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# Preferential expression of NF-κB-inducing kinase (NIK) in blood vessels of rheumatoid arthritis synovial tissue containing ectopic lymphoid neogenesis

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## Introduction

Approximately 30% of synovial tissues (ST) derived from rheumatoid arthritis (RA) patients contain ectopic lymphoid neogenesis (ELN). NF-κB transcription factors can be activated via two distinct pathways. The non-canonical NF-κB pathway, with its key mediator 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.

## Aim

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

## Patients and methods

ST was obtained via mini-arthroscopy from inflamed joints of RA patients. RA ST were analyzed by microarray and the expression of NIK was evaluated using immunohistochemistry (IHC) and immunofluorescence (IF) microscopy. NIK expression was also studied in Grawitz tumour and breast cancer tissues.

## Results

Microarray analysis showed increased expression of non-canonical NF-κB pathway associated genes in ST containing ELN ($p<0.05$). Next, we confirmed these findings by IHC: NIK expression was significantly higher in ST with ELN (15/40) 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 expressed by vascular structures. NIK co-localised with the EC marker vWF, but not with lymphatic vessel markers. We observed expression of NIK in EC not only in RA ST, but also in Grawitz tumor and breast cancer tissue. Preliminary in vitro studies in EC point towards a role of non-canonical NF-κB signaling in angiogenesis.

## Conclusion

NIK is preferentially expressed in RA ST containing ELN and is highly expressed in EC. These findings point towards an important role of the non-canonical NF-κB pathway in either angiogenesis or the activation of endothelial cells to attract immune cells. This could be exploited for the development of future new therapies, which would not only be applicable for RA but also for other diseases.

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