Karolinska Institutet

Institutionen för Medicin, Enheten för Reumatologi

IMMUNOPATHOGENIC STUDIES ON INFLAMMATION AND BONE DESTRUCTION IN RA

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Föreläsningssalen CMM (L8:00)

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av

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic systemic joint disease characterized by synovial inflammation, leading to destruction of cartilage and bone. Local recruitment of immune cells and defective apoptosis results in chronic inflammation with increased synovial citrullination and local hypoxia. Synovial inflammation by itself can promote destruction of bone by modulating the RANKL/RANK/OPG system. Recently it has been suggested that the two mechanisms are at least partly uncoupled.

The aim of this thesis was to better understand pathogenic mechanisms responsible for inflammation and bone destruction and to study their modulation by effective anti-rheumatic treatment.

We demonstrated that T cells-resistance to apoptosis and protein citrullination are important features of the rheumatoid joints, potentially contributing to perpetuation of local inflammation. Intra-articular glucocorticoids fail to modulate synovial apoptosis but successfully decreased synovial citrullination both *in vivo* and *in vitro*. Modulation of synovial citrullination appears to be a drug specific effect rather than a consequence of decreased inflammation as far as methotrexate showed no effect when tested both *in vivo* and *in vitro.*

We have identified synovial RANKL expression and hypoxia as two important factors mediating bone destruction independent of inflammation. First we showed that high levels of the RANKL/OPG ratio characterize early-untreated RA. Methotrexate treatment modulates synovial expression of RANKL and protects against future radiographic progression independent of the anti-inflammatory effect. The direct effect of methotrexate on bone metabolism was confirmed *in vitro* where dual mechanisms of action were identified consisting in both RANKL modulation and direct cellular effects on osteoclasts. Second we demonstrate that hypoxia modulates RANKL and OPG expression in osteoblasts through a HIF-2α mediated mechanism. Hypoxia promotes osteoclastogenesis and bone destruction acting both through up-regulation of the RANKL/OPG ratio and direct cellular effects on osteoclasts. The additive effect of hypoxia and inflammation observed in our *in vitro* osteoclastogenesis assays further support the idea that inflammation is not the only mechanism responsible for bone destruction in RA.

In conclusion we have identified T cell resistance to apoptosis, citrullination, synovial expression of RANKL and hypoxia as important denominators of chronic inflammation and bone destruction in RA. Specific targeting of these molecular pathways might provide further insight in the complex pathogenesis of the disease and lead in the future to new therapeutic concepts.

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