General introduction and aim of the thesis

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Chapter 1

GENERAL INTRODUCTION AND AIM OF THE THESIS

Rheumatoid arthritis is a chronic inflammatory disease, located in the synovial joints. This inflammatory process leads to degradation of cartilage and bone in the joints with consequent disability and reduced quality of life.

Drugs that are intended to inhibit both the inflammatory and destructive processes in RA are the so-called DMARDS (disease modifying anti-rheumatic drugs). Even the gold standard of these drugs, methotrexate (MTX), has limited efficacy and its use may be hampered by side-effects. The breakthrough in treatment of RA in the last decade has been the development of TNF-blockers, thereby recognizing the key role of TNF-α in the inflammatory process. Although treatment efficacy of RA has dramatically improved with TNF-blockers, still not all patients do respond to this treatment. Moreover these drugs are expensive and severe side effects have been reported.

A novel approach to treat inflammatory diseases might be the inhibition of intracellular signal transduction pathways. In short, signal transduction is the process by which a cell converts an extracellular signal into a response. A key role is played by proteins called kinases, which act as regulators of cell function by catalyzing (facilitating) the addition of a negatively charged phosphate group to proteins, resulting in the activation of the catalytic potential of the protein involved. One of the major signal transduction pathways in inflammation is the p38 mitogen-activated protein kinase (MAPK) pathway. Specific inhibitors for this pathway have been developed but until now only two of them have entered phase II clinical trials for RA. It still remains to be elucidated which pathways are important in inflammatory disease and especially in RA and what maybe the clinical importance of signal transduction inhibitors.

The aim of the thesis was to investigate the potential of inhibition of signal transduction pathways in treatment of rheumatoid arthritis (RA)

The study was performed in vitro using cells, which in some way are relevant players in the inflammatory process in RA. The main focus was on inhibition of the p38 MAPK pathway, but in addition the involvement of the NF-κB and the JAK/STAT pathways was investigated.

In chapter 2 a general review is given on signal transduction pathways, which play a role in inflammatory processes in general and in RA more specifically.

In chapter 3 the effects of p38 MAPK inhibition on inflammatory mediator production by rheumatoid synovial fibroblasts is investigated. These cells display aggressive invasive behaviour and are to a large extent responsible for the destructive process in the synovial joints in RA.

In chapter 4 the effects of p38 MAPK inhibition on the products of monocyte-derived macrophages from healthy controls and RA patients was evaluated. In inflammation macrophages are responsible for the production of the major pro-inflammatory cytokines TNF-α and IL-1β, the key cytokines in RA.

In chapter 5 the differences in reactivity towards p38 MAPK inhibition between monocytes and monocyte-derived macrophages were evaluated. In this study the use
of a new technique, the kinase array is introduced. This technique allows the simultaneous determination of the activity of a large number of kinases in a cell lysate. In chapter 6 the effects of p38 MAPK inhibition on activated endothelial cells was investigated. These cells line the blood vessels and play an important role in recruitment of inflammatory cells into the inflamed synovium in RA.

In chapter 7 the previous study was expanded by using both an NF-κB inhibitor as well as the p38 MAPK inhibitor in investigating the effects on endothelial cells. In chapter 8 the effects of p38 MAPK inhibition on the acute phase response (APR) was evaluated. Although the APR predominantly is regulated by the JAK/STAT pathway there is cross-talk between the pathways. In the case of p38 MAPK treatment in RA patients this could mean that the production of acute phase proteins may be influenced both directly as well as indirectly by the treatment.

REFERENCES