

Chemokine receptors in inflammation: an overview

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Abstract

Chemokine receptors play a key role in directing the migration of inflammatory cells into various injured or infected organs. However, migration of inflammatory cells into tissues can in itself be a cause and amplifier of tissue damage and disease, particularly in chronic autoimmune or allergic disorders. On this basis, much effort is currently devoted at the identification of molecular signals regulating the recruitment of inflammatory cells into tissues and at developing novel strategies to inhibit discrete pathways in this process. Great progress has recently been made in identification of a number of chemokine receptors involved in the process of leukocyte migration. The challenge is now to elucidate the specific contribution and involvement of the different receptors in distinct inflammatory processes and diseases and to prove that interference with any of these pathways may lead to development of novel therapeutics.

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1. Introduction

The human chemokine system comprises about 50 distinct chemokines and 20 G-protein-coupled chemokine receptors (Zlotnik and Yoshie, 2000). Chemokines are produced by a variety of cell types either constitutively or in response to inflammatory stimuli.

The biological activities of chemokines range from the control of leukocyte trafficking in basal and

inflammatory conditions to regulation of hematopoiesis, angiogenesis, tissue architecture and organogenesis (Rossi and Zlotnik, 2000; Sallusto et al., 2000). The basis for such diversified activities rests, on one hand, upon the ubiquitous nature of chemokine production and chemokine receptor expression. Indeed, virtually every cell type can produce chemokines and expresses a unique combination of chemokine receptors. On the other hand, chemokine receptors make use of a flexible and complex network of intracellular signaling machineries that can regulate a variety of cellular functions ranging from cell migration, growth, differentiation and death (Thelen, 2001).

As the size of chemokine and chemokine receptor families rapidly reaches completeness much is still to be uncovered in terms of functional architecture of the chemokine system. The disparity between the large number of chemokines and that smaller of receptors is balanced by the promiscuity in ligand–receptor inter-

Abbreviations: EAE, experimental autoimmune allergic encephalomyelitis; MOG, myelin-derived oligodendrocyte glycoprotein; IBD, inflammatory bowel disease; MS, multiple sclerosis; COPD, chronic obstructive pulmonary disease; BAL, bronchoalveolar lavage fluid; Th, T helper cell.

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actions, with multiple chemokines binding to the same receptor and several chemokines binding to more than one receptor (Rossi and Zlotnik, 2000).

Evidences for the role that many chemokines and receptors play in the pathogenesis of different acute or chronic inflammatory diseases are rapidly increasing (Gerard and Rollins, 2001). Optimistically, every chemokine receptor may be an interesting pharmacological target for therapeutic intervention. The challenge for the future is to identify the unique

pathogenic process and specific disease in which any given chemokine receptor may potentially be implicated. In the meanwhile, current data already suggest a critical role for chemokine receptors in the pathogenesis of a number of relevant acute and chronic inflammatory diseases (Proudfoot, 2002) (Table 1). Here, we will briefly summarize the most recent evidence for the involvement of chemokine receptors in some of the most relevant chronic inflammatory disorders.

Table 1
Chemokine receptors, expression pattern, ligands and involvement in disease

Receptors	Ligands	Receptor-expressing cells	Diseases
CCR1	CCL3, CCL5, CCL7, CCL8, CCL13, CCL14, CCL15, CCL23	monocyte, dendritic cell (immature), T cell, neutrophil, eosinophil, mesangial cell, platelet	MS, RA, transplant, asthma, nephritis
CCR2	CCL2, CCL7, CCL8, CCL13	monocyte, dendritic cell (immature), T cell, basophil, natural killer cell, fibroblast, endothelial cell	MS, RA, transplant, asthma, atherosclerosis
CCR3	CCL5, CCL7, CCL8, CCL11, CCL13, CCL14, CCL15, CCL24, CCL26	eosinophil, basophil, mast cell, T cell (Th2), platelets, airway epithelial cell	asthma, atopic dermatitis
CCR4	CCL17, CCL22	dendritic cell, basophil, T cell (Th2, Treg, skin-homing), platelets	asthma, atopic dermatitis
CCR5	CCL3, CCL4, CCL5, CCL8, CCL11, CCL13, CCL14	T cell (Th1), dendritic cell, monocyte, natural killer cell	MS, RA, transplant, nephritis, IBD, AIDS
CCR6	CCL20	dendritic cell (immature), T cell, B cell	psoriasis
CCR7	CCL19, CCL21	dendritic cell (mature), T cell, B cell, natural killer cell	transplant
CCR8	CCL1, CCL16	T cell (Th2, Treg), monocyte, natural killer cell, B cell, endothelial cell	Asthma
CCR9	CCL25	T cell (gut-homing)	IBD
CCR10	CCL27, CCL28	T cell (skin-homing), melanocyte, Langerhans cell, dermal endothelium, dermal fibroblast	Psoriasis, Atopic dermatitis
CCR11	CCL19, CCL21, CCL25	astrocyte	
CXCR1	CXCL5, CXCL6, CXCL8	neutrophil, monocyte, endothelial cell, astrocyte	sepsis, atherosclerosis, COPD, psoriasis
CXCR2	CXCL1, CXCL2, CXCL3, CXCL5, CXCL7, CXCL8	neutrophil, monocyte, eosinophil, endothelial cell	sepsis, atherosclerosis, COPD, psoriasis
CXCR3	CXCL9, CXCL10, CXCL11	T cell (Th1), B cell, mesangial cell, smooth muscle cell, microglia	MS, RA, transplant, sarcoidosis, COPD
CXCR4	CXCL12	T cell, dendritic cell, monocyte, B cell, neutrophil, platelet, astrocyte	AIDS, cancer
CXCR5	CXCL13	B cell, T cell (T _{FH}), astrocyte	cancer
CXCR6	CXCL16	T cell (Th1)	RA
XCR1	XCL1, XCL2	T cell	
CX ₃ CR1	CX ₃ CL1	T cell (Th1), natural killer cell, astrocyte	RA, atherosclerosis

Th, T helper cell; T_{FH}, T follicular helper cell; Treg, regulatory T cell; MS, multiple sclerosis; RA, rheumatoid arthritis; COPD, chronic obstructive pulmonary disease.

2. Chemokine receptors in asthma and other pulmonary diseases

Asthma is a chronic inflammatory disease of the small airways that is characterized by mononuclear, eosinophil and mast cell infiltration of the submucosa along with mucous gland hyperplasia and subepithelial fibrosis (Wills-Karp, 1999). The inflammatory response in asthma is tightly associated with airway hyperreactivity. CD4⁺ Th2 cells are believed to play a crucial role in orchestrating airway inflammation in asthma by regulating the production of IgE and the growth and differentiation of mast cells, basophils and eosinophils.

Data obtained from animal models of allergic airway inflammation and asthmatic patients have indicated a key role for chemokines in regulating lung inflammation (reviewed in (D'Ambrosio et al., 2001)). Chemokines such as CCL3, CCL5 and CCL12 are up-regulated early on after allergen challenge but cannot easily be correlated with the recruitment of defined leukocyte subsets (Gutierrez-Ramos et al., 2000). In contrast, the kinetics of production of CCL2, CCL11, CCL17 and CCL22 correlates with the recruitment of specific leukocyte subsets expressing the receptors for these chemokines (Jia et al., 1996; Lamkhioued et al., 1997; Rothenberg et al., 1997; Gonzalo et al., 1998, 1999; Lloyd et al., 2000). Studies reporting neutralization of CCL11, CCL12, CCL5, CCL2, CCL17 and CCL22 support the contribution of each of these molecules in allergic airway responsiveness and inflammatory cell migration (Lukacs, 2001).

In asthmatic patients there is evidence of an increased expression of CCL11 in the bronchial mucosa and a correlation between the expression in the bronchial mucosa of CCL11 and airway hyperresponsiveness (Ying et al., 1997). CCR3, which binds CCL11, CCL24 and CCL26, is expressed on eosinophils, basophils, mast cells, Th2 cells and even on bronchial epithelial cells (Garcia-Zepeda et al., 1996; Gonzalo et al., 1996; Sallusto et al., 1997; Romagnani et al., 1999; Stellato et al., 2001). However, the induction of cell infiltration and airway hyperreactivity in CCR3-deficient mice appears to vary depending on the route of immunization (Humbles et al., 2002; Ma et al., 2002), and CCR3 was not found on T cells infiltrating the bronchial mucosa of asthmatic patients (Panina-Bordignon et al., 2001).

Neutralization of CCL2 showed a beneficial effect in reducing pulmonary cell infiltrate and airway hyper-reactivity (Campbell et al., 1999a). However, some studies on CCR2-deficient mice, a receptor of CCL2, showed exacerbation of the disease suggesting a complex involvement of CCL2 in asthma pathogenesis (MacLean et al., 2000; Kim et al., 2001b), perhaps acting through different receptors.

The expression of CCR4 on T cells infiltrating the lung, and of its ligands CCL17 and CCL22, by airway epithelial cells after allergen challenge in animal models and asthmatic patients strongly suggests the involvement of CCR4 in allergic lung inflammation (Gonzalo et al., 1999; Lloyd et al., 2000; Panina-Bordignon et al., 2001). However, analysis of CCR4-deficient mice revealed a surprisingly unchanged cellular recruitment and induction of airway hyperreactivity (Chvatchko et al., 2000).

CCR8 is a receptor highly expressed on activated Th2 cells and found on lung-infiltrating T cells of asthmatic patients (D'Ambrosio et al., 1998; Panina-Bordignon et al., 2001). Interestingly, disruption of the murine CCR8 gene results in a marked reduction of eosinophil infiltration and allergen-induced airway hyperreactivity (Chensue et al., 2001).

Overall, these results suggest that multiple chemokine receptors may have redundant functions in the pathogenesis of allergic airway inflammation, while highlighting a unique critical role for CCR8.

Chronic obstructive pulmonary disease (COPD) is characterized by progressive development of airflow limitation associated with a chronic inflammatory process with increased recruitment of neutrophils, macrophages and IFN- γ -producing CD8⁺ T cells in the lungs (O'Shaughnessy et al., 1997). Pulmonary sarcoidosis is characterized by pulmonary infiltration of IFN- γ -producing T lymphocytes and macrophages, and the formation of non-caseating granulomas in the lung. A Th1-type chronic inflammatory response appears to be a common pathogenetic feature of these severe lung diseases. In COPD patients, levels of CXCL8 and CXCL10 are increased and correlate with infiltration of neutrophils and CD8⁺ T cells that produce IFN- γ . Analysis of chemokine receptor expression in COPD indicates that lung-infiltrating T cells express CXCR3, which is the receptor for CXCL10 (Keatings et al., 1996; Sietta et al., 2002). Similarly to COPD, the majority of T cells infiltrating

the lungs of sarcoidosis patients produce IFN- γ and express the chemokine receptor CXCR3 (Agostini et al., 1998). Moreover, CXCL10 is found elevated both in the bronchoalveolar lavage (BAL) fluid and in the lung of patients with active sarcoidosis (Agostini et al., 2000). These data indicate a potential role for CXCR3 in the recruitment of pathogenic Th1/Tc1 cells into chronically inflamed lungs. It is notable that CXCL10 neutralization appears to inhibit also allergic airway inflammation (Medoff et al., 2002), suggesting a broad role for CXCR3 not limited to Th1-dominated lung inflammatory responses.

3. Chemokine receptors in psoriasis and atopic dermatitis

Psoriasis and atopic dermatitis are most common chronic relapsing inflammatory diseases of the skin. Psoriasis is characterized by neutrophil and T cell infiltration of the skin associated with epidermal thickening and hypertrophic papillary dermis (Nickoloff et al., 2000). The hallmarks of atopic dermatitis are the presence of edema and infiltration of the skin by T cells, dendritic cells and eosinophils (Leung and Soter, 2001).

Expression of numerous inflammatory chemokines has been reported in chronically inflamed skin of psoriasis and atopic dermatitis patients. However, great attention has been placed on chemokine receptors expressed on a subset of circulating memory T cells that exhibit selective homing to the skin and can be identified by virtue of expression of cutaneous lymphocyte-associated antigen (CLA) (Picker et al., 1990a,b). CLA⁺ T cells preferentially express CCR4 and CCR10 (Campbell et al., 1999b; Morales et al., 1999; Homey et al., 2000b). The CCR4 ligand CCL17 and the CCR10 ligand CCL27 are displayed by endothelial cells of dermal venules of patients with psoriasis or atopic dermatitis (Campbell et al., 1999b; Homey et al., 2002). T cells infiltrating the inflamed skin express CCR4 and CCR10, and keratinocytes, dermal fibroblasts and dendritic cells from inflamed skin abundantly express ligands of these receptors (Vestergaard et al., 1999, 2000; Kakinuma et al., 2001; Vulcano et al., 2001; Homey et al., 2002).

Although animal models of skin inflammation fail to closely resemble the complex clinical features of

human diseases, they have been useful to study the role of chemokine receptors in T cell recruitment in inflamed skin. In a mouse model of cutaneous inflammation, neutralization of CCL27 was shown to reduce T cell recruitment to the skin (Homey et al., 2002). Surprisingly, analysis of CCR4-deficient mice failed to show defective recruitment of T cells in inflamed skin (Chvatchko et al., 2000; Reiss et al., 2001). However, when CCL27-neutralizing antibodies were employed in CCR4-deficient mice the contribution of CCR4 to the T cell recruitment became evident (Reiss et al., 2001). These findings suggest that CCR4 and CCR10 may play a partially redundant role in the recruitment of T cells to the inflamed skin.

Expression of CXCR3 ligands CXCL9, CXCL10 and CXCL11 has been documented in psoriatic lesions and CXCR3 expression was found on skin infiltrating T cells (Flier et al., 2001). Furthermore, expression of CCL20 by keratinocytes and CCR6⁺ T cells have been reported in psoriatic human skin (Homey et al., 2000a). Finally, enhanced expression of CCR3 and its ligand CCL11 was found in the skin lesions from atopic dermatitis patients (Gerber et al., 1997; Yawalkar et al., 1999). These findings indicate that multiple receptors may participate in regulating T cell recruitment to the inflamed skin.

4. Chemokine receptors in rheumatoid arthritis

Rheumatoid arthritis is a chronic disease characterized by a mixed Th1-type inflammatory cell infiltrate (Th1 cells, neutrophils, monocytes) of synovial joints associated with cartilage destruction and bone remodeling (Davidson and Diamond, 2001; Feldmann, 2001).

Synovial fluid from inflamed joints contains several chemokines, including CCL2, CCL3, CCL5, CXCL8 and CXCL10 (Suzuki et al., 1999; Godessart and Kunkel, 2001; Patel et al., 2001). These chemokines are produced by resident synovial cells as well as by infiltrating leukocytes. CCR5 and CXCR3 have been shown on the surface of T cells infiltrating the synovial tissue (Qin et al., 1998; Suzuki et al., 1999; Ruth et al., 2001). CXCR1 on neutrophils, CCR1 and CCR2 on monocytes and CXCR6 on T cells have also been involved in the pathogenesis of the disease (Konig et al., 2000; Hayashida et al., 2001; Kim et al., 2001a).

In mouse models of arthritis, neutralizing antibodies to CCL2 reduced the severity of disease (Gong et al., 1997; Ogata et al., 1997), indicating a potential role for CCR2 in monocyte recruitment and disease development. An antagonist of CCR1 and CCR5, met-RANTES was also effective in reducing inflammation in experimental mouse models of arthritis (Plater-Zyberk et al., 1997; Bruhl et al., 2001). Notably, some studies have reported a reduced incidence and severity of disease in individuals carrying the $\Delta 32$ -CCR5 allele, which encodes for a mutated non-functional CCR5 (Garred et al., 1998; Zapico et al., 2000). Involvement of other chemokine receptors awaits validation in relevant knockout models or through protocols employing chemokine receptor antagonists.

5. Chemokine receptors in multiple sclerosis (MS)

Multiple sclerosis is a chronic relapsing neuro-inflammatory disease in which a perivascular infiltrate of T cells and macrophages appears in the central nervous system causing demyelination and neuronal damage (Carroll, 2001). The pathogenesis of this disease is obscure and although it is generally believed that a Th1-type response directed to a tissue-specific antigen is the cause of disease, it is still puzzling that the Th1-promoting cytokine IFN- β is beneficial in reducing the frequency of relapses (Siniaglia et al., 1999; Hohlfeld and Wekerle, 2001).

A large body of clinical observations indicate that many chemokines may influence the course of MS (Kivisakk et al., 2001; Trebst and Ransohoff, 2001). CCL2, CCL3, CCL7, CCL8, CXCL9 and CXCL10 have been found in active lesions in the CNS and elevated levels of CCL3 are found in the cerebrospinal fluid of patients with relapses (Miyagishi et al., 1995; McManus et al., 1998; Sorensen and Sellebjerg, 2001). Infiltrating macrophages express CCR2 and CCR5, while T cells and reactive astrocytes in active lesions express CXCR3 and CCR5 (Balashov et al., 1999; Sorensen et al., 1999; Simpson et al., 2000). Once again, several receptors may be implicated in the recruitment of inflammatory cells into the brain (Sorensen and Sellebjerg, 2001; Sorensen et al., 2001).

The best animal model for MS is experimental autoimmune encephalomyelitis (EAE). This disease

can be induced in mice by immunization using myelin-derived antigens such as oligodendrocyte glycoprotein (MOG). Many of the same chemokines found in human brains affected by MS have also been documented in EAE. Increased expression of CCL2, CCL3, CCL4, CCL5 and CXCL10 has been found to correlate with the severity of disease (Godiska et al., 1995; Karpus et al., 1995). Chemokine receptors CCR1, CCR2, CCR5 and CXCR3, which are found expressed on T cells and macrophages infiltrating the lesions and brain resident cells such as astrocytes, have received most of the attention (Fife et al., 2000, 2001a,b; Izikson et al., 2000; Rottman et al., 2000).

Studies with neutralizing antibodies to CCL2, CCL3 and particularly CXCL10 either inhibited the onset or reduced severity of EAE, documenting a role for each of these chemokines in disease development (Karpus and Kennedy, 1997; Liu et al., 2001). Knock-out mice for certain chemokine receptors have been utilized to identify their relevance in EAE pathogenesis. CCR1- and CCR2-deficient mice exhibited a reduction in disease severity and incidence (Fife et al., 2000; Izikson et al., 2000; Rottman et al., 2000), while disruption of the CCR5 gene did not affect the course of disease (Tran et al., 2000). Consistent with a critical role for CCR2, CCL2-deficient mice or neutralization of CCL2 showed a marked protective effect on disease severity (Karpus and Kennedy, 1997; Kennedy et al., 1997; Huang et al., 2001). Interestingly, analysis of CCL3-deficient mice showed no effect on incidence and severity of EAE, while antibody-mediated neutralization of CCL3 inhibited EAE (Karpus et al., 1995; Karpus and Kennedy, 1997; Tran et al., 2000), illustrating the different outcomes of inhibiting the action of a chemokine throughout development versus acute blocking in disease. Overall, these findings suggest that multiple chemokine receptors may be useful therapeutic targets in MS.

6. Chemokine receptors in inflammatory bowel disease (IBD)

Crohn's disease and ulcerative colitis are chronic inflammatory conditions of the gastrointestinal tract characterized by a mixed inflammatory cell infiltrate of the gut mucosa (Braegger and MacDonald, 1994).

The pathogenesis of inflammatory bowel diseases has been linked to an inappropriate immune response to the bacterial flora of the gut. Recent findings suggest that Crohn's disease is associated with a Th1 response, while eosinophils and Th2 cells appear to be involved in ulcerative colitis (Farrell and Peppercorn, 2002; Shanahan, 2002). Several chemokines and chemokine receptors are potentially implicated (Ajuebor and Swain, 2002).

Expressions of CXCL8, CXCL5, CCL2, CCL11, CXCL10 and CX₃CL1 have been documented in human disease and animal models of gastrointestinal inflammation (Mazzucchelli et al., 1994; Gerber et al., 1997; MacDermott et al., 1998; Ugucioni et al., 1999; Muehlhoefer et al., 2000; Williams et al., 2000; Hogan et al., 2001; Ajuebor and Swain, 2002). CCL25 and its specific receptor CCR9, which is preferentially expressed on gut-homing (integrin $\alpha_4\beta_7^+$) intestinal memory T cells (Zabel et al., 1999; Agace et al., 2000; Kunkel et al., 2000), are found up-regulated in small bowel but not colonic Crohn's disease (Papadakis et al., 2001), suggesting that homing of T cells to distinct gastrointestinal portions is differentially regulated in both inflammatory and basal conditions. Consistent with the involvement of Th1 cells in the pathogenesis of Crohn's disease, expression of CXCR3 has been reported on T cells infiltrating the inflamed gastrointestinal submucosa of patients (Yuan et al., 2001). By contrast, in patients with ulcerative colitis associated with eosinophil infiltration, an increased number of CCR3⁺CD4⁺ Th2 cells was observed (Gerber et al., 1997).

Analysis of colitis induction in mice deficient in CCR2 or CCR5 showed significant protection from disease (Andres et al., 2000). Furthermore, in a rat model of chronic colitis, the CCR1 and CCR5 antagonist met-RANTES reduced cellular infiltration and inflammation (Ajuebor et al., 2001). However, individuals carrying $\Delta 32$ -CCR5 mutation are equally susceptible to colitis (Martin et al., 2001), indicating that CCR5 is not necessary for development of disease.

7. Conclusions

Treatment of chronic inflammatory diseases is based on the use of broadly acting anti-inflammatory

agents such as corticosteroids and immunosuppressants. The strategy of blocking leukocyte recruitment to the site of inflammation in organ-specific chronic inflammatory diseases is appealing due to the potential for a more specific therapeutic intervention. Chemokine receptors are holding a great promise for the development of a novel class of more specific and powerful anti-inflammatory agents (Baggiolini and Moser, 1997; Proudfoot, 2002). One aspect of chemokine receptor biology that makes this class of receptors particularly attractive is their potential specificity of action. Although extensive redundancy in ligand–receptor binding is observed *in vitro*, different ligands may act in a topographically, temporally distinct and hierarchical fashion *in vivo*. Thus, antagonism of a given chemokine receptor could have a specific action and avoid deleterious side effects.

Another attracting feature of chemokine receptors is the fact that they belong to the GPCR superfamily, which have brought the development of about 40% of current therapeutics, thanks to their amenability to development of small molecular weight orally active compounds. Despite these upsides, some considerations still need to be addressed and potential limitations to this approach should be kept in mind. First, the benefits of controlling inflammation by limiting mobilization of inflammatory cells must be carefully weighed against the costs of interrupting specific immune system's functions. Second, as numerous chemokine receptors are expressed on any given cell type, the recruitment of inflammatory cells may still proceed in the absence of a single receptor and it may be necessary to inhibit multiple receptors to achieve therapeutic effects. Given these considerations, further studies with chemokine receptor-deficient mice, neutralizing antibodies or modified chemokine antagonists and small molecular weight antagonists are warranted and eagerly awaited.

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