Published in final edited form as:

Expert Opin Ther Targets. 2010 September ; 14(9): 911–922. doi:10.1517/14728222.2010.504716.

CCR6 as a possible therapeutic target in psoriasis

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Abstract

Importance of the field—Psoriasis is a common, chronic autoimmune disease of the skin. Despite a number of effective treatments, new therapies are needed with enhanced efficacy, safety, and convenience. Chemokine receptors are G protein-coupled receptors that control leukocyte trafficking, and like other G protein-coupled receptors, are good potential drug targets. The chemokine receptor CCR6 is expressed on the Th17 subset of CD4⁺ T cells, which produces IL-17A/F, IL-22, TNF- α and other cytokines, and which has been implicated in the pathogenesis of psoriasis. CCR6 and its ligand, **CCL20/MIP-3 α** , are highly expressed in psoriatic skin and CCR6 is necessary for the pathology induced in a mouse model of psoriasis-like inflammation.

Areas covered in this review—This review will summarize the evidence for the **importance of the IL-23/Th17 axis**, and in particular CCR6 and CCL20 in psoriasis, dating from 2000 to the present, and discuss the possibility of inhibiting CCR6 as treatment for the disease.

What the reader will gain—The review will inform the reader of the current thinking on the mechanisms of inflammation in psoriasis and the possible roles for CCR6 (and CCL20) in disease pathogenesis.

Take home message—We conclude that CCR6 should be investigated as a potential therapeutic target in psoriasis.

Keywords

Psoriasis; Chemokines; Inflammation; Autoimmune disease

1. Introduction

Psoriasis is the most common autoimmune disease of the skin, affecting 0.5–5% of individuals worldwide, depending on the ethnic group [1]. Psoriasis is a chronic disease that can occur in one of several forms, the most common being plaque psoriasis, which presents as well demarcated plaques of erythematous skin covered with white, flaky scales [1]. While typically pain-free, the skin lesions of psoriasis significantly affect quality of life because of pruritus and **cosmetic considerations**. Moreover, in a proportion of cases, psoriasis leads to a destructive arthritis [1]. The cost of treating psoriasis comes to several billion dollars per year [2].

The histology of the skin lesions in psoriasis includes thickening of the live-cell layers of the epidermis (acanthosis), decreased differentiation of keratinocytes with the retention of nuclei in the superficial layers (parakeratosis), thickening of the cornified layer (hyperkeratosis), hyperproliferation of the basal layer of keratinocytes, collections of neutrophils in the epidermis (Munro's microabscesses), elongated rete ridges, dilated blood vessels in the dermis, and infiltration of a mixed population of inflammatory cells in the dermis and epidermis [1, 3]. Despite a good deal of information as to the cellular and molecular elements contributing to psoriatic inflammation, many gaps remain in our understanding of the pathophysiology of the disease. Both experimental models and clinical data have implicated T cells, which have been the targets of many of the current anti-psoriasis therapies. Historically, psoriasis has been considered a disease mediated by Th1 cells, CD4⁺ (helper) T cells whose signature cytokine is IFN γ and that also produce TNF α [4, 5]. TNF- α is clearly important in the disease, since inhibiting TNF- α is highly effective therapy for both psoriasis and psoriatic arthritis [6].

Recently, a subset of CD4⁺ T cells that produce IL-17 (also called IL-17A) as well as other cytokines have been implicated as critical mediators of tissue damage in models of autoimmune diseases [7–11]. These Th17 cells, as well as their effector molecules IL-17A, IL-17F, TNF- α , IL-22, and IL-26 are abundant in psoriatic lesions [12–14]. Besides TNF- α , IL-22 is of particular interest. Serum levels of IL-22 are elevated in individuals with chronic plaque psoriasis and diminish after effective therapy [15, 16]. Recently, a subset of skin-homing CD4⁺ T cells that produce IL-22, but not IL-17A, so-called Th22 cells, have been described in humans [17, 18], and cells of this phenotype have been found in inflammatory diseases of the skin, including psoriasis [19, 20].

Psoriatic lesions also contain high levels of IL-23, a growth and differentiation factor for Th17 cells [13, 21, 22]. IL-23 contains p40, a subunit shared with IL-12, and an IL-23-specific subunit, p19 [23]. Genome-wide analyses have revealed associations between the occurrence of psoriasis and polymorphisms in the genes for both the p40 and p19 subunits of IL-23, and the IL-23-specific chain of the IL-23 receptor [24–27]. Moreover, ustekinumab, a monoclonal antibody that blocks the p40 subunit of IL-12 and IL-23, has produced dramatic clinical responses in patients with chronic plaque-type psoriasis [28–32]. A second anti-p40 antibody, briakinumab has also shown promise in psoriasis and is currently in phase III trials [32]. In further support of a role for the IL-23/Th17 axis in psoriasis, direct intradermal injection of IL-23 into mouse skin results in psoriasis-like changes including acanthosis, hyper- and parakeratosis, and dermal inflammatory infiltrates [33–35]. Additionally, IL-17A/F and IL-23 play critical roles in a recently described mouse model of psoriasis-like inflammation induced by topical imiquimod [36]. In light of these new data, current models of psoriasis pathogenesis include important contributions for both Th1 and Th17 cells [3].

Besides CD4⁺ T cells, other lymphocyte populations and dendritic cells have been implicated in the immunopathogenesis of psoriasis. CD8⁺ T cells in psoriatic lesions can express effector cytokines similar to those produced by CD4⁺ T cells, including IFN γ and IL-17 [37–40]. Both NK cells and NKT cells, a T cell subset that expresses natural killer (NK) cell markers, have been suggested to have roles in autoimmune disease and in psoriasis in particular [41–43]. Following isolation from individuals with psoriasis, NKT cells can express IFN γ when co-cultured with CD1d⁺ keratinocytes. Also, NKT cells generated from peripheral blood of patients with active psoriasis can induce psoriatic lesions when injected into autologous non-lesional skin grafted onto SCID mice [44, 45]. Of potential relevance, a subset of IL-22-producing cells with NK-cell markers has been described in the gastrointestinal tract [46, 47]. Despite the NK cell-like surface markers, these cells, which to our knowledge have not been found in the skin, have a lineage separate from conventional NK cells [48, 49].

Dendritic cells of the skin can be broadly classified into two main subgroups, dermal dendritic cells and Langerhans cells, depending on their localization and expression of key lineage makers [50]. Both inflammatory, myeloid dendritic cells and plasmacytoid dendritic cells are known to accumulate in the dermis of active psoriatic lesions [51–53], and dendritic cells cultured from such lesions are able to stimulate spontaneous T cell proliferation more potently than dendritic cells derived from blood [54]. Dendritic cells from lesional skin express IL-23 and IL-6 but not IL-12, again pointing to the importance of the IL-23/Th17 axis in psoriasis [21]. Nonetheless, lesional skin dendritic cells can stimulate allogeneic T cells to produce both IFN γ and/or IL-17 [55].

2. Chemokines and chemokine receptors

For psoriatic lesions to develop, inflammatory cells must be able to migrate into lesional skin. Leukocyte migration from blood to tissue is a multi-step process involving selectin-mediated rolling on endothelium and chemoattractant-mediated integrin activation leading to firm arrest, followed by diapedesis and chemotaxis up a chemoattractant gradient [56]. The chemokines constitute the largest family of chemoattractants, with more than forty members, and they signal through a corresponding family of nineteen G protein-coupled, seven transmembrane domain receptors [56]. In the blood, chemokines are displayed on the surfaces of endothelial cells, and in tissue they form fixed gradients on extracellular matrix. T cells that traffic to skin are distinguished by their expression of cutaneous lymphocyte antigen (CLA), a carbohydrate modification that binds to E-selectin [57].

The patterns of expression of chemokine receptors on effector/memory T cells are complex, and the factors controlling chemokine receptor expression on T cells are not well understood. Whereas some chemokine receptors play dedicated roles for trafficking to specific tissue compartments, others are differentially induced along pathways of T cell lineage differentiation (Th1, Th2, etc.), and others show no clear association with tissue sites or lineage commitments [58–64]. There are no skin-specific chemokines/chemokine receptors. Nonetheless, the chemokine receptors CCR4 and CCR10, and to a lesser extent CCR6, have been implicated specifically in migration of T cells to the skin. Greater than 90% of skin-infiltrating or resident skin T cells express one or more of these three receptors [65].

3. Chemokines and chemokine receptors in psoriasis

The expression of a number of chemokines, including CCL2/MCP-1, CCL5/RANTES, CCL17/TARC, CCL20/MIP-3 α , CCL22/MDC, CCL27/CTACK, CXCL1/GRO α , CXCL8/IL-8, CXCL9/MIG, CXCL10/IP-10, and CX3CL1/Fractalkine and the chemokine receptors CCR4, CCR6, CCR10, CXCR1, CXCR2, CXCR3, and CX3CR1 are increased in active psoriatic lesions as compared to non-lesional skin or normal donor skin [66–80]. Associations between polymorphisms in *CX3CR1* and the incidence of psoriasis provide additional support for the involvement of CX3CR1/CX3CL1 in the disease [81, 82]. Recent data related to various aspects of psoriasis pathogenesis have focused attention on CCR6.

The human *CCR6* gene is located on chromosome 6q27, outside the CC chemokine receptor cluster at 3p21, and, correspondingly, the CCR6 sequence is not closely related to other CC receptors [83]. CCR6 was initially identified on dendritic cells and T cells [84, 85], and was found to be expressed on B cells and subsets of effector/memory T cells from peripheral blood [86–94]. In addition to its expression on effector/memory T cells, CCR6 is found on a subset of CD4⁺ suppressor (Treg) cells, and may, therefore, be involved in Treg trafficking [95]. CCR6 can also be up-regulated on neutrophils after treatment with cytokines in vitro [96]. Unlike many chemokine receptors, CCR6 has only one known chemokine ligand, CCL20, and unlike many chemokines, CCL20 does not bind to or signal through any of the

other known chemokine receptors [84, 85, 88, 97]. The anti-bacterial peptides, β -defensins, have also been shown to elicit chemotaxis through CCR6 [98], although the activity of β -defensins on CCR6 has been questioned [99]. CCL20 can be induced in a variety of cell types by lipopolysaccharide (LPS) and by pro-inflammatory cytokines such as TNF- α and IL-17A and is highly expressed in epithelia overlying lymphoid organs such as tonsils and Peyer's patches [71, 85, 100–105].

Both CCR6 and CCL20 are expressed at significantly higher levels in lesional psoriatic skin than in non-lesional or normal donor skin, and CCR6 expression is higher on circulating PBMCs from psoriasis patients compared to normal donors [71]. β -defensin-2 is also highly expressed in lesional skin [106–109]. The majority of T cells infiltrating the skin in psoriasis express CCR6, and CLA⁺ T cells cultured from psoriatic lesions responded more vigorously to CCL20 than those from normal skin [65, 71]. However, more than 75% of resident T cells in normal skin also express CCR6, as compared with approximately 40% of the CD4⁺ memory cells in peripheral blood, suggesting that CCR6 and CCL20 may not only be involved in inflammatory migration to the skin, but also in migration in the steady state [110]. The resident epidermal dendritic cells of the skin, i.e. Langerhans cells, as well as the CD1c⁺ Langerhans cell precursors, are also strongly attracted to CCL20 [100].

In psoriatic lesions, CCL20 is expressed mainly in the suprabasal layer of the epidermis, suggesting that keratinocytes may be the primary source of the chemokine [71]. In fact, Langerhans cells and T cells are found in close proximity to CCL20⁺ keratinocytes in lesional skin [71]. However, cell types other than keratinocytes found in the skin are also capable of producing CCL20 once stimulated. After in vitro treatment with IL-1 β and TNF α , two cytokines highly expressed in lesional skin, keratinocytes, endothelial cells, melanocytes, dendritic cells, $\gamma\delta$ T cells, and dermal fibroblast were all able to express CCL20 [71, 111]. Moreover, CCL20 was primarily responsible for the arrest of a subset of T cells on TNF α -activated human dermal microvasculature endothelial cells in in vitro assays of adhesion under flow [112].

In addition to the circumstantial evidence reviewed above, recent data implicating IL-23 and Th17 cells in psoriasis coupled with connections made between CCR6 and Th17 cells as summarized here, have stimulated interest in CCR6 in psoriasis pathogenesis. In analyzing cells from peripheral blood, CCR6 was found on all T cells that, after activation ex vivo, were able to express IL-17A and/or IL-17F and/or IL-22 – although not all CCR6⁺ cells could express these cytokines [11, 61–64] and Satya P. Singh and J.M.F., unpublished observations.) The CCR6⁺ IL-22-producing cells in human blood include the “Th22” cells described as skin-homing due to their co-expressing CCR10 [17, 18]. These data established a relationship between CCR6 and Th17/Th22 cells analogous to the relationships between CXCR3 and Th1 cells and CCR4 and Th2 cells [58–60]. Consistent with the findings for CCR6 on Th17 cells, *CCR6* (and *CCL20*) were found to be genes induced by ROR γ t, a critical transcription factor for Th17 differentiation [113–115]. The association of Th17 effector cytokine expression and CCR6 expression is maintained in psoriatic skin. CCR6⁺ T cells from psoriatic lesions do not express Th2 cytokines and are as likely to express IFN γ or IL-10 as their CCR6-counterparts, but are the only cells that produce Th17 cytokines [11]. In addition, patients who suffer from psoriatic arthritis have a higher circulating number of IL-17-producing T cells, and these cells uniformly express CCR6⁺ [116]. It is important to note, however, that IL-17- and/or IL-22-producing T cells can also express other chemokine receptors in various combinations [17, 18, 61–63], including those found in lesional skin, such as CCR4, CCR10, and CXCR3.

4. CCR6 and the IL-23-induced model of psoriasis-like inflammation

Several animal models have been used to investigate the pathogenesis of psoriasis. These models vary in how well they represent the pathology of human psoriasis, and none wholly recapitulate the clinical and histological hallmarks of disease [117]. Chan and colleagues originally described a model of psoriatic inflammation in which recombinant murine IL-23 was injected intradermally every other day [33]. The resulting inflammation resembled human psoriasis in many respects [33–35]. Intradermal IL-23 induced acanthosis, hyper- and parakeratosis, neutrophilic microabscess formation, and dermal inflammatory cell infiltrates, and induced Th17 cytokines IL-17A, IL-17F and IL-22 [34, 35], as well as TNF- α , IL-19 and IL-24 [33–35]. Zheng and colleagues reported that following the intradermal injection of IL-23, ear swelling and histological changes were much reduced in IL-22-deficient (*Il22*^{-/-}) mice versus wildtype (WT) controls [34]. These data indicated a critical role for IL-22 in this model, and it was presumed that the IL-22 was being produced by Th17 cells [34]. IL-22 is known to affect the expression of genes in human keratinocytes that are involved in psoriasis, up-regulating genes for antimicrobial proteins and proteins important for motility, and down-regulating genes for differentiation of keratinocytes [118–121]. Given the growing evidence that cells and cytokines of the human IL-23/Th17 axis are essential inflammatory mediators in psoriasis, and the direct similarities in pathology in the IL-23 injection model and the human disease, we conclude that the IL-23 injection model likely mimics some of the relevant components of psoriasis immunopathogenesis.

We examined the role of CCR6 in the inflammation induced after injecting ears with IL-23, and found that, in contrast to WT mice, mice deficient in CCR6 (*Ccr6*^{-/-}) failed to develop significant psoriasis-like histological changes or ear swelling (Figure 1) [35]. IL-23 injection induced CCL20 expression in the ear skin, consistent with a role for CCR6 and CCL20 in this model, and CCL20 expression was the same in WT and *Ccr6*^{-/-} mice. At the endpoint of the study, Day 15, *Ccr6*^{-/-} mice failed to increase the numbers of CD4⁺ T cells and CD11c⁺ CD11b⁺ dendritic cells in the IL-23-injected ears, unlike their WT counterparts. As described above, both of these cell types can express CCR6. No differences were observed in the ears of the WT versus *Ccr6*^{-/-} mice in other populations of inflammatory cells examined including NK cells, $\gamma\delta$ T cells, macrophages or neutrophils. Significantly less IL-22 expression was induced in the IL-23-injected ears of *Ccr6*^{-/-} versus WT mice, whereas intradermal injection of IL-22 induced equal swelling and histological changes in WT and *Ccr6*^{-/-} mice. Given that the IL-23-induced inflammation had been shown to be IL-22-dependent, these data were consistent with diminished levels of IL-22 in the ears of the *Ccr6*^{-/-} mice being an important factor in the animals' resistance to inflammation.

Our initial hypothesis was that in the absence of Ccr6, IL-22-producing Th17 cells would fail to traffic to the IL-23-injected skin. However, we found equal expression of *Il17a* and *Il17f* and equal numbers of T cells capable of producing IL-22 or IL-17A in the IL-23-injected ears of WT and *Ccr6*^{-/-} mice at Day 15. These data suggested that the primary abnormality in the *Ccr6*^{-/-} mice was in a T-cell independent component that was required for T cell activation. The importance of a T-cell independent contribution to the inflammation was supported by our finding that IL-23 injection of ears of *Rag-1*^{-/-} mice, which lack lymphocytes, produced early changes in the skin identical to what we saw in the WT mice – although inflammation in the WT mice was sustained, whereas inflammation in the *Rag-1*^{-/-} mice peaked at five days and declined thereafter. Dendritic cells, NK cells, and neutrophils have been reported to express CCR6 under various conditions [84, 122, 123], and each of these cell types may contribute to psoriasis. Of these, only CD11c⁺CD11b⁺ dendritic cells were decreased in IL-23-injected ears of the *Ccr6*^{-/-} mice, which suggests that the dendritic cells may be playing a significant role in this model. Although CCR6 has been reported to be a critical trafficking receptor on dendritic cell precursors and/or

immature dendritic cells in mouse and human skin [102, 124], immature dendritic cells express additional chemokine receptors, such as CCR2 and CXCR4 [102, 125], that might serve redundant functions.

Together, the data suggested both T-cell independent and T-cell dependent components to the IL-23-induced pathology in WT mice. The absence of any appreciable inflammation in the *Ccr6*^{-/-} mice despite WT numbers of Th17/Th22 cells in the skin suggested a broad role for CCR6 in IL-23-induced inflammation, one not limited to the regulation of Th17 cell trafficking. It is important to point out, however, some of the deficiencies of this study as it relates to the question of CCR6 as a drug target in psoriasis. We were not, of course, studying psoriasis, but only a mouse model that may mimic a limited aspect of the disease, and we were using *Ccr6*^{-/-} mice, so that we were analyzing the induction of disease, and not therapy once disease was established.

5. Conclusions

We believe that the data reviewed above, when taken together and despite its limitations, provide a rationale for investigating inhibitors of CCR6 and/or CCL20 as drugs for treating psoriasis. To summarize the salient points: CCL20 is highly expressed in lesional skin and CCR6 is found on the lesion-infiltrating CD4⁺ T cells. The IL-23/Th17/IL-22 axis has been recently implicated in the pathophysiology of psoriasis, in part through genome-wide studies linking psoriasis with polymorphisms in genes for components of IL-23 and its receptor. CCR6 and CCL20 are expressed on and made by, respectively, Th17 cells, and *Ccr6* and *Ccl20* are strongly induced by ROR γ t, a critical transcription factor for Th17 differentiation. *Ccr6*^{-/-} mice are resistant to IL-22-dependent, psoriasis-like pathology induced in mouse skin by the direct injection of IL-23.

6. Expert opinion

Therapeutic targeting of the chemokine system is appealing, in part because so many small molecule antagonists (and agonists) of GPCRs have been developed and used clinically. Although there are as yet no clinical data on CCR6 antagonists, a significant number of small molecule antagonists and/or neutralizing antibodies against chemokine receptors such as CXCR2, CXCR3, CXCR4, CCR2, CCR4 and CCR5 have been and continue to be evaluated in clinical studies [126, 127]. Despite the interest in using chemokine receptor antagonists to treat autoimmune/inflammatory disease, the first two such antagonists that have obtained FDA approval were not, in fact, approved to treat inflammatory disorders. Maraviroc (Selzentry™), a CCR5 antagonist, blocks the ability of CCR5-using strains of HIV-1 to enter cells and is approved for use as an anti-viral in HIV-1-infected individuals [128, 129]. Plerixafor (Mozobil™) is a CXCR4 antagonist that is indicated for use with G-CSF for mobilizing hematopoietic stem cells from bone marrow for autologous transplantation in patients with non-Hodgkins lymphoma and multiple myeloma [130, 131].

Thus far, there have been no successful applications of chemokine receptor antagonists in the treatment of inflammatory disease [126, 127]. At least one small molecule, T487, developed as a CXCR3 inhibitor by Tularik and Chemocentryx, was evaluated in a Phase II trial for psoriasis [132]. Whereas the rationale for the study seemed sound, given that all Th1 cells express CXCR3 and Th1 cells were thought to be critical effector cells in psoriatic lesions, we can presume that the trial was not encouraging, since there is no indication that clinical development of T487 is being pursued.

One explanation offered for the generally discouraging results of studies inhibiting individual chemokine receptors has been functional redundancy among many chemokines and receptors. This surely might be a limitation to anti-CCR6 therapy in psoriasis, given that

no leukocyte is likely to express CCR6 in the absence of additional chemokine receptors. Considerations of redundancy have led to the proposal that drugs should be developed targeting combinations of receptors [133]. It is also possible, however, that some agents tested to date lacked efficacy due to sub-optimal pharmacokinetics [134]. In our view, clinical evaluation of chemokine receptor antagonists is in its early stages, and we believe that it is premature to conclude that this class of drugs will inevitably fail in the treatment of inflammatory disease. Much more needs to be learned about the roles of chemokines and their receptors in pathology. Our data on Ccr6 in the IL-23 injection model is a case in point, since although the receptor was necessary for IL-23-induced inflammation, our initial hypothesis that Ccr6 would be important for the trafficking of Th17 cells into the skin was incorrect, and our data pointed instead to previously unappreciated roles for non-T cells (and Ccr6) in this model. In addition, a recent report of clinical efficacy in a Phase II/III trial of a CCR9 antagonist in moderate-to-severe Crohn's disease provides encouragement that with the proper matching of drug and disease, chemokine receptor antagonists may find important therapeutic application [135].

Although small molecules would seem to offer real benefits in regard to drug production and their ability to be taken orally, neutralizing antibodies against chemokine receptors or chemokines are also options as inhibitors. As an example, an anti-CCR2 antibody has been evaluated for inflammatory diseases in clinical trials [136]. In the mouse models of experimental autoimmune encephalomyelitis (EAE) and collagen induced arthritis, anti-mouse Ccr6 antibodies have been effective in preventing or treating disease [64, 137], and anti-human CCR6 antibodies could presumably be developed for clinical use.

In a fundamentally different strategy, anti-CCR6 antibodies could be used to deplete CCR6-expressing cells. The effects of such depletion would likely be more profound and long-lasting than simply inhibiting the activity of the receptor. There are as yet no data in animal models of disease using this approach. A similar approach is currently in phase I clinical trials for the treatment of cutaneous T cell lymphomas using CCR4 as a target for a defucosylated, humanized monoclonal antibody, which induces rapid depletion of CCR4-expressing lymphocytes by antibody-dependent cellular cytotoxicity [138, 139]. One method that has been tried for depleting cells based on the expression of chemokine receptors, although not CCR6, is the fusion of chemokines and toxins. Fusions of diphtheria toxin and CXCL10 or CCL5 have been tested and shown to be effective in a mouse EAE model [140, 141]. Similarly, a fusion between the CCR4 ligand CCL17 and a truncated fragment of *Pseudomonas* exotoxin was able to eradicate an experimental CCR4-expressing cutaneous lymphoma [142]. Presumably, any individual toxin fusion would be limited in the number of administrations due to the induction of anti-toxin antibodies.

Anti-chemokine antibodies are another approach. A neutralizing antibody against CXCL8, a neutrophil chemoattractant that is expressed in psoriatic lesions and signals through CXCR1 and CXCR2, has been tested in phase II clinical trials for treatment of psoriasis without success [143]. The presence in psoriatic skin of other neutrophil-attracting CXCR2 ligands is one obvious possible explanation for the failure of this agent [74]. Because CCL20 is the only chemokine ligand for CCR6, anti-CCL20 antibodies might have effects identical to blocking CCR6, and therefore be candidates as therapeutics. The possible activity of β -defensins as CCR6 ligands in the skin is, however, a potentially complicating factor.

An important issue is how CCR6/CCL20-targeted therapy might compare with the significant number of treatments currently available for psoriasis. These therapies include psoralen ultraviolet A, narrowband and broadband ultraviolet B, immunosuppressive drugs such as methotrexate, cyclosporin A, and mycophenolate mofetil, and the biologics alefacept (anti-CD2), efalizumab (anti-CD11a), etanercept (binds TNF- α and β), infliximab (anti-

TNF- α), adalimumab (anti-TNF- α), and ustekinumab (anti-p40, the shared subunit of IL-12 and IL-23). Limitations of these therapies include some non-responding patients, parenteral administration (biologics), inadequate data on long-term efficacy, and concerns about potentially significant side effects, such as infections, malignancies, and paradoxical inflammatory skin rashes that are both distinct from and identical to psoriasis [144, 145]. However, at least 50% of patients treated with the biologics infliximab, ustekinumab, alefacept, etanercept or adalimumab achieve a sustained 75% reduction in the psoriasis area severity index. The effects of many of these biologics may be due to blocking Th17 cell function [146, 147].

One advantage of the TNF- α inhibitors is their effectiveness in treating psoriatic arthritis [6], a destructive and potentially debilitating component of the disease. Ustekinumab has shown efficacy in the therapy of psoriatic arthritis, suggesting a possible role for the IL-23/Th17 axis [148]. In regard to CCR6, CCL20 is expressed at high levels in the synovial fluid of psoriatic joints [149]. It is of additional interest that CCR6 is implicated in rheumatoid arthritis, which shares features with the psoriatic disease. Blocking Ccr6 was effective in suppressing disease in a mouse model of rheumatoid arthritis [64], and a variant of the *CCR6* gene has now been associated with susceptibility to rheumatoid arthritis in humans [150]. Nonetheless, much more needs to be learned in order to establish a role for CCR6 in autoimmune arthritis.

CCR6/CCL20-targeted therapy using a small molecule CCR6 antagonist or biologic inhibitor would represent a new class of drug in treating psoriasis. The biggest hurdle for chemokine receptor antagonists as a class has been with regard to efficacy rather than safety. Nonetheless, off-target effects are always a potential concern, and there is the possibility of unwanted side effects resulting from interfering with CCR6-dependent immune function. In regard to host-defense, mouse models have suggested both beneficial [151–153] as well as deleterious [154] roles for Ccr6. Based on these models, if there were a negative consequence of CCR6 blockade in host defense in the skin and other sites, it might be from impaired presentation of pathogen-derived antigens by phagocytes and/or dendritic cells [152, 153] resulting in sub-optimal T cell activation. In regard to anti-tumor immunity, it has been suggested that Ccr6 is important for the recruitment of dendritic cells leading to anti-tumor cytotoxicity in a mouse model [155]. On the contrary, in analyzing human breast cancers, it has been suggested that CCR6 is important for recruitment of tumor-infiltrating Tregs, whose numbers correlated with poor prognosis [156]. It is currently impossible to predict the unwanted side effects, if any, that might result from CCR6/CCL20 blockade.

The above considerations notwithstanding, inhibiting CCR6 would very likely have a more limited immunosuppressive effect than the current systemic therapies targeting more pleiotropic factors. Therefore, a CCR6 antagonist, if efficacious either alone or in combination with other agents, might diminish requirements for more potent drugs. Regimens with less profound immunosuppression/immunomodulation would presumably expose patients to fewer short- and long-term risks. With respect to convenience, it is likely that a CCR6 antagonist could be developed for oral administration, unlike the biologics currently used to treat psoriasis. Although we are not aware of clinical trials evaluating inhibitors of CCR6 and/or CCL20 in the treatment of psoriasis or other disorders, there are reports of such inhibitors under preclinical development [157]. It is certainly premature to assert that targeting CCR6 will be a safe and effective therapeutic strategy. Nonetheless, the accumulating data suggest that additional investigations toward this end are warranted, both in animal models and in humans.

Article highlights

- Psoriasis is the most common autoimmune disease of the skin, affecting 0.5–5% of individuals worldwide, depending on the ethnic group.
- Genome-wide analyses and recent data from clinical trials suggest an important role for the IL-23/Th17/IL-22 axis in psoriasis.
- The expression of several chemokines and chemokine receptors, including CCL20/MIP-3 α and CCR6, respectively, are highly expressed in skin affected by psoriasis.
- CCR6 is expressed on virtually all human IL-17A/F- and IL-22-producing CD4⁺ T cells, which also produce CCL20, implicating CCR6 and CCL20 in IL-23/Th17/IL-22-mediated inflammation.
- Mice deficient in CCR6 fail to develop IL-23-induced, IL-22-dependent psoriasis-like inflammation.
- The accumulating data suggest that additional investigations are warranted into targeting CCR6 as a therapeutic strategy, both in animal models and human disease.

This box summarizes key points contained in the article.

Acknowledgments

Declaration of interest This work was supported by the Intramural Research Program of the NIH, NIAID and NCI, and an NIH/DFG Research Career Transition Award of the National Institutes of Health and the German Research Foundation to A.S.L.

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Figure 1. CCR6KO (*Ccr6*^{-/-}) mice are resistant to IL-23-induced acanthosis and dermal inflammation

Ears of wildtype (WT) control and CCR6KO mice were injected intradermally every other day for sixteen days with 20 μ l PBS, either alone or containing 500 ng IL-23. **(A)** Ear thickness was measured on days between injections. Data points are means $\pm$ SEM from five experiments containing a total of at least thirty mice per group, * $P < 0.01$ vs. all other groups. **(B)** H&E-stained sections of PBS- or IL-23-injected ears from WT and CCR6KO mice at Day 15. (k), hyper-parakeratosis with intracorneal neutrophilic microabscess, (a), acanthosis, (b), increased proliferative activity of basal layer epidermal keratinocytes, (d), dermal lymphocytic infiltrate, and (v), telangiectasia of dermal blood vessels. Original magnification, 400 $\times$. Sections are representative of two experiments. Data are reproduced from: Hedrick MN, Lonsdorf AS, Shirakawa AK, Richard Lee CC, Liao F, Singh SP, et al. CCR6 is required for IL-23-induced psoriasis-like inflammation in mice. *J Clin Invest* 2009 Aug;119(8):2317-29.