Background: Interstitial lung disease (ILD) is a common extra-articular manifestation of rheumatoid arthritis (RA). Discrepancy in the effect of biologic agents on synovial and lung inflammation exists, indicating that the nature of inflammation in the synovium and lung may be different in RA.

Objectives: To gain a better understanding of the pathogenesis of rheumatoid arthritis-associated interstitial lung disease (ILD), we sought to identify the characteristics of lung-infiltrating cells in SKG mice with ILD.

Methods: We injected curdian in SKG mice at 8 weeks of age, and identified the presence of ILD by PET-MRI at 20 weeks post-injection and histological analysis at 22 weeks post-injection. Lung-infiltrating cells were examined by flow cytometry. Analysis of serum cytokines by the Luminex multiplex cytokine assay was performed at 14 and 22 weeks post-injection, and cytokine profiles before and after the development of ILD were compared. Opal multiplexed immunofluorescent staining of lung tissue was also performed.

Results: At 20 weeks post-injection, curdian-treated SKG mice developed not only arthritis but also lung inflammation combined with fibrosis, which was identified by PET-MRI and histological analysis. The majority of inflammatory cells that accumulated in the lungs of curdian-treated SKG mice were CD11b+Gr1+ neutrophils, which co-expressed IL-17A and GM-CSF, rather than TNF-α and IL-7R α. IL-17A+GM-CSF+ neutrophils are the major prevalent and clinical phenotype of anti-CarP and GM-CSF, but not TNF-α and IL-7R α phenotype in SKG mice with ILD.

Conclusions: This is the first study to demonstrate the presence of anti-CarP in patients with pure PR. Anti-CarP was associated with ACPA positivity and higher ACPR cytokines. Anti-CarP isotypes differed between PR and RA, with lower isotype use in PR. Anti-CarP positivity in PR patients indicates a more refractory disease, with lower rates of remission and greater predisposition to evolve to RA.

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TIE2 INDUCES AN INFLAMMATORY PHENOTYPE IN RHEUMATOID ARTHRITIS AND PSORIATIC ARTHRITIS PATIENTS DRIVEN BY ANGIOPOIEIN-2

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Background: Several studies have shown that angiopoietin signalling to TIE2 may play a role in the initiation and perpetuation of disease rheumatoid arthritis (RA) and psoriatic arthritis (PsA). However, the cell type(s) involved in this process, as well as the specific role of TIE2 signalling in the synovium of arthritis patients, remains unclear.

Objectives: To examine the role TIE2 signalling in macrophages and fibroblast-like synoviocytes (FLS) within the context of the synovial microenvironment of arthritic patients.

Methods: Peripheral blood (PB) monocytes from healthy donors (HD) were differentiated with synovial fluid (SF) of RA and PsA patients. PB and SF monocytes from RA and PsA patients were differentiated into pro-inflammatory macrophages with IFN-γ. TIE2 expression was analysed by flow cytometry and quantitative PCR. Macrophages, RA FLS and synovial tissue explants were stimulated with Ang-1 or Ang-2 (200 ng/ml) alone or in combination with TNF (10 ng/ml) for 4 hour or 24 hour. mRNA and protein expression of inflammatory mediators was analysed by quantitative PCR and ELISA and luminex, respectively. Arthritis was induced in wild type (WT) and TIE2 over-expressing (Tie2-TG) mice by intraperitoneal injection of 100 ml of K/BxN serum on day 0 and day 2. Mice were sacrificed on day 14 after serum transfer.

Results: Tie2 expression was observed in IFN-γ-differentiated macrophages, from RA and PsA patients, as well as HD macrophages differentiated with RA and PsA SF. In all cases, both Ang-1 and Ang-2 stimulation significantly enhanced TNF-α induced expression of pro-inflammatory cytokines (IL-6, IL-12β, and chemokines (IL-8, CCL-3 and CCL-6). Tie2 activation also enhanced TNF-mediated production of these inflammatory mediators in RA FLS. The clinical severity of synovial-induced arthritis was significantly higher in Tie2-TG mice compared to WT mice, associated with enhanced synovial expression of IL-6, IL12β, NOC, CCL-2 and CCL-3.

Finally, we found that Ang-2, and to a lower extent Ang-1, induced the production of IL-6, IL-12β, IL-8, and CCL-3 in the synovial tissue explants of RA and PsA patients. Importantly, Ang-2 blockade with a specific neutralising anti-Ang2 antibody suppressed the production of IL-6 and IL-8 in synovial tissue of RA patients.

Conclusions: These results suggest that Tie2 signalling, even within the complex microenvironment of affected synovial tissue, has an important pro-inflammatory role.