating T cells in the peripheral blood, Clark *et al.* (2006) recently estimated that 90% of skin-resident T cells express CLA, and 80% of these cells are

effector memory T cells (Picker *et al.*, 1993). However, as E-selectin is not exclusively expressed by the cutaneous vascular complex but also on endothelium in various tissues under inflammatory conditions, other skin-specific factors seem to contribute to the homing of CLA+ T cells. CCR4 and CCR10 expression in particular seems to be associated with a CLA+ skin-homing phenotype of circulating T cells (Homey *et al.*, 2000a, 2002; Schaerli *et al.*, 2004) and has been found to be critical for T-cell recruitment to the skin in two different inflammation models (Reiss *et al.*, 2001; Campbell *et al.*, 2007).

The majority of CLA+ lymphocytes in the peripheral blood co-expresses CCR4 (Campbell *et al.*, 1999), with subsets (30–40%) showing additional expression of CCR10 (Hudak *et al.*, 2002). The CCR10 ligand, CCL27, is exclusively produced by epidermal keratinocytes (Morales *et al.*, 1999; Homey *et al.*, 2002) and CCL17—a CCR4 ligand—is synthesized by activated keratinocytes, DCs, and endo thelial cells in the skin (Campbell *et al.*, 1999; Campbell and Butcher, 2000). Although CCL17 expression is not skin-specific, Reiss *et al.* (2001) have suggested a model in which CCR4 and CCR10 share partly redundant or overlapping roles in the recruitment of leukocytes to the skin.

Apart from supporting immune cell recruitment to tissues, chemokines are thought to play an active role in the positioning of distinct T-cell subsets within different tissue compartments.

Notably, a high binding affinity of CCL27 to proteins of the extracellular matrix has been documented, suggesting a possible mechanism for the maintenance of chemokine gradients within the skin compartment (Homey *et al.*, 2002). In addition, the accumulation of epidermal CCL27 in skin-draining lymph nodes may influence the homing of CCR10+ T cells (Huang *et al.*, 2008). Worbs *et al.* (2007) recently reported that CCR7 ligands present within secondary lymphatic tissue stimulate the intranodal motility and positioning of T cells *in vivo*. Conclusive *in vivo* studies investigating an analogous scenario for chemokines expressed in the skin compartment are eagerly awaited.

T-cell differentiation

The role of chemokine receptor expression as a determinant for the functional properties and lineage commitment of T-cell subsets has been the focus of intense research efforts. Chemokines may influence T-cell differentiation indirectly by stimulating antigen-presenting cells to induce or repress polarizing cytokines, such as IL12 (Braun *et al.*, 2000). Alternatively, chemokines have been shown to regulate T-cell polarization by acting directly on activated T cells (Karpus *et al.*, 1998). Experimental evidence from several studies indicates that CCR5–CCL3 and CCL2 interactions in particular might be alternate or complementary pathways to IL-12 and IL-4 in dominating T-cell polarization (reviewed by Luther and Cyster, 2001).

With immunotherapeutics targeting the chemokine network forthcoming, the disease-related contribution of chemokine/chemokine receptor interactions in Th1 and Th2-cell polarization and effector functions is evolving (Kim *et al.*, 2001).

Chemokine-mediated effects on skin-resident DCs

Chemokine/chemokine receptor interactions are not limited to targeting naive, memory, and effector lymphocytes but extend to all subsets of leucocytes, including mature leucocytes of the innate immune system, as well as their hematopoietic precursors (Moser and Willimann, 2004).

Dendritic cells represent an integral link between components of the innate and the adaptive immune system. As professional antigen-presenting cells, they possess the unique ability to take up and process antigen in peripheral tissues to activate resting lymphocytes in secondary lymphoid organs and elicit an adaptive immune response. Thus, the directed migration of DC from the skin to the skin-draining lymph nodes is an essential factor in their immunostimulatory function and pathogenetic involvement in T-cell-mediated skin diseases.

The skin contains two major subsets of DCs: dermal DCs and Langerhans cells (LCs) in the epidermis (Loser and Beissert, 2007; Udey and Nagao, 2008). A complex interplay between cytokines, adhesion molecules, matrix metalloproteinases, and lipid mediators, as well as chemokines and their receptors, orchestrates the *in situ* positioning of DC and directs their relocation from peripheral tissues to the draining lymph nodes (Moser and Willimann, 2004; Adema *et al.*, 2005).

During maturation, DCs undergo a rapid and coordinated switch in their chemokine receptor profile (Sallusto *et al.*, 1998b). Immature DCs have been reported to express a distinct subset of chemokine receptors, including CCR1, CCR2, CCR5, CCR6, CCR8, and CXCR1 (Villablanca *et al.*, 2008), enabling them to migrate to inflamed tissues, including the skin (Gombert *et al.*, 2005). Conversely, CXCR4 and CCR7 are expressed at very low levels on immature DCs, but are markedly upregulated once DCs undergo maturation after antigen capture (Sallusto *et al.*, 1998b).

Although identifying CCR7 as an indispensable regulator for the entry of dermal DCs and LCs into afferent dermal lympathics, studies from Ohl *et al.* (2004) propose that CCR7 may be dispensable for the initial step of LC mobilization within the epidermis, that is, migration from the epidermis toward the dermis. Correspondingly, studies using human skin explants revealed that CXCR4 and its ligand, CXCL12, expressed by dermal endothelial cells, are crucial factors for LC migration from the epidermis to the dermis, whereas CCR7 is not essential (Avniel *et al.*, 2006; Ouwehand *et al.*, 2008). In addition, Kabashima *et al.* (2007a) have confirmed an important role for CXCR4 expression of mature DCs in their migration to skin-draining lymph nodes.

In light of these findings, a two-step model for LC migration to skin-draining lymph nodes has recently been proposed by Villablanca and Mora (2008). Under homeostatic conditions, immature LCs that do not express CXCR4 and CCR7 remain mostly confined to the epidermis. In a first step, the

upregulation of CXCR4 in response to inflammatory stimuli is thought to enable the maturing LCs to enter the dermal compartment of the skin, following a chemokine gradient of enhanced CXCL12 expression by dermal endothelial cells in inflamed skin. TNF-α, expressed at elevated levels in the skin under inflammatory conditions such psoriasis or AD, contributes to the disconnection between LCs from the keratinocytes of the epidermis by downregulating CCR6 expression on maturing LCs and thus rendering them insensitive to keratinocyte-derived CCL20 (Randolph *et al.*, 2005; Villablanca *et al.*, 2008). Once in the dermis, high levels of CCR7 expression on their cell surface subsequently permit the mature LCs and dermal DCs to exit the tissue and migrate to skin-draining lymph nodes, where the CCR7 ligands, CCL19 and CCL21, are readily expressed (Forster *et al.*, 1999; Saeki *et al.*, 1999).

Along these lines, it is noteworthy that besides the most extensively studied chemotactic effects, recent reports have pointed toward new functions of chemokine receptor interactions in DC biology. Analogous to effects described on T cells, CXCR4–CXCL12 interactions might also affect LC survival and maturation (Kabashima *et al.*, 2007b), whereas CCR7 engagement seems to be involved in the regulation of cytoarchitecture and endocytosis, survival, maturation, and the migratory speed of DCs (Sanchez-Sanchez *et al.*, 2006).

Survival pathways

Several chemokines have been reported to trigger downstream prosurvival signals. In particular, activation of the intracellular downstream effector molecules, phosphatdylinositol-3-kinase (P13K) and prokinase B (Akt), has been shown to lead to increased resistance to apoptosis on chemokine receptor engagement (Youn *et al.*, 2002; Murakami *et al.*, 2003). CCL1 has been described as a potent antiapoptotic factor for thymocytes, and CCL1–CCR8 interactions have been shown to provide survival signals to malignant T cells in adult T-cell lymphoma (Ruckes *et al.*, 2001). Murakami *et al.* (2003) reported that CCR10 engagement by locally produced CCL27 in the skin allows melanoma cells to escape the host's immune antitumor killing mechanisms, possibly through the activation of PI3K/Akt. Similar mechanisms might contribute to the survival and maintenance of pathogenic T cells in the skin in other neoplastic or inflammatory skin diseases, in which selected chemokines are abundantly expressed.

Microbicidal activity

In addition to providing a physical barrier, keratinocytes of the human epidermis constitutively or inducible express a number of molecules with bactericidal or bacteriostatic properties, such as human beta-defensins, LL-37, psoriasin (S100A7), and cystatin A (Harder *et al.*, 1997; Schittek *et al.*, 2001; Zaiou and Gallo, 2002; Harder *et al.*, 2004; Glaser *et al.*, 2005). The protein family of these so called antimicrobial peptides is a fundamental element of the innate defense system of epithelial and endothelial tissues, including the skin.

Accumulating evidence indicates that the members of the chemokine family and antimicrobial peptides not only share structural similarities but also exert substantially overlapping functions (Yang *et al.*, 2002, 2003). Although a number of antimicrobial peptides are chemotactic for selected classes and subsets of leukocytes (Yang *et al.*, 2004), many chemokines have a substantial antimicrobial activity against a broad range of microorganisms (Yang *et al.*, 2003). Human β-defensins exhibit chemotactic activity by sharing the chemokine receptor, CCR6, with its sole chemokine ligand, CCL20, expressed in the skin by epidermal keratinocytes and activated endothelial cells (Yang *et al.*, 1999). Correspondingly, data from recent studies suggest that CCL20 also has antimicrobial activity, predominantly against Gram-negative bacteria (Hoover *et al.*, 2002).

For CCL28, an additional role in mucosal immunity beyond being a chemoattractant for CCR10- and/or CCR3-expressing immune cells is being implicated by studies from Hieshima *et al.* (2003), reporting broad antimicrobial activity of high concentrations of CCL28 on mucosal surfaces. For CCL27, the CCR10 ligand expressed in the skin, the current data are more controversial. In this regard, it is noteworthy that most antimicrobial assays are performed *in vitro* under non-physiological conditions. A high concentration of chemokines, low pH, and salt-free conditions as used in many assay systems are unlikely to occur *in vivo*. However, the observation that chemokines, such as CCL27, may reach high local concentrations due to their high binding affinity to proteins of the extracelluar matrix (Homey *et al.*, 2002) indicates that chemokine measurements from biological fluids may significantly underestimate the levels reached in tissue compartments, such as the skin.

Comprehensive screening showed that about two-thirds of the 30 human chemokines tested have antimicrobial activity under the specific experimental conditions (Yang *et al.*, 2003).

It is persuasive to speculate that different chemokine levels in diseased skin may partially account for an altered susceptibility to cutaneous bacterial infections, such as in AD.

However, the relative importance of the antimicrobial activity of chemokines *in vivo* remains a field of much controversy and emphasizes the need for testing in appropriate animal model systems.

Decoy receptors

In addition to the traditional functions of the signaling chemokine receptors delineated above, a new group of nonsignaling chemokine-binding receptors has recently been characterized by virtue of their failure to initiate conventional signaling cascades or mediate chemoattraction.

Three of these so-called decoy or scavenger receptors have been described so far: D6, DARC (duffy antigen receptor for chemokines), and CCX–CKR (ChemoCentryx chemokine receptor). Their unique structural and functional properties, distinct specificity and tissue distribution, as well as their pivotal role in modulating immune responses have been

comprehensively discussed in a recent review (Mantovani *et al.*, 2006).

The best-characterized decoy receptor, D6, is a promiscuous seven-transmembrane-domain G-protein-coupled receptor, typically expressed on lymphatic vessels in the skin, gut, and lungs (Nibbs *et al.*, 2001). D6 binds most inflammatory, but not homeostatic, CC chemokines and is subsequently internalized in a ligand-independent way from the plasma membrane to endocytic compartments, wherein chemokines are targeted for degradation (Weber *et al.*, 2004; Martinez de la Torre *et al.*, 2005).

Similar to D6, DARC shares structural similarities with a conventional chemokine receptor but lacks the sequence motif required for signal transduction. DARC expression has been reported on erythrocytes and endothelial cells in tissues under steady state and inflammatory conditions, including the skin (Rot, 2005). Although binding of homeostatic chemokines to DARC has not been reported yet, DARC interacts in a promiscuous manner with several inflammatory chemokines of both the CXC- and CC subfamilies (Gardner *et al.*, 2004). Data from multiple studies indicate complex roles of DARC in inflammation, tumorigenesis, and angiogenesis, and a lack of DARC expression has been associated with greater susceptibility to certain tumors and inflammatory diseases (Segerer *et al.*, 2003; Bandyopadhyay *et al.*, 2006; Wang *et al.*, 2006). Recently, Pruenster *et al.* (2009) reported that, unlike other known non-signaling chemokine receptors, DARC does not act as a decoy but instead supports chemokine transcytosis and chemokine-induced leukocyte migration *in vitro* and *in vivo*.

Nevertheless, studies from several animal models have highlighted the importance of chemokine scavenging in the regulation of inflammatory and antitumor immune responses in the skin (Bonecchi *et al.*, 1998; Shenoy and Lefkowitz, 2003; Martinez de la Torre *et al.*, 2005; Nibbs *et al.*, 2007). D6-deficient mice show exacerbated inflammatory responses in a model of phorbol ester-induced skin inflammation, with prominent cutaneous T-cell infiltration and psoriasiform changes of the epidermis (Jamieson T, Nature Immunol 2005). Conversely, a transgenic D6 expression in keratinocytes was found to dampen cutaneous inflammation and bestow substantial protection from the development of chemically induced skin tumors in different animal models (Nibbs *et al.*, 2007). An expanded appreciation of the complex biological activities and functions of this newly identified group of atypical chemokine receptors will significantly contribute to a more comprehensive understanding of the pathophysiology of inflammatory and neoplastic diseases.

THE CHEMOKINE NETWORK IN THE PATHOGENESIS OF T-CELL-MEDIATED SKIN DISEASE

Psoriasis

The fundamental contribution of chemokines in skin-specific leukocyte homing and inflammation is shown impressively in the pathogenesis of psoriasis. Psoriasis, one of the most common chronic inflammatory skin disorders, is characterized by hyperproliferation of basal keratinocytes and a prominent cutaneous inflammatory infiltrate.

The inflammatory infiltrate of psoriatic skin is predominantly composed of Th1- and Th17-polarized lymphocytes of a memory phenotype, as well as neutophils, macrophages, and increased numbers of DCs (Prens *et al.*, 1995). An early cellular event in the development of a psoriatic lesion is the influx of activated T cells into the affected skin, the proinflammatory cytokines of which trigger a cycle of cutaneous inflammation and epidermal hyperplasia, resulting in the psoriatic phenotype (Bata-Csorgo *et al.*, 1995).

The complex cellular events leading to psoriatic skin inflammation require a controlled interplay between circulating leukocytes and resident skin cells and seem to be vitally coordinated by chemokine interactions (Table 1).

Studies from Homey *et al.* (2000b) identified CCL27 as a new skin-specific chemokine, exclusively produced by epidermal keratinocytes (Morales *et al.*, 1999). In psoriatic patients, elevated serum levels of CCL27, which correlate with disease activity, have been reported (Morales *et al.*, 1999; Homey *et al.*, 2002; Kakinuma *et al.*, 2003a). The constitutive expression of CCL27 by keratinocytes in the skin can be upregulated by inflammatory mediators (IL-1 and TNF-α), and is found at elevated levels not only in psoriatic lesions but also in Th2-dominated inflammatory skin diseases, such as AD (Homey *et al.*, 2002). Thus, CCL27–CCR10 interactions seem to be involved in the recruitment of memory T cells to the skin regardless of their Th1 or Th2 polarization, and a CCL27 gradient in the skin has been postulated to contribute to the epidermal positioning of CCR10+ T cells (Morales *et al.*, 1999; Homey *et al.*, 2000b) (Figure 1).

In addition to CCR10, CCR4 is highly expressed on a subset of memory T cells with a CLA+ skin-homing phenotype, and both receptors seem to cooperate in the recruitment of memory T cells to the skin under inflammatory conditions (Reiss *et al.*, 2001) (Figure 1). Although the expression of the CCR4 ligand, CCL17, is not skin specific, its expression by the dermal vascular endothelium under inflammatory conditions may collaborate with keratinocyte-derived CCL27 in mediating leukocyte migration into inflamed skin.

Recent research has drawn attention to the involvement of CCL20 and its only known receptor, CCR6, in the pathogenesis of psoriasis (Figure 1). In lesional psoriatic skin, both CCL20 and CCR6 have been detected at significantly elevated levels (Homey *et al.*, 2000a). CCL20, primarily expressed by epidermal keratinocytes and activated endothelial cells, is a highly potent chemoattractant for CCR6+ epithelial Langerhans-type DCs and memory T cells (Liao *et al.*, 1999; Dieu-Nosjean *et al.*, 2000). Skin-homing CLA+ memory T cells express high levels of CCR6, and both CCL20 and CCR6 have been reported to colocalize with epidermal T cells in psoriatic skin (Fitzhugh *et al.*, 2000; Homey *et al.*, 2000a). CLA+ T cells isolated from psoriatic skin respond to lower concentrations of CCL20 as compared with T cells from healthy donors, whereas CCL20 production by keratinocytes

Table 1. Synopsis of main chemokine/chemokine receptor interactions reported to be involved in the pathogenesis of psoriasis, atopic dermatitis and/or mycosis fungoides/Sézary syndrome

Chemokine receptor	Ligand(s) expressed in the skin (alternate acronym)	Preferential expression on T-cell subsets	Disease connection	References
CCR4	CCL17 (TARC) CCL22 (MDC)	Skin-homing CD4+ CLA+ T cells Th2 cells Th17 cells Treg	Mycosis fungoides Sézary syndrome Atopic dermatitis Psoriasis	Fierro *et al.* (2006); Sokolowska-Wojdylo *et al.* (2005); Campbell *et al.* (1999); Kakinuma *et al.* (2001); Ishida *et al.* (2003)
CCR6	CCL20 (MIP-3α, LARC)	Th17 cells Treg	Psoriasis	Homey *et al.* (2000a); Kleinewietfeld *et al.* (2005); Hedrick *et al.* (in press)
CCR8	CCL1 (1309)	Th2 cells, γδ T cells Treg	Atopic dermatitis	Gombert *et al.* (2005)
CCR10	CCL27 (CTACK)	Skin-homing CLA+ CD4+, and CD8+ T cells	Psoriasis Atopic dermatitis Mycosis fungoides	Hudak *et al.* (2002); Morales *et al.* (1999); Homey *et al.* (2000b); Homey *et al.* (2002); Notohamiprodjo *et al.* (2005); Sokolowska-Wojdylo *et al.* (2005); Kakinuma *et al.* (2003a, b)
?	CCL18	Receptor unknown, CCL18 induces migration of CLA+ memory T cells into the skin	Atopic dermatitis	Pivarcsi *et al.* (2004); Park *et al.* (2008)
CXCR3	CXCL9 (MIG) CXCL10 (IP-10) CXCL11 (IP-9, I-TAC)	CD4+ CD45RO+ T cells	Psoriasis Low-grade mycosis fungoides	Flier *et al.* (1999); Kallinich *et al.* (2003)
CXCR4	CXCL12 (SDF-1)	CD4+ CD45RO+ T cells	Mycosis fungoides	Kallinich *et al.* (2003)

can be induced by proinflammatory cytokines (that is, IL-1 and TNF-α) commonly found in psoriatic skin (Homey *et al.*, 2000a). Interestingly, CCR6 has lately been described as a marker for human and murine Th17 cells, and their hallmark cytokines IL-17 and IL-22 have been implicated to be critically involved in the pathogenesis of several autoimmune inflammatory diseases, including psoriasis (Murphy *et al.*, 2003; Langrish *et al.*, 2005; Acosta-Rodriguez *et al.*, 2007; Annunziato *et al.*, 2007; Blauvelt, 2008; Singh *et al.*, 2008). A recent study assessed the role of CCR6 in an IL-23-induced mouse model of psoriasiform dermatitis in which the psoriatic phenotype has previously been reported to be predominantly meditated by the Th17 cytokine, IL-22 (Chan *et al.*, 2006; Zheng *et al.*, 2007). Interestingly, CCR6-deficient mice were resistant to IL-23-induced psoriatic skin inflammation in this model. Although the pathology was absolutely dependent on CCR6 expression, further investigation surprisingly revealed that CCR6 is mainly required for the recruitment and/or function of a non-T-cell source of IL-22 in this model (Hedrick *et al.*, in press).

Atopic dermatitis

Atopic dermatitis, or atopic eczema, is a common pruritic and chronically relapsing inflammatory skin disease with a steadily increasing prevalence (Leung and Bieber, 2003; Asher *et al.*, 2006). The pathogenesis of AD is generally multifactorial and may involve both genetic and environmental factors (Palmer *et al.*, 2006; Weidinger *et al.*, 2007). Acute lesions emerge as erythematous macules or papules with a typical distribution pattern and severe pruritus, whereas chronic lesions show characteristic lichenification or thickening and hypertrophy of the epidermis.

In addition to acanthosis and hyperkeratosis, AD skin lesions show histopathologically a marked inflammatory infiltrate, predominantly consisting of CLA+ CD4+ memory T cells (Leung and Bieber, 2003). Clinical and experimental evidence points toward a crucial role of the composition of the T-cell infiltrate in the immunopathogenesis of the disease (Woodward *et al.*, 2001; Leung and Bieber, 2003).

Chemokines have complex functions regarding the development and composition of the inflammatory infiltrate in AD (Table 1). Homey *et al.* (2006) recently suggested an amplification cycle of atopic skin inflammation in which chemokine interactions play a critical role. Patient scratch is thought to induce mechanical injury and facilitate superinfection of atopic lesions, resulting in the production of proinflammatory cytokines and chemokines, which are thought to orchestrate the recruitment of pathogenic leukocytes into the skin. Although multiple homeostatic and inflammatory chemokines have been shown to relate to the AD phenotype (reviewed by Homey

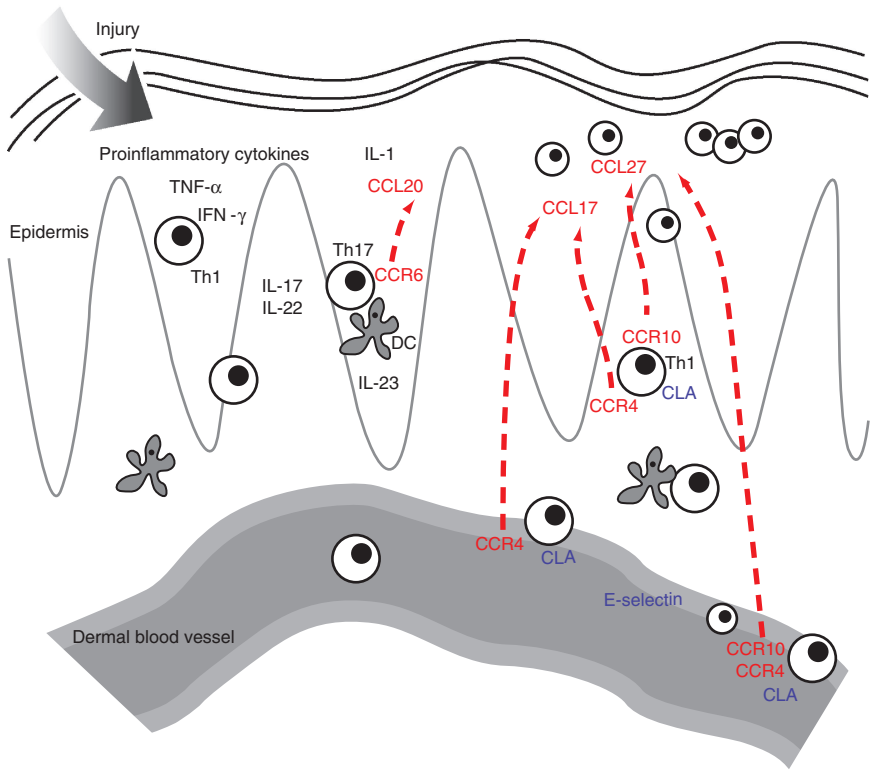

Figure 1. Roles for chemokines and their receptors in psoriasis. Common events in lesional psoriatic skin include activation of skin dendritic cells and keratinocytes, recruitment and activation of predominantly Th1- and Th17-polarized T cells, followed by keratinocyte damage. Inflammatory mediators (TNFα, IL-1, and so on) enhance the production of CCL27 by keratinocytes, as well as endothelial cell-derived CCL17, and may collaborate in mediating the homing of CCR10+ CCR4+ skin-homing memory T cells to the site of cutaneous inflammation. In addition, elevated levels of CCL20 may further contribute to the homing and *in situ* positioning of CCR6+ memory Th17 cells in psoriatic skin.

et al., 2006), the roles of CCR10 and CCR4 in AD have been particularly well documented (Figure 2).

Both CCR10 and its ligand, CCL27, exhibit strong immunohistochemical staining in skin biopsies from AD patients (Vestergaard *et al.*, 2003). CCL27, constitutively expressed by human keratinocytes, can be upregulated by proinflammatory cytokines (that is, IL-1 and TNF-α) present in inflamed tissue (Morales *et al.*, 1999; Homey *et al.*, 2002), and serum levels of CCL27 show a significant correlation with disease severity (Kakinuma *et al.*, 2003a). In mouse models mimicking AD and allergic contact dermatitis, neutralization of CCL27 resulted in a significantly impaired memory T-cell recruitment to the skin and a decreased tissue inflammation (Homey *et al.*, 2002).

Th2 clones derived from the lesional skin of AD patients have been found to highly express CCR4 on their surface, but little or no CXCR3 (Campbell *et al.*, 1999; Biedermann *et al.*, 2002). Correspondingly, high levels of the CCR4 ligands, CCL17 and CCL22, have been detected in the lesional skin of AD patients and in the skin of a mouse model of AD (NC/Nga model) (Galli *et al.*, 2000; Vestergaard *et al.*, 2003). Similar to CCL27, the plasma levels of the CCR4 ligands, CCL17 and CCL22, show an elevated level in AD patients compared with those in healthy controls, and seem to correlate closely with disease activity (Kakinuma *et al.*, 2001; Wakugawa *et al.*, 2001). Although the contribution of both CCL17 and CCL27 for the recruitment of memory T cells to sites of skin inflammation is well established, a specific association with an AD phenotype has not been demonstrated (Figure 2).

By contrast, a comprehensive study of the expression of chemokines in various chronic inflammatory or autoimmune skin diseases revealed a specific association of the chemokine, CCL18, with an AD phenotype (Pivarcsi *et al.*, 2004). The CCL18 mRNA expression in lesional skin from AD patients was found to be more than 100-fold higher than levels of CCL17. An additional DNA microarray analysis revealed the strongest association of CCL17 with AD, compared with DNA isolated from skin of psoriasis patients or from healthy controls. In addition, a recent study showed an increased protein expression of CCL18 in the serum of patients with extrinsic AD, compared with patients with non-allergic type of AD (intrinsic AD), with a significant decrease after specific immunotherapy (Park *et al.*, 2008). Although the receptor for CCL18 has yet to be identified, CCL18 has been reported to bind to CLA+ memory T cells in the blood of AD patients *in vitro* and induce their migration into human skin *in vivo* (Gunther *et al.*, 2005).

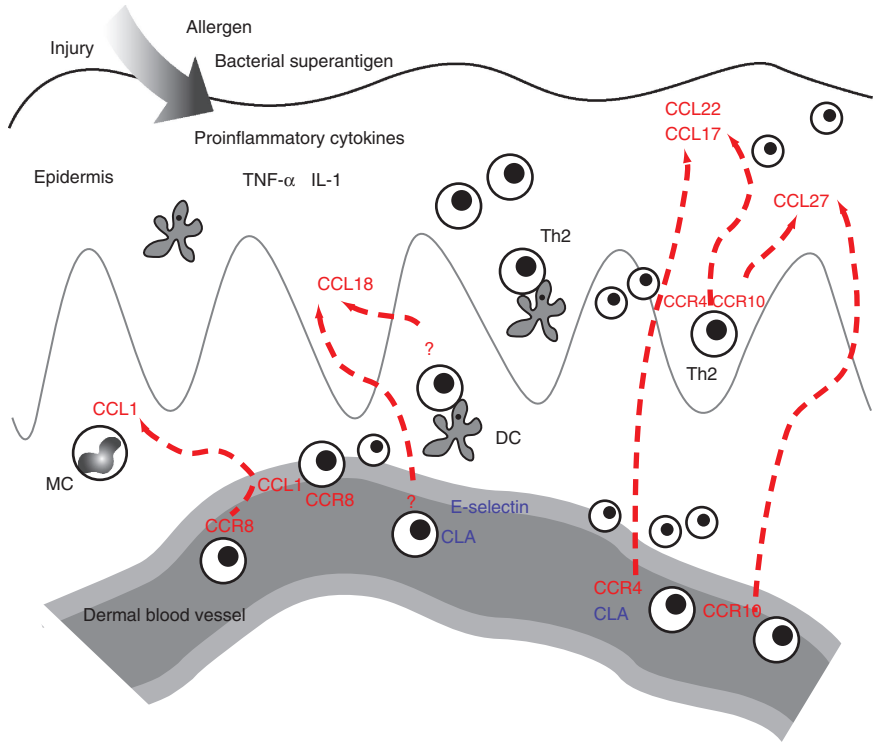

Figure 2. Roles for chemokines and their receptors in atopic dermatitis. Mechanical injury, such as patient scratch, and superinfection trigger atopic skin inflammation by the induction of inflammatory cytokines and chemokines**.** CCL17–CCR4 and CCL27–CCR10 interactions contribute to the extravasation and homing of CLA+ memory T cells to the site of cutaneous inflammation. CCL18 production by skin-resident DC can be strongly induced by allergen exposure as well as by staphylococcal superantigens, and is thought to further sustain the migration of CLA+ memory T cells from the peripheral blood to atopic skin lesions. In addition, CCL1 production by endothelial cells and mast cells during atopic skin inflammation may contribute to the recruitment of CCR8-expressing T cells and DC, as well as sustaining their maintenance and survival at the site of cutaneous inflammation (MC: mast cell; ?: unknown receptor).

In light of these findings, it is noteworthy that CCL18 was reported to be produced mainly by dermal DCs in close proximity to infiltrating T cells in atopic skin and to be strongly induced by allergen exposure and staphylococcal superantigens (Pivarcsi *et al.*, 2004). Interestingly, 90% of AD patients show a colonization of lesions with *Staphylococcus aureus,* and anti-staphyloccocal therapy frequently supports a clinical improvement (Breuer *et al.*, 2000, 2002) (Figure 2).

In addition to CCL18, CCL1 has recently been found to be another chemokine that is specifically and selectively upregulated in AD compared with other inflammatory skin disorders and healthy skin (Gombert *et al.*, 2005) (Figure 2). Gombert *et al.*, identified mast cells and endothelial cells as the major source of CCL1 during atopic skin inflammation and demonstrated that, analogous to CCL18, CCL1 expression can be significantly induced by *S. aureus* superantigens and by allergen exposure. CCR8, the sole receptor for CCL1, was abundantly expressed on subsets of DCs *in vitro,* as well as on a small subset of circulating T cells (Bonecchi *et al.*, 1998). Interestingly, CCL1 has been previously described as a potent antiapoptotic factor for thymocytes (Ruckes *et al.*, 2001). CCR8 interactions may thus not only contribute to immune cell recruitment but also to their maintenance and survival at sites of atopic skin inflammation.

The specific association of CCL18 and CCL1 with an AD phenotype, in conjunction with its regulation by allergen exposure and microbial products, is suggestive of a significant involvement of CCL18 and CCL1/CCR8 interactions in the induction and/or augmentation of atopic skin inflammation.

Mycosis fungoides and Sézary syndrome

Mycosis fungoides is the prototypic and most frequent form within the broad group of CTCLs, accounting for approximately 72% of reported CTCL cases (Weinstock and Gardstein, 1999; Criscione and Weinstock, 2007). In MF, the neoplastic T cells display a strong epidermotropism and preferentially localize to the skin.

Although a *de novo* presentation of the advanced stages of the disease are possible, MF classically presents itself with a slow, indolent course that may progress over years from patches and plaques to tumor stages, and with a possible subsequent involvement of lymph nodes and the peripheral blood. The Sézary syndrome (SS), which was previously often categorized as a variant of MF, has now been classified as a separate entity by WHO and EORTC (Willemze *et al.*, 2005). According to ISCL (International Society for

Cutaneous Lymphoma), the diagnosis of SS is based on the verification of an extensive, clonal population of abnormal T cells with hyperconvoluted, cerebriform nuclei in the peripheral blood in addition to erythroderma.

Histologically, patches and plaques of MF are characterized by the often band-like accumulation of lymphocytes in the upper dermis and fairly specific Pautrier microabscesses, consisting of aggregates of malignant T cells clustering around LCs in the epidermis (Pimpinelli *et al.*, 2005). However, an early disease of MF and SS may not show the entirely developed typical histopathological changes and can clinically mimic benign inflammatory skin disorders such as psoriasis and AD, often impeding an early diagnosis.

Although development and disease activity seem to be controlled by a population of tumor-specific CD8+ Tcells, the malignant cells are thought to originate from CD4+ CD45RO+ memory T cells, which frequently lack the expression of certain T-cell surface markers, such as CD26, CD49d, and CD7 (Vowels *et al.*, 1994; Berger *et al.*, 1996; Bernengo *et al.*, 2001). CD26, also known as dipeptidylpeptidase IV, proteolytically cleaves and inactivates the CXCR4 ligand, CXCL12. Given the abundant CXCR4 expression that has recently been reported on malignant T cells in MF patches (Kallinich *et al.*, 2003), the loss of CD26 expression strongly suggests a potential role for CXCR4 in the skin-homing of Sézary cells (Sokolowska-Wojdylo *et al.*, 2005; Narducci *et al.*, 2006) (Table 1). The inactivation of CD26 has been shown to enhance the migratory potential of cell lines derived from patients with SS in response to CXCL12, whereas the presence of soluble CD26 is inhibitory (Narducci *et al.*, 2006).

CXCR4 engagement has previously been reported to result in the upregulation of the key prosurvival kinases, PI3K and Akt, with relevance in the progression of solid malignancies such as melanoma (Lee *et al.*, 2006). Given the constitutive expression of CXCL12 in the skin, the loss of CD26 on Sézary cells might sustain their chemokine-driven, cutaneous migration, and activation of downstream effectors of this antiapoptotic pathway contributes to their survival in the skin compartment (Hwang *et al.*, 2008).

In line with characteristic epidermotropism, the malignant T cells typically display a CLA+ skin-homing phenotype. In addition to CLA interactions, the unique expression pattern of chemokine receptors can in part explain the cutaneous tropism of the malignant T cells (Figure 3). Supporting the notion of a Th2 origin of malignant cells, high levels of CCR4, but not of CCR5 and CXCR3 expressions, have recently been demonstrated on skin-infiltrating T cells in SS (Fierro *et al.*, 2006). Serum levels of the related chemokines, CCL17, CCL22, and CXCL10, are significantly increased in both SS patients and patients suffering from erythroderma due to inflammatory dermatoses. However, the results from these studies support the perception of SS being a Th2 disorder with a selective expression of CCR4, whereas inflammatory erythroderma shares overexpression of both Th1-and Th2-related chemokine receptors (Fierro *et al.*, 2006).

In addition to the predominant Th2 profile of malignant cells in MF and SS, Berger *et al.* (2005), recently reported the *in vitro* conversion of malignant T cells to cells with a Treg phenotype after stimulation with cryptic self-antigens that might be uncovered during apoptosis. The adoption of Treg-suppressor functions by CTCL may offer

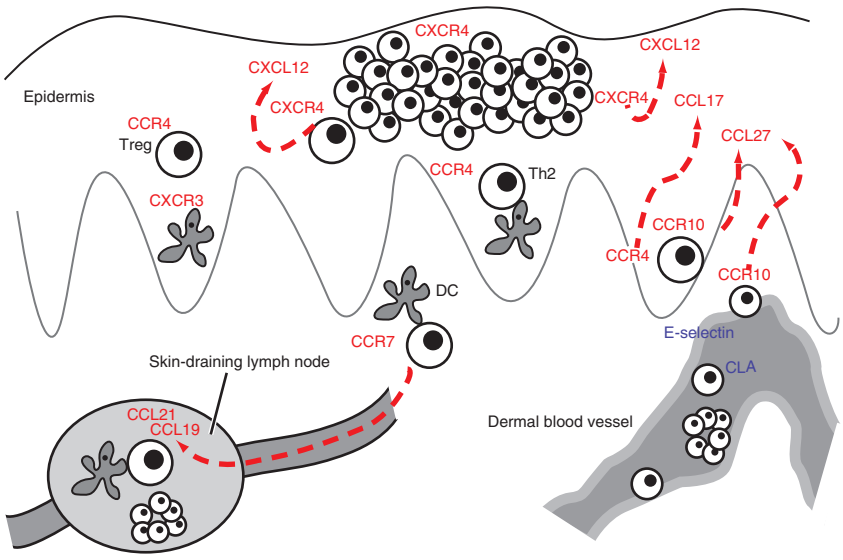

Figure 3. Roles for chemokines and their receptors in mycosis fungoides and Sézary syndrome. Chemokine receptors such as CCR10 and CCR4 permit skin-specific homing of malignant T cells and support the efficient engagement of DC and the subsequent release of pro-inflammatory cytokines. Apart from a role in cutaneous homing of Sézary cells, CXCR4 might sustain their chemokine-driven survival in the skin compartment by activating intracellular key pro-survival signals. During disease progression, changes in the expression pattern of selected chemokine receptors such as CCR4 and CXCR3 seem to correlate with reduced epidermotropism of the malignant T cells. The directional migration of CCR7-expressing malignant T cells from the skin to the draining lymph nodes is effectively supported by the release of CCL19 and CCL21 by stromal cells of the lymphatic vessels and the lymph node.

a possible explanation for the immunosuppressive nature of the disease and increased susceptibility of MF and SS patients to opportunistic infections (Axelrod *et al.*, 1992).

CCR4 and CCR10 in particular are frequently present on malignant T cells in MF and SS and play a potential role in their homing to the skin (Notohamiprodjo *et al.*, 2005; Sokolowska-Wojdylo *et al.*, 2005) (Figure 3). CCL17—a major CCR4 ligand expressed by activated keratinocytes, DC, and endothelial cells—is increased in the serum of MF patients, with levels correlating with disease activity (Kakinuma *et al.*, 2003b). Similarly, the CCR10 ligand, CCL27, is found at elevated levels in patients with MF and SS and might serve as an indicator for disease activity (Fujita *et al.*, 2006; Kagami *et al.*, 2006). CCR10–CCL27 interactions are proposed to play an early role in the pathophysiology of MF from the patch stage. Fujita *et al.*, (2006) reported significantly higher numbers of circulating CCR10+ CD4+ cells in the peripheral blood of MF patients compared with those in healthy controls or patients with AD and an accumulation of CCR10+ skin-infiltrating tumor cells in MF lesions. By contrast, serum levels of CCL27, although considerably elevated compared with those in healthy controls, showed no significant differences in comparison with patients with AD. In patients with MF and SS, an unfavorable outcome of the disease was associated with an overexpression of CCR4 by malignant CD4+ T cells (Ishida *et al.*, 2003, 2004b).

Chemokines may not only facilitate the recruitment of tumor cells to certain tissues like the skin but may also induce tissue infiltration by various immunosuppressive cells, such as Tregs, leading to an escape from immunosurveillance and an unfavorable outcome in malignant diseases. Suppressive CCR4-expressing CD4+CD25 high Tregs are being recruited to sites of cutaneous lymphoma that express high levels of CCL17 or CCL22 (Ishida *et al.*, 2003).

A change in the expression patterns of selected chemokine receptors during disease progression seems to correlate to the reduced epidermotropism of malignant T cells generally observed in skin biopsies from advanced stage MF and SS. Kallinich *et al.*, (2003) compared the chemokine receptor expression in different stages of MF and reported decreased expression levels of CCR4 and CXCR3 lesional skin of tumor-stage patients with MF, whereas levels of the lymph-node-homing receptor, CCR7, were remarkably increased. Moreover, a recent report revealed that the addition of CXCL13 to CCL19 or to CCL21, the selective CCR7 agonists responsible for lymph node homing, strongly enhances the migration of CCR7+ Sézary cells (Picchio *et al.*, 2008). Although a prognostic implication has not yet been validated, these findings correlate with the clinical enlargement of peripheral lymphnodes and greater leukemic burden seen in patients with advanced stage MF.

NEW TOOLS—NEW QUESTIONS

During the past decade, we have observed the development of potent immunotherapeutics directed against surface molecules that are involved in the migration and/or function of immune cells. The diversity of chemokine receptors and their preferred expression on distinct leukocyte subsets that have been implicated in the pathogenesis of different inflammatory or neoplastic diseases offer the opportunity for their selective targeting.

Monoclonal antibodies that target inflammatory cytokines or adhesion molecules, such as the anti-α4-integrin mAb, Natalizumab, have been successfully used for the treatment of inflammatory and autoimmune diseases (von Andrian and Mackay, 2000). However, given the considerable promiscuity in the chemokine network, with multiple chemokines often sharing the same receptor, strategies favoring the selective targeting and inactivation of chemokines by blocking antibodies seem to be less promising.

Conversely, agents that block chemokine receptors expressed on distinct leucocyte subsets are expected to be more specific. In preclinical studies, mAbs directed against CCR4 successfully controlled CCR4-expressing malignant T-cell clones by eliciting antibody-dependent natural killer-mediated cytotoxicity (Niwa *et al.*, 2004; Ishida *et al.*, 2004b).

However, a distinct chemokine receptor expression has not only been documented on subsets of pathogenic T cells in various disease but also on immune cells exerting regulatory function, such as Treg cells (Kleinewietfeld *et al.*, 2005). Notably, the antibody used in the described study did not only lyse malignant CCR4+ T-cells *in vitro* but also reduced the expression of Foxp3 mRNA, suggesting a possible effect in depleting regulatory T cells (Ishida *et al.*, 2004a, b). Although the inhibition of Treg functions by means of chemokine receptor antagonism has been demonstrated to be favorable for tumor control, the disruption of normal endogenous immune regulatory mechanisms may result in broader, unfavorable effects, such as increased inflammatory responses and risk for infection (Unsoeld *et al.*, 2007).

A new approach takes advantage of the physiological endocytosis of chemokine receptors after ligation, eventually enhancing the presentation of tumor-derived peptides on the cell surface (Biragyn *et al.*, 2004). Data from a recently published animal study provided proof-of-principle that chemokine receptor-expressing tumors can be successfully controlled by the delivery of toxins through their chemokine receptors (Baatar *et al.*, 2007). Biragyn and colleagues have generated chemokine-toxin fusion proteins, chemokines fused with toxic moieties that are nontoxic unless delivered into the cell cytosol. Treatment with CCL17-expressing chemotoxin efficiently eradicated CCR4-expressing CTCL established in NOD-SCID mice (Baatar *et al.*, 2007). While strengthening the concept that the targeting of chemokine receptors such as CCR4 or CCR10 permits the control of growth and dissemination of certain tumors, this study on the whole showcases the complexity and challenges in the field. Despite the initial tumor control by CCL17-chemotoxin treatment, the malignancy eventually relapsed. Importantly, after tumor

relapse, the malignant cells seemed resistant to additional and repeated treatment with the chemokine toxin. It remains to be seen whether such a highly specific treatment in heterogenous malignancies selects for tumor variants and thus supports the outgrowth of tumors with an aberrant receptor expression.

During the last decade, particular attention has been paid to the development of small molecule antagonists directed against chemokine receptors.

As synthetic small-molecule antagonists directed against G-protein-coupled receptors have been used effectively in the treatment of various diseases, the finding that chemokines signal through this large class of receptors has raised hope for their therapeutic application in targeting specific chemokine receptors.

Nevertheless, despite intense research efforts and promising results from animal studies more than two decades after the discovery of chemokines and their receptors, only few synthetic receptor antagonists have found their way into a clinical application.

Recently, the small-molecule antagonist, Mavaviroc, directed against the HIV co-receptor, CCR5, became the first Food and Drug Administration-approved antiretroviral agent that targets a human host protein rather than a viral component (MacArthur and Novak, 2008). AMG487, a small-molecule antagonist directed against CXCR3 from Tularik-Amgen, progressed to Phase II clinical trials for the treatment of psoriasis in 2003, but has been withdrawn because of lack of efficacy. Although the significance of the relative contribution of Th1 cells opposed to that of Th17 cells in autoimmune inflammatory diseases such as psoriasis is not yet fully understood, data from preclinical studies in rheumatoid arthritis models suggest that CCR6 inhibition holds promise for the treatment of Th17-related diseases (Hirota *et al.*, 2007). Although a small-molecule antagonist directed against CCR6 has yet to be developed, the targeting of a different subset of pathogenic effector T cells in psoriasis by means of CCR6 inhibition may be particularly effective and reasonable in combination with established systemic therapies targeting Th1-related cytokines, such as the anti-TNF-α mAbs (Eternacept, Infliximab).

Another noteworthy level of complexity is added by the finding that some chemokines may naturally exert either agonistic or antagonistic effects.

An emerging concept in the field is the regulation of Th1 and Th2 responses by natural chemokine antagonism. The Th2-type associated chemokine, CCL26, an agonist for CCR3, has been found to be an antagonist for CCR2, thus, negatively regulating the migration of human monocytes (Ogilvie *et al.*, 2003), and in a model of allergen-induced airway inflammation, the CXCR3 ligand, CXCL9, which is generally associated with Th1-responses, evolved as a negative regulator of eosinophil recruitment by the antagonism of CCR3 (Fulkerson *et al.*, 2004). The demonstration that a chemokine can function both as an agonist for one and as an antagonist for a different chemokine receptor has added another level to the regulation of Th1/Th2-mediated responses, with possible implications for the development of anti-inflammatory therapies.

Truncated or otherwise modified chemokines have demonstrated profound inhibitory effects on inflammatory responses in several animal models, providing ground for optimism for the many ongoing human trials (reviewed by Mackay, 2008).

An additional, yet widely ignored strategy is the exploitation of chemokine decoy receptors to fine-tune the distribution and bioavailability of chemokines. The broad specificity of decoy receptors with a distinct set of ligands may identify them as valuable tools of efficient chemokine-targeting strategies in the therapy and prophylaxis of various diseases.

The appreciation of the role of chemokines and their receptors in leukocyte trafficking and other key biological functions suggests a promising potential for their therapeutic targeting in a wide range of diseases. In practice, however, the strategy to antagonize chemokine receptors in order to therapeutically control the homing of pathogenic T cells to the cutaneous compartment has proven to be challenging. Over the years, the close association of chemokine receptor expression with the functional properties of T-cell subsets has been convincingly documented and the key molecules have been well defined. However, several key conceptual issues based on the experimental evidence outlined above have risen in recent years and future studies will need to address these key challenges.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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