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THU0089 IL-17A+GM-CSF+ NEUTROPHILS ARE THE MAJOR INFILTRATING CELLS IN INTERSTITIAL LUNG DISEASE IN AN AUTOIMMUNE ARTHRITIS MODEL

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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 curdlan 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, curdlan-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 curdlan-treated SKG mice were CD11b⁺Gr1⁺ neutrophils, which co-express IL-17A and GM-CSF, rather than TNF- α . Compared with 14 weeks post-injection, serum levels of GM-CSF, MCP1, IL-17A, IL-23, TSLP, and IL-17R α had increased at 22 weeks post-injection, whereas those of IFN- γ , IL-22, IL-6, and TNF- α remained unchanged. Furthermore, IL-23, CXCL5, IL-17A, and GM-CSF, but not TNF- α , were observed in immunofluorescent-stained lung tissue.

Conclusions: We found that IL-17A⁺GM-CSF⁺ neutrophils represented the major inflammatory cells in the lungs of curdlan-treated SKG mice. In addition, GM-CSF and IL-17A appear to play a more important role than TNF- α in ILD development.

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THU0090 PREVALENCE AND CLINICAL PHENOTYPE OF ANTI-CARBAMYLATED PROTEIN ANTIBODIES IN PALINDROMIC RHEUMATISM

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Background: Anti-carbamylated protein antibodies (anti-CarP) are a newly-identified antibody family present in the sera of rheumatoid arthritis (RA) patients whose specificity is close to that of ACPA but whose sensitivity is lower. Palindromic rheumatism (PR) is an intermittent form of arthritis that may progress to RA. Patients with PR may present the characteristic autoantibody profile seen in RA, even in the absence of evolution to RA. There are no studies on the presence of anti-CarP antibodies in PR.

Objectives: To analyse the prevalence of anti-CarP in patients with PR and evaluate their clinical phenotype and relationship with ACPA.

Methods: Patients diagnosed with PR attended by the Arthritis Unit, Rheumatology Service, Hospital Clínic de Barcelona were included according to the criteria of Guerne et al. Only patients considered as pure PR (patients without evidence of RA or other chronic rheumatic disease at the time of the first determination of anti-CarP) were analysed. An established RA control group was included. Anti-CarP were analysed by a home-made ELISA using a fibrin/chimeric flaggrin homocitrullinated peptide as antigen. IgG, IgA and IgM isotypes were measured. ACPA were analysed with a commercial CCP2 test. The clinical and therapeutic characteristics were compared according to anti-

CarP positivity/negativity and to the clinical evolution, including the progression to RA during the follow-up.

Results: Anti-CarP were analysed in 54 patients with pure PR and 53 RA patients. Anti-CarP were detected in 16.7% and 37.7% (p: NS) of patients with PR and RA, respectively. All PR patients positive for anti-CarP were ACPA positive and had higher ACPA titers. IgG was the predominant isotype (100%), only one patient presented IgA (11.1%) and none IgM. In the RA group, the percentages of IgG, IgA and IgM were 55%, 50% and 40%, respectively, in anti-CarP positive patients. More anti-CarP positive patients developed RA (33.3% vs. 13.6%), although the difference was not significant, during a mean follow-up of 3.8 $\pm$ 1.1 years. Remission at the last follow-up visit was more frequent in patients who were anti-CarP negative (22% vs. 60.5% p<0.05). Anti-CarP positive patients were receiving DMARD more frequently than anti-CarP negative patients (100% vs. 60% p<0.05).

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 ACPA titers. Anti-CarP isotypes differed between PR and RA, with lower isotype use in PR. Anti-CarP positivity in PR patients could indicate a more refractory disease, with lower rates of remission and greater predisposition to evolve to RA.

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THU0091 TIE2 INDUCES AN INFLAMMATORY PHENOTYPE IN RHEUMATOID ARTHRITIS AND PSORIATIC ARTHRITIS PATIENTS DRIVEN BY ANGIOPOIETIN-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, remain 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 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-induced expression of pro-inflammatory cytokines (IL-6, IL-12B) and chemokines (IL-8, CCL-3 and CXCL-6). Tie2 activation also enhanced TNF-mediated production of these inflammatory mediators in RA FLS. The clinical severity of serum-induced arthritis was significantly higher in Tie2-TG mice compared to WT mice, associated with enhanced synovial expression of IL-6, IL12B, iNOS, CCL-2 and CXCL-10.

Finally, we found that Ang-2, and to a lower extent Ang-1, induced the production of IL-6, IL-12B, 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-