Current status of CCR1 antagonists in clinical trials

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Introduction

The chemokine receptor, CCR1, is believed to play a crucial role in the migration of leukocytes to sites of inflammation. It has been shown to be expressed on monocytes, T cells, dendritic cells, and in some cases, neutrophils [1–4]) and interacts with at least 7 different ligands including CCL3 (MIP-1α, macrophage inflammatory protein-1α), CCL5 (RANTES, regulated on activation, normal T cell expressed and secreted), CCL7 (MCP-3, monocyte chemotactic protein-3), CCL14 (HCC-1, hemofiltrate C-C chemokine-1), CCL8 (MCP-2, monocyte chemotactic protein-2), CCL15 (leukotactin-1), and CCL23 (MPIF, myeloid progenitor inhibitory factor-1) [5, 6]. These ligands have been shown to have potent chemotactic activity in vitro [4] and, in some cases in vivo where intradermal injection of CCL3 or CCL5 induced a robust cellular infiltration [3, 7]. Further, these chemokines can be produced by the very cells they attract to inflammatory sites. For example, peripheral blood monocytes can secrete CCL3 following activation, potentially setting up an amplification loop whereby monocytes migrate into tissue in response to CCR1, then become activated and secrete CCR1 ligands such as CCL3, thereby recruiting more cells and setting up a state of chronic inflammation. These properties suggest that CCR1 may play an important role in perpetuating inflammatory responses.

In addition to mediating cell migration, CCR1 signaling has been shown to upregulate integrins such as Mac-1 (CD11b), thus promoting the firm adherence of leukocytes to the endothelium [8]. CCR1 signaling may also contribute to tissue damage and inflammation through the enhancement of T cell activation [9], regulation of TH-1/TH-2 polarization [10, 11] and stimulation of macrophage function [12] and protease secretion [8, 13, 14]. Taken together, these properties support CCR1 as an attractive therapeutic target to modulate leukocyte infiltration and decrease the associated tissue damage common to autoimmune diseases.
Evidence for the role of CCR1 in rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting 0.5–2% of the population in the western world, the majority of whom are female. Central to the pathogenesis of this disease is the infiltration of monocytes into synovial tissue. This is supported by the predominance of monocytes found in the joint during flare [15, 16], the role of monocyte-derived proinflammatory mediators in disease progression (e.g., TNF, IL-1) [17, 18] and the ability of monocytes to secrete tissue-damaging proteolytic enzymes that participate in joint destruction [19]. Two chemokines thought to play a major role in the recruitment of monocytes into synovial tissues are the CCR1 ligands CCL3 and CCL5. Evidence in support of this is provided by a number of studies which have demonstrated an elevation of these chemokines in the synovial tissue and fluid of RA patients [20–24]. In support of their role in the pathogenesis of disease, the level of CCL3 and monocytes in synovial tissue were shown to be directly proportional to the magnitude of joint pain [16]. The role of CCR1 in the pathogenesis of RA is also supported by human genetic association studies [25] and by animal models of arthritis [26–28].

Evidence for the role of CCR1 in multiple sclerosis

Multiple sclerosis (MS) is a chronic, progressive, immune-mediated disease of the central nervous system. The disease course is highly variable but characterized by initial demyelination of nerve fiber followed by axonal loss. Key leukocytes believed to be involved in the pathogenesis of this disease include autoreactive T cells, which may initiate the disease, and monocytes, which may be responsible for the demyelination [29]. As such, inhibition of T cell and monocyte infiltration into the central nervous system (CNS) may provide a viable new strategy for disease treatment. The first clinical evidence in support of this strategy was derived from Phase 2 studies conducted with natalizumab; an α4 integrin antibody which blocks leukocyte infiltration into the CNS resulting in robust efficacy in MS patients [30].

Evidence for the role of CCR1 and its ligands in MS include their expression in demyelinating lesions, animal model data, and genetic association studies. Analysis of the cerebrospinal fluid of MS patients demonstrated increased levels of CCR1 during early and acute demyelinating stages as well as during relapse [31]. In addition, the CCR1 ligands, CCL3 and CCL5, have been detected in active regions of demyelination [32, 33] and CCL5 has been reported to be elevated in the cerebrospinal fluid of MS patients [34]. Additional evidence for the role of CCR1 in the pathogenesis of MS is provided by studies conducted in an animal model of CNS inflammation, experimental autoimmune encephalomyelitis (EAE). In this model, inhibition of the CCR1 ligands, CCL3 and CCL5 have been shown to decrease disease severity [35, 36]. Further, CCR1−/− animals have shown reduced