A47 TANGIOPOIETINS-1 AND -2 ARE DIFFERENTIALLY REGULATED AND MAKE DISTINCT CONTRIBUTIONS TO SYNOVIAL TIE2 ACTIVATION IN PATIENTS WITH RHEUMATOID ARTHRITIS AND PSORIATIC ARTHRITIS

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Background and objectives The angiogenic factors angiopoietin-1 (Ang-1) and Ang-2 are differentially expressed in the serum and synovial fluid of patients with different forms of arthritis. Ang-1 and Ang-2 contribute to inflammation and joint destruction in rheumatoid arthritis (RA), but the underlying mechanisms for their differential expression and their consequences for synovial Tie2 activation are unknown. Here the authors examined relationships between synovial expression of Ang-1 and Ang-2, and Tie2 activation in patients with RA and psoriatic arthritis (PsA), and the expression of transcription factors (TF) regulating Ang expression.

Materials and methods Ang-1, Ang-2, Tie2 and phosphorylated (p) active Tie2 expression was examined by immunohistochemistry combined with digital image analysis in synovial biopsies from 20 RA and 19 PsA patients. Relationships between Ang expression and Tie2 activation were compared. *In silico* analysis was conducted to identify possible TF candidates in the Ang-1 promoter, using four different TF binding site prediction programmes. RA synovial expression of TF and Ang-1 was examined in publicly available gene expression data sets. Candidate TF were characterised by immunohistochemistry.

Results Synovial Ang-1 expression was elevated approximately fourfold in patients with RA ($p<0.05$), while Ang-2 expression was similar in RA and PsA. The ratio of Ang-1 expression to Ang-2 was increased in RA (integrated optical density±SEM, 4.87±1.02) versus PsA (0.57±0.20) ($p<0.001$), and Ang-1 expression inversely correlated with Ang-2 expression in RA synovial tissue ($r=-0.784$, $p<0.005$). Tie2 activation was enhanced in RA (0.62±0.10) compared to PsA (0.18±0.11) ($p<0.05$), and a strong positive correlation was observed between Tie2 engagement and the ratio of Ang-1/Ang-2 expression ($r=0.786$, $p<0.01$). Expression of three potential Ang-1 TF, USF-1, NF-YA and Elf-1 correlated strongly with Ang-1 expression in RA synovial tissue ($p<0.05$) and were readily detected by immunohistochemistry.

Conclusions In RA, synovial Tie2 engagement is driven primarily by enhanced local Ang-1 production. Expression of Ang-1 is differentially regulated in RA and PsA, correlating with enhanced expression of putative Ang-1 TF in RA.