



**Karolinska
Institutet**

**Institutionen för Medicin, Enheten för
Reumatologi**

Studies on the therapeutic modulation of inflammation in the synovial membrane of rheumatoid arthritis

AKADEMISK AVHANDLING

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation of the synovial membrane that can lead to joint deformity and physical disability. Despite recent progress in the therapeutic field of RA, the exact molecular mechanisms responsible for chronic joint inflammation are not yet completely understood. The overall aim of this thesis was to identify new molecular mechanisms responsible for inflammation in the rheumatoid joint and to understand how distinct anti rheumatic drugs act upon these mechanisms.

I first focused on validating arthroscopy as a research tool for better understanding of the molecular mechanisms of action of anti rheumatic drugs, demonstrating that rheumatologic arthroscopy is a safe method, with very few complications and allowing retrieval of representative tissue in clinical longitudinal studies. We also propose an easy to perform way to quantitate macroscopic joint changes based on photos acquired during arthroscopies.

Based on our validation study we then used this method to perform several mechanisms of action studies. We first investigated the effect of etanercept on synovial expression of lymphotoxin- α (LT- α) and tumor necrosis factor- α (TNF- α). As predicted from previous in vitro studies etanercept was able to decrease synovial expression of both LT- α and TNF- α . The effect was however limited to good clinical responders. We propose LT- α modulation as an additional but not essential mechanism to explain the clinical efficacy observed with this drug in clinical practice.

Defective apoptosis of lymphocytes is linked to pathogenesis of RA and glucocorticoids are good in vitro inducers of lymphocyte apoptosis. We therefore investigated the effect of intra articular glucocorticoids on synovial apoptosis demonstrating that in the complex milieu of rheumatoid joint glucocorticoids actually fail to induce lymphocyte apoptosis. We further demonstrate that monocytes are essential in rescuing synovial T cells from glucocorticoid-induced apoptosis through a soluble factor mediated mechanism, a feature that is specific for RA-derived synovial lymphocytes.

LL-37 is an anti microbial peptide belonging to the cathelicidin family with important functions in innate immune response but recently also implicated as a modulator of acquired immune responses. We therefore investigated a potential role for LL-37 in RA pathogenesis, demonstrating that the peptide is present at low levels in healthy synovium, but up regulated in the context of inflammation. We also identified synovial neutrophils and to a lesser extent macrophages as the main cell types expressing LL-37. Distinct modulation patterns of LL-37 by some but not all anti rheumatic drugs and correlation with local levels of inflammation suggest a potential direct contribution of LL-37 to synovial pathology in RA.

In conclusion, we demonstrated that arthroscopy is a safe and reliable research tool for studies on mechanisms of action of anti rheumatic drugs and pathogenic traits of the inflamed rheumatoid joint.

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