Linking fms-like tyrosine kinase 3 and urokinase signalling to survivin expression in experimental arthritis

Akademisk avhandling

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Rheumatoid arthritis (RA) is a systemic autoimmune joint disease, in which chronic inflammation and hyperplastic synovial tissue mediates destruction of cartilage and bone. Survivin is known as an intracellular inhibitor of apoptosis and a positive regulator of cell division. Previous studies have shown that extracellular survivin can be detected in blood and synovial fluid from patients diagnosed with RA and that survivin in blood can predict destructive course of arthritis and poor response to anti-rheumatic treatment. The role of survivin in arthritis, the cellular source and processes leading to the release of survivin are far from understood. Two proteins, the differentiation factor Fms-like tyrosine kinase 3 ligand (Flt3L) and the Urokinase plasminogen activator (uPA) were positively associated to survivin in rheumatoid arthritis patients. The aim of this thesis was to investigate the role of Flt3 signalling for survivin production for arthritis development using the mBSA arthritis model and the role of survivin and urokinase signalling for the arthritogenic properties of synovial fibroblasts.

Intracellular survivin expression was evaluated in the mBSA arthritis model after Flt3 activation with Flt3L or inhibition using an Flt3 inhibitor, sunitinib. Changes in the frequencies of immune cell populations and the effect on arthritis development were evaluated after Flt3 inhibition. In addition, RNA silencing was used to directly target survivin in in vitro and in a human/SCID chimera model to study the impact of survivin on the arthritogenic properties of fibroblasts.

The results presented in this thesis show that survivin is expressed in bone marrow and DCS in response to activation of the receptor tyrosine kinase Flt3 in vivo. Inhibition of Flt3 reduces survivin production, dendritic cell formation and synovial inflammation. uPA release from fibroblasts is survivin dependent and silencing of survivin in human fibroblasts reduced cartilage destruction in the knee joints of SCID mice. In conclusion, survivin may enhance the survival of antigen presenting dendritic cells and the arthritogenic properties of synovial fibroblasts in the RA joint.

Keywords: survivin, rheumatoid arthritis, dendritic cells, fibroblasts, Flt3 ligand, Flt3, uPA, uPAR