proinflammatory cytokine (TNF-α, IFN-γ, IL-2, GM-CSF, IL-17A, IL-22, IL-4) production was markedly different between ACPAneg and ACPAplos RA patients with hierarchical clustering and PCA analysis revealing endotype specific cytokine profiles with ACPAneg RA patient synovial T cells showing increased TNF-α (P=0.01) expression. RNAseq analysis of RA patient synovial tissue revealed significant disease endotype specific gene signatures with specific enrichment for B cell receptor signalling and T cell specific pathways in ACPAspos compared to ACPAneg RA patients. Additionally, significantly different chemokine receptor expression based on RA patient ACPA status was observed with increased CXCR3 (P<0.001), CCR7 (P=0.002), and CCR2 (P=0.004) but decreased CXCR7 (P=0.007) expression in ACPAspos compared to ACPAneg RA patient synovial biopsies.

Conclusion: ACPA status associates with unique synovial tissue immune cell and gene profile signatures highlighting differences in the underlying immunological mechanisms involved, therefore reinforcing the need for a treat to target approach for both endotypes of RA.

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Figure 1. RNAseq analysis of synovial tissue biopsies revealed specific T cell related pathway enrichment in ACPA positive compared to ACPA negative RA patients (n=50, analysis performed with the DESeq2 and pathfinder pipelines in R).

INTERLEUKIN 40 (IL-40) IS UP-REGULATED IN RHEUMATOID ARTHRITIS (RA) AND ASSOCIATED WITH DISEASE ACTIVITY, LEVELS OF AUTOANTIBODIES AND CHEMOKINES

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Background: Interleukin 40 (IL-40) is a newly identified B cell - associated cytokine implicated in humoral immune responses and in B cell development. As B cells play a pivotal role in autoimmunity, we aimed to investigate the function of IL-40 in rheumatoid arthritis (RA).

Objectives: The aim of our study was to determine the function of IL-40 in RA.

Methods: IL-40 expression in the synovial tissue was determined by immunohis-tochemistry and immunofluorescence (n=4-5). IL-40 was analysed in the serum, synovial fluid of patients with RA (n=69), systemic lupus erythematosus (SLE; n=69), osteoarthritis (OA; n=44), and in healthy controls (HC; n=25). The association of IL-40 with B cells, we analysed the effect of rituximab therapy on the serum IL-40 in 19 patients with RA after 16 and 24 weeks of the therapy. The clinical activity of patients with RA was assessed according to the 28 joint count Disease Activity Score (DAS28). Levels of C-reactive protein (CRP) and autoantibodies were measured by routine laboratory techniques. In vitro experiments were performed in RA synovial fibroblasts (n=9). Levels of cytokines and inflammatory mediators were determined in serum, synovial fluid and superna-

tants using ELISA or multiplex immunoassay.

Results: IL-40 was overexpressed in RA synovial tissue compared to OA, particularly by synovial fibroblasts and immune cells such as B and T lymphocytes, macrophages and neutrophils. The levels of IL-40 were significantly higher in the synovial fluid of RA patients compared to OA (33.2 (6.6-68.9) vs. 0.7 (0.2-4) ng/ml; p<0.0001). In addition, IL-40 was increased in the serum of RA patients compared to SLE; OA or HC (4.8 (1.7-24.9) vs. 1.4 (1.0-18), 1.6 (0.6-3.1)) or 1.5 (0.7-2.7) ng/ml; p<0.0001 for all) and decreased after 16 (p<0.01) and 24 weeks (p<0.001) in subgroups of rituximab treated patients with RA. IL-40 levels in RA patients correlated with autoantibodies rheumatoid factor (IgM) and anti-citrullinated protein antibody (ACPA) in the serum (p<0.0001 and p<0.01) as well as in the synovial fluid (p<0.0001 and p<0.01). IL-40 in RA synovial fluid was also significantly associated with DAS28 (p<0.05), synovial fluid leukocyte count (p<0.01), number of swollen joints (p<0.05) and neutrophil attractants IL-8 (p<0.01) and MIP-1α (p<0.01). RA synovial fibroblasts exposed to recombinant IL-40 increased secretion of IL-8 (p<0.01), MCP-1 (p<0.05) and MMP-13 (p<0.01) compared to unstimulated cells in in vitro conditions.

Conclusion: Our results show for the first time that IL-40 is elevated in RA and decreases following B cell depleting therapy. The association of IL-40 with autoantibodies and chemokines may imply its potential involvement in RA development. Moreover, IL-40 up-regulates the secretion of chemokines and MMP-13 by synovial fibroblasts, indicating its role in the regulation of inflammation and tissue destruction in RA.

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NEUTROPHIL AND MONOCYTE EXTRACELLULAR TRAPS IN RHEUMATOID ARTHRITIS: POTENTIAL SOURCE OF DIAGNOSTIC BIOMARKERS

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Figure 1. Evaluation of peripheral blood neutrophils and monocytes ability to generate NET and MET spontaneously and after induction in vitro in RA.

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Results: Mean contamination fraction of neutrophils and monocytes in the reference group did not exceed 3% and 2%, respectively. Mean purity of neutrophil fraction in RA group was 93.1±6.1%, and cell viability in every sample was above 95.4±5.1%. Mean purity of monocyte fraction in RA group was 98.4±6.4%, cell viability in every sample was above 93.4±8%. Spontaneous NET and MET formation was observed in neutrophils and monocytes isolated from both RA patients and, significantly less, in healthy controls. Neutrophils from ACPA-positive RA patients were found to reveal increased spontaneous and induced NETs formation compared to ACPA-negative RA patients. Monocytes did not demonstrate any difference between these subgroups.

Conclusion: NETs could probably be considered as a candidate source of citrulline autoantigen participating in autoantibody production, whereas METs may play less important role in this phenomenon. NETs and ETs can be considered as potential diagnostic biomarkers of RA. Further studies of NETosis and ETosis in RA patients can promote emerging researches for targeted therapy of RA.

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