Differentiation factor Fms-like tyrosine kinase 3 ligand is a modulator of cell responses in autoimmune disease

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I. Dehlin, M, Bokarewa, M, Rottapel, R, Foster, SJ, Magnusson, M, Dahlberg, LE, Tarkowski, A. **Intra-articular Fms-like Tyrosine Kinase 3 Ligand is a Driving Force in Induction and Progression of Arthritis.**
PlosOne, 2008;3(11):e3633.

II. Dehlin, M, Andersson, S, Erlandsson, M, Brisslert, M, Bokarewa, M. **Inhibition of fms-like tyrosine kinase 3 alleviates experimental arthritis by reducing formation of dendritic cells and antigen presentation.**
Journal of Leukocyte biology, 2011, Oct;90(4):811-7

III. Dehlin, M, Bjersing, J, Erlandsson, M, Andreasen, N, Zetterberg, H, Mannerkorpi, K, Bokarewa, M. F. **Cerebrospinal Flt3-ligand correlates to tau protein levels in primary Sjögren's syndrome.**
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Differentiation factor Fms-like tyrosine kinase 3 ligand is a modulator of cell responses in autoimmune disease

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Abstract: Fms-like tyrosine kinase 3 (Flt3) is a receptor on common stem cell progenitors and has a crucial role in hematopoesis, regulating cell proliferation and differentiation in man and mice. The growth factor Flt3 is activated by its soluble ligand, Flt3-L, leading to differentiation of multipotent stem cells and lymphoid progenitors. Flt3-L functions as a differentiation factor for dendritic cells (DC) in the periphery. These properties of the Flt3/Flt3-L system lead us to further investigate the role of the growth factor Flt3-L in rheumatic disease.

In paper I, Flt3-L was found to be strongly expressed at the site of inflammation in human RA, the joint. Levels of Flt3-L were significantly higher in the synovial fluid compared to serum in RA patients and levels of Flt3-L in RA synovial fluid were significantly higher compared to synovial fluid from non-inflammatory joint diseases. Furthermore, intra-articular administration of a B-cell line overexpressing Flt3-L resulted in highly erosive arthritis while inoculation of the same B-cell line without hyperexpression of Flt3-L did not induce erosivity and caused arthritis in a minority of cases. Thus, Flt3-L is expressed at the site of inflammation in human RA and facilitates tissue destructive properites in the joint cavity.

In paper II, mice with antigen-induced arthritis, mBSA-arthritis, were treated with the Flt3-inhibitor sunitinib. Treatment was started together with mBSA immunization or together with the induction of arthritis. Abrogation of Flt3 signalling reduced the intensity of synovitis and the frequency of bone destruction. Inhibition of Flt3 reduced also the number of differentiated (mature) dendritic cells concomitant with reduction of antibody production and bone metabolism. In addition to this, we investigated the ability of mouse bone marrow cells to migrate towards Flt3-L in a migration assay. Flt3-L was found to be a potent chemoattractant facilitating mobilization of $Flt3^+$ cells from the bone marrow. Thus, the processes of antigen presentation, influx of leukocytes into synovial tissue and bone remodelling are mediated by Flt3 signalling in antigen-induced arthritis.

In paper III, Flt3-L in CSF correlated to levels of Tau and pTau of patients with Sjögrens syndrome, fibromyalgia and Alzheimers disease, implying involvement of Flt3L in brain homeostasis. Furthermore, CSF Flt3-L in pSS correlated to a marker for microglia activation, MCP-1. Levels of Flt3-L in CSF were significantly decreased in pSS, and AD, compared to FM. Low levels of Flt3-L were associated to low levels of amyloid degradation peptides in pSS and AD patients. Thus, in CNS of patients with pSS Flt3-L is strongly correlated to neuroaxonal plasticity and microglia activation and reduced levels of CSF-Flt3-L in pSS are linked to changes in tau and amyloid turnover resembling processes ongoing in AD patients.

Taken together, these results indicate that Flt3-L is involved in the inflammatory and tissue remodelling processes in joints and neuroaxonal structures of the brain. Flt3/Flt3-L signalling is an essential regulator of antigen-induced processes in autoimmune diseases.

Keywords: Flt3-L, rheumatoid arthritis, Sjögren's syndrome
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