TARGETING CHEMOKINES AND ANGIOGENESIS IN RHEUMATOID ARTHRITIS*

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1 INTRODUCTION

Inflammatory rheumatic diseases, such as rheumatoid arthritis (RA), are associated with leukocyte ingress into the synovial tissue. In arthritis, leukocytes extravasate through the vascular endothelium. The transendothelial migration of white blood cells involve numerous inflammatory chemokines and chemokine receptors [1–14]. Angiogenesis, the growth of new capillaries from pre-existing vessels, is perpetuated during the progression of inflammatory synovitis. A number of cell-surface-bound and soluble mediators may promote neovascularization [3, 6–9]. In addition, some chemokines are also involved in synovial angiogenesis [3, 10, 15]. On the other hand, some naturally released mediators, including chemokines as well as synthetic compounds, may suppress RA-associated blood vessel formation [3, 4, 6, 8, 9, 13, 16]. There is an imbalance between pro- and anti-inflammatory chemokines, as well as angiogenic and angiostatic mediators in favor of accelerated inflammation and neovascularization in RA [1–15]. Strategies of chemokine and/or angiogenesis blockade or the administration of angiostatic agents may control synovial leukocytic inflammation and thus the perpetuation of arthritis [1–16].

In this chapter, we will briefly review the role of chemokines, chemokine receptors, and angiogenesis in the pathogenesis of arthritis. We will draw special attention to chemokines involved in neovascularization. Finally, we will describe studies on chemokine and angiogenesis targeting obtained in animal models of arthritis as well as in humans.

2 CHEMOKINES AND CHEMOKINE RECEPTORS IN ARTHRITIS

Chemokines drive inflammatory leukocytes into the inflamed synovial tissue [1–5, 17–19]. Chemokines have been classified into the CXC, CC, C, and CX_3C supergene families. Chemokines bind to their respective receptors, which have been assigned a designation of CXCR, CCR, CR, and CX_3CR [1–3, 17, 20–22]. Each chemokine has its own traditional name (see later), however, they are also considered as CXCL, CCL, XCL, and CX_3CL chemokine ligands. Both designations will

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