6. Lymphocytes, lymphoid cells and ectopic lymphoid structures

A125 PREFERENTIAL EXPRESSION OF NF-κB-INDUCING KINASE IN BLOOD VESSELS OF RHEUMATOID ARTHRITIS SYNOVIAL TISSUE CONTAINING ECTOPIC LYMPHOID NEOGENESIS

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Background Approximately 30% of rheumatoid arthritis (RA) synovial tissues (ST) is characterised by ectopic lymphoid neogenesis (ELN). This results in structures that may resemble germinal centres. Nuclear factor-κB (NF-κB) transcription factors are essential for the expression of pro-inflammatory cytokines, but can also induce regulatory pathways. The non-canonical NF-κB pathway, with its key mediator NF-κB inducing kinase (NIK), may play an important role in ELN as this pathway can be triggered by stimuli like CD40L and lymphotoxin that are abundantly present in ELN.

Objectives To investigate the expression and distribution of NIK in RA ST in relation to ELN and to study the role of non-canonical NF-κB signalling in RA.

Materials and methods ST was obtained via mini-arthroscopy from inflamed knee or ankle joints of RA patients with active disease. RA ST samples were analysed by microarray analysis. Expression of NIK was evaluated using immunohistochemistry (IHC) and immunofluorescence (IF) microscopy. NIK expression was also studied in Grawitz tumour and breast cancer tissues. In vitro angiogenesis/tube formation assays were performed with human umbilical vein endothelial cells (HUVEC).

Results Microarray analysis revealed increased relative expression of non-canonical NF-κB pathway associated genes in ST containing ELN compared to ST without ELN ($p<0.05$). The authors confirmed these findings by IHC: NIK expression was significantly higher in ST with ELN and more abundantly present within lymphocyte aggregates (1.53 ± 0.32 vs 0.62 ± 0.19; $p<0.05$). Of interest, in the tissue away from the lymphocyte aggregates, NIK was also expressed by vascular structures. NIK positive cells were negative for the lymphatic vessel markers lymphatic vessel endothelial hyaluronan receptor 1 and podoplanin, but IF microscopy demonstrated that NIK co-localised with the endothelial cell (EC) marker von Willebrand Factor in the smaller vessels. Furthermore, NIK was also expressed in EC in Grawitz tumour and breast cancer tissues. In vitro, HUVEC treated with stimuli that activate non-canonical NF-κB signalling exhibited increased angiogenic potential and increased vascular cell adhesion molecule 1 expression.

Conclusion NIK is preferentially expressed in RA ST containing ELN. NIK was also expressed by small EC in RA ST and tumour tissues. In vitro, non-canonical NF-κB signalling inducing stimuli resulted in EC activation and increased angiogenesis. These findings point towards an important role of the non-canonical NF-κB pathway in either angiogenesis, the activation of EC or both. This could be exploited for the development of new therapies, which would not only be applicable for RA but also for other diseases.

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