Chemokine receptor blockade in rheumatoid arthritis
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General introduction
Rheumatoid arthritis (RA) is considered a systemic inflammatory disease. It occurs in up to 1% of the adult population, in females more than in males. Disease onset is typically between ages 40-70 years, though earlier manifestation is commonly seen. The predominant clinical features are chronic pain, swelling, and stiffness of peripheral joints. As the disease progresses, erosions of cartilage and bone adjacent to the joints are often observed, ultimately leading to malfunction of joints and disability (1).

Treatment focuses on immunomodulation and pain relief and should be started as early as possible since many studies have confirmed that early intervention with immunomodulating therapies can prevent or delay joint erosion (2). Because the available therapies can have severe side effects, loose their therapeutic effect over time or sometimes even have no effect on individual patients, the need for new therapies for RA remains.

Although certain genetic and demographic characteristics have been recognized as predisposing factors, the cause of RA is unknown. Clinical signs include all classic features of inflammation and histological examination of the synovium of affected joints supports the notion that inflammatory processes are critically involved in the pathogenesis. Healthy synovium is a thin, loosely structured lining of joints containing few blood vessels and cells. RA synovium is thickened, irregularly shaped, highly vascularized and contains many immune cells of all lineages (3). Looking closer, it has become apparent that macrophages easily outnumber the other cell types present. On top of that, the abundant expression of macrophage-derived pro-inflammatory proteins in RA synovium suggests a prominent role for this cell type in the pathogenesis of RA (4). A suspicion that is reinforced by the fact that all clinically effective therapies studied so far have shown that their clinical effect is accompanied by a significant drop in the number of macrophages in the synovium (5-7). These observations support the hypothesis that a therapeutic approach aimed at decreasing macrophage numbers in the synovium might ameliorate RA. The accumulation of macrophages cannot be explained by local proliferation, and it has been suggested that the influx of monocytes from the bloodstream into the synovium is a major contributor to the markedly increased macrophage numbers in the synovium (8).

Chemotactic ligands to monocytic chemotactic receptors are abundantly present in RA synovial tissue and fluid, supporting the hypothesis that the monocytes are directed into the joints via the interaction between the chemotactic ligands and matching receptors (9;10). To address the therapeutic benefit of interfering with cell migration, this thesis focuses on proof of concept studies in RA patients using targeted drugs directed at receptors involved in chemotaxis: C5aR, CCR1, CCR2, and CCR5.
Chapter 1

Outline of this thesis

Chapter 2 provides a review of the literature regarding the role of chemokines in RA.

Complement activation, resulting in the abundant presence of the chemoattractant C5a, has since long been considered an important factor in the onset of and continuous inflammation in RA. C5a is not a chemokine and thus its receptor C5aR strictly seen is not a chemokine receptor. However, C5aR has both structural and functional resemblance to chemokine receptors, being a 7-transmembrane G-coupled receptor expressed on monocytes and macrophages. Chapter 3 describes the results of a multi-center, double-blind, placebo-controlled phase II study with a C5aR blocking small molecule.

CCR1 blockade has shown promising results in a small study in RA patients. Chapter 4 describes the results of a larger multi-center, double-blind, placebo-controlled phase II study with a CCR1 blocking small molecule.

Blocking CCR2 has led to contradicting results in animal models of arthritis. Chapter 5 describes the results of a multi-center, double-blind, placebo-controlled phase II study with a monoclonal antibody against CCR2.

Chapter 6 describes the results of a multi-center, double-blind, placebo-controlled phase II study with a CCR5 blocking small molecule.

Chapter 7 presents data on in vitro chemotaxis experiments using monoclonal antibodies against CCR2 and CCR5.

Chapter 8 summarizes the main findings of the studies presented in this thesis and provides suggestions for future research.
Reference List