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Institutionen för Biovetenskaper och Näringslära

Persistent Inflammatory Pathways in Rheumatoid Arthritis Despite Anti-rheumatic Treatment

AKADEMISK AVHANDLING
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ABSTRACT

The past years have witnessed tremendous progress in the treatment of rheumatoid arthritis, a chronic debilitating autoimmune disease mainly characterized by joint inflammation with progressive tissue destruction and loss of function. This condition affects 0.5-1% of the population, is associated with important co-morbidities and represents a heavy economical burden. New strategies, employing early and aggressive therapies with classical drugs or new agents, have resulted in impressive improvements in controlling disease activity. In some cases they even lead to clinical remission. Despite potent and efficient biological agents that specifically modulate distinct pathological pathways a large proportion of patients remain unresponsive to these therapies; drug-free remission is also difficult to achieve since attempting discontinuation of treatment usually results in disease flare.

In rheumatoid arthritis joints there is a constant activation of complex networks of cytokines and factors mediating immune interactions and inflammation, in which prostaglandin E_2 (PGE_2) and leukotriene B_4 (LTB_4) are important players and contributors to pathogenesis. Our research aimed to investigate the synovial expression of enzymes controlling prostaglandin E_2 synthesis and degradation – cyclooxygenase (COX) 1 and 2, microsomal prostaglandin E_2 synthase 1 (MPGES1) and 15-prostaglandin dihydrogenase (15-PGDH) as well as enzymes involved in leukotriene synthesis, such as 5-lipoxygenase (LO) and 15-LO. In addition, we evaluated how traditional and new therapies influence these pathways, by analyzing enzyme expression before and after systemic treatment with tumor necrosis factor (TNF) antagonists, rituximab or methotrexate, as well as before and after intra-articular treatment with glucocorticoids. We also evaluated the *in vitro* effects of TNF antagonists and glucocorticoids on synovial fluid cells and that of methotrexate on synovial fibroblasts.

We demonstrated that synovial tissue from RA patients displayed an important expression of enzymes involved in the metabolism of PGE_2, as well as 5-LO and 15-LO. MPGES1 and COX-2, the inflammation-inducible enzymes co-localized mainly in fibroblasts and macrophage-like cells and accounted for the local PGE_2 production. Intra-articular glucocorticoids significantly reduced all enzymes involved in the PGE_2 cascade – COX-1 and COX-2, MPGES1 and 15-PGDH, but also 5-LO, responsible for leukotriene formation. However, they did not influence the expression of 15-LO, an enzyme involved in the formation of both pro-and anti-inflammatory lipid mediators. Regarding the effects of TNF blockers, rituximab or methotrexate, they did not alter the expression profile of enzymes involved in PGE_2 metabolism despite showing clinical efficiency in improving disease activity. Although anti-TNF agents reduced the *in vitro* expression of MPGES1 and COX-2 in synovial fluid cells, the lack of effect *ex vivo* in biopsies emphasized once again the differences between synovial compartments and possibly the difficulty in mimicking the micro-environment at the site of inflammation *in vitro*.

In conclusion, this thesis demonstrates that potent anti-rheumatic drugs currently used in the clinic with good efficiency also leave inflammatory pathways un-affected, which may account for subclinical ongoing disease activity. Blocking the PGE_2 pathway by using MPGES1 inhibitors as combination therapy may show benefit in dampening ongoing local inflammation.

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