conditions, as has been previously reported.² However, loss of PDPN on osteocytes leads to significantly more bone erosions in the resolving phase of the KBxN ST model compared to non-deleted controls. Deletion of osteocyte PDPN has no effect on pannus formation, cartilage loss and osteoclast numbers.

Conclusions Osteocyte-derived PDPN has been suggested as an important sensor for bone damage and this study demonstrates its bone-protective function during inflammatory arthritis.

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Disclosure of Interest None declared.

P125 IL-36 AXIS IS AN EMERGING THERAPEUTIC TARGET IN PSORIATIC ARTHRITIS SYNOVIAL TISSUE

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Career situation of first and presenting author Post-doctoral fellow.

Introduction The IL-36 family of cytokines includes three agonists (IL-36 α , β and γ) and two established or hypothetical antagonists (respectively IL-36Ra and IL-38). IL-36 agonists are pro-inflammatory cytokines highly expressed in skin, cleaved and activated by neutrophil proteases and involved in the pathogenesis of psoriasis. They have only limited effect in driving synovial inflammation in rheumatoid arthritis (RA) but little is known about the expression and biologic functions of the IL-36 axis in synovial tissue of psoriatic arthritis (PsA).

Objectives In this study, we aimed to investigate the expression pattern and role of the IL-36 cytokines in early treatment-naïve PsA synovium in comparison with RA.

Methods Synovial tissue samples were collected from patients with early (disease duration <12 months) RA and PsA DMARDs (Disease Modifying Anti-Rheumatic Drugs) and steroids-naïve. All patients underwent an ultrasound-guided synovial biopsy before starting the treatment and after six months of treatment with conventional DMARDs. The expression of IL-36 family members was investigated in synovial tissue at gene level by RNA-Sequencing (87 RA, 15 PsA), at protein level by immunostaining (20 RA, 26 PsA) and in plasma by ELISA (22 RA, 38 PsA). RA and PsA-fibroblasts-like-synoviocytes (FLS) were treated *in vitro* to assess their response to IL-36 stimulation.

Results Gene and protein expression of IL-36 agonists was comparable between RA and PsA synovial tissue; conversely, the antagonists were significantly lower in PsA compared to RA. Accordingly, the agonists/antagonists ratio was considerably higher in PsA synovium, also characterized by a strong neutrophil-signature, suggesting an activation of the IL36 pro-inflammatory pathway. Among the immune cells infiltrating the PsA synovium, macrophages (CD68+) and plasma cells (CD138+) were the primary IL36 α -expressing cells. At baseline, the synovial expression of IL-36 α was significantly higher in PsA patients who did not respond to DMARDs treatment at 12 months; this differential synovial expression of IL-36 α

between responders and non-responders was also maintained at six months. In keeping with this observation, we showed that treatment with DMARDs did not reduce the expression of IL-36 in PsA cells *in vitro*. Finally, we observed that PsA-FLS produced significantly higher levels of IL-8 upon stimulation with IL-36 α in comparison with cells isolated from RA patients.

Conclusions The impaired balance between IL-36 agonists and antagonists observed in PsA synovial tissue might contribute to the persistent inflammation characterising the diseased tissue. The exogenous replacement of the IL-36 antagonists may be a novel promising therapeutic target for PsA patients.

Disclosure of Interest None declared.

P126/O29 MTOR BLOCKADE BY RAPAMYCIN DECREASES ARTHRITIS AND SPONDYLITIS DEVELOPMENT AND SEVERITY IN HLA-B27 TRANSGENIC RATS

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Introduction TNF and IL-17A have been demonstrated as key inflammatory cytokines in Spondyloarthritis (SpA), whereas targeting bone remodeling remains an unmet clinical need in SpA. The mammalian target of rapamycin (mTOR) regulates IL-17 expression and osteogenesis and could therefore be a promising therapeutic target in SpA.

Objectives To investigate if blockade of mTOR with rapamycin inhibits the pathological processes in inflammation and bone in SpA.

Methods Cytokines were measured by ELISA in the supernatant from SpA patient PBMCs stimulated with anti-CD3/CD28, with various concentrations of rapamycin. SpA FLS were cultured in osteogenesis conditions with rapamycin, supplemented with TNF, IL-17A or both cytokines and stained for alkaline phosphatase (ALP) and Alizarin red. 6-weeks-old HLA-B27/Hu β 2m transgenic rats were immunized with 60–90 μ g heat-inactivated *M. tub* in IFA. Rats were treated with 1.5 mg/kg rapamycin or vehicle intraperitoneally (3x a week) in prophylactic and therapeutic settings and monitored for spondylitis and arthritis incidence and severity. Inflammation, bone destruction and formation were evaluated by histology after 5 weeks of treatment. IL-17A, IL-17F and TNF mRNA expression were tested in the metacarpophalangeal (MCP) joints.

Results TNF and IL-17A protein production by SpA PBMCs after stimulation were decreased in the presence of 1 nM rapamycin ($p < 0.05$). Rapamycin also reduced ALP and Alizarin red staining during SpA FLS osteogenesis ($p < 0.05$). *In vivo*, prophylactic rapamycin treatment decreased the incidence of spondylitis (18.2% (2/11)) and arthritis (36.7% (4/11)) compared to controls (92.3% (12/13); $p < 0.0001$) and 100% (13/13; $p < 0.05$). Rapamycin treatment reduced arthritis severity (0.5 versus 7.2 on a 0–12 scale ($p < 0.0001$)) and spondylitis severity (0.2 versus 2.1 on a 0–3 scale ($p < 0.0001$)). In line with the clinical findings, histological analyses revealed diminished inflammation ($p < 0.0001$),