arthritis. Especially CD11b⁺CD11c⁺ and monocyte derived inflammatory seem to play a role in inflammatory arthritis, suggesting that they could be an important therapeutic target.

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Disclosure of Interest None declared.

P123

EXTRACELLULAR MATRIX ATTENUATED MATRIX-DEGRADING EFFECTS OF VISFATIN DURING ADIPOGENIC MSC DIFFERENTIATION

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Introduction Osteoporosis (OP) is the most common age-related disorder characterized by bone loss and correlates with increased bone marrow adiposity due to a shift of osteogenic towards adipogenic differentiation of bone marrow mesenchymal stem cells (MSC). Therefore, bone marrow adipocytes are in direct contact with the altered bone matrix in OP. Adipose tissue is metabolically active. Therefore, adipocyte-derived factors such as adipokines might influence MSC differentiation.

Objectives We analyzed the presence of adipokines (visfatin, resistin and leptin) in bone tissue and their effects on MSC differentiation under standard culture vs. spongiosa.

Methods RNA and MSC were isolated from spongiosa of femoral heads of osteoarthritis patients after hip replacement surgery, or after osteoporotic femoral neck fracture. Adipogenic MSC differentiation was performed with/without adipokines and visfatin inhibitor Apo866 as well as SB203580 p38-MAPK inhibitor. For the transfer and differentiation of MSC on cancellous bone, bone fragments were purified and sterilized. Gene expression was evaluated by Realtime PCR. Protein production was analyzed by ELISA.

Results Visfatin and leptin levels were increased in OP bone vs. non-osteoporotic OA bone, however, resistin was reduced. Visfatin induced the secretion of proinflammatory factors during adipogenesis in standard cell culture as well as on cancellous bone. Visfatin-induced cytokine release was markedly reduced during differentiation on spongiosa (e.g. 14d IL6, x-fold: standard culture 151±110, spong. 40±30, n=7). Significantly elevated MMP13 mRNA as well as protein expression induced by visfatin could be observed during adipogenesis in standard cell culture as well as on

spongiosa, however visfatin-mediated MMP13 expression was reduced on cancellous bone (e.g. 21d, x-fold: standard culture 81±89, spong. 13±21, n=7). The visfatin inhibitor Apo866 inhibited the visfatin-induced cytokine release. However, the MMP13 expression was not influenced during adipogenesis in culture (n=4). In contrast to Apo866, the p38-MAPK inhibitor did not reduce cytokine release during adipogenesis.

Conclusions Visfatin and leptin levels were elevated in osteoporotic bone. Therefore, visfatin-mediated increase of MMPs and proinflammatory cytokines during adipogenic differentiation might influence bone turnover at the adipose tissue/bone interface. Our results support the idea that the extracellular matrix attenuates visfatin-mediated detrimental effects during adipogenesis. The observed visfatin-mediated effects most likely depend on different signaling pathways.

Disclosure of Interest None declared.

P124/027

OSTEOCYTE-DERIVED PODOPLANIN IS AN IMPORTANT REGULATOR OF BONE REMODELLING IN THE KBXN SERUM TRANSFER MODEL OF RHEUMATOID ARTHRITIS

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Introduction Osteocytes derive from bone-forming osteoblasts and are located deep inside the bone matrix. They are encysted in cavities (lacunae) and form dendritic extensions to develop a dense sentinel network inside the bone. Osteocytes are not passive cells. They modulate bone remodelling through regulation of both osteoclast and osteoblast activity. Immature osteocytes express the transmembrane glycoprotein podoplanin (PDPN/gp38)¹ which is important for dendrite elongation and osteocyte function.² Moreover it has been reported that PDPN expression is regulated by inflammatory cytokines including TNFα, IL-6, IL-22, TGF-β1, IFN-γ³ and is highly expressed in synovial tissues from RA patients.⁴ However the role of PDPN in osteocytes during inflammatory disease has not previously been investigated.

Objectives In this study we investigated the effect of osteocyte-specific deletion of PDPN in the KBxN serum transfer (ST) mouse model of rheumatoid arthritis.

Methods Dmp1 Cre mice were crossed with PDPN^{flx/flx} mice to generate osteocyte specific conditional knockout mice as well as appropriate PDPN^{flx/fox} controls. KBxN ST arthritis was used to study the effect of PDPN deletion on mouse arthritis progression. PDPN expression was assessed by immunohistochemistry. Osteoclast numbers were calculated by TRAP staining. Loss of cartilage and pannus formation was evaluated by Safranin-O and H and E staining. Standard microCT and synchrotron microCT analysis was used to assess bone density parameters, osteocyte location and bone erosions.

Results PDPN is expressed in osteocytes at sites of bone erosions in inflamed joints of KBxN ST mouse model. Osteocyte-specific PDPN deletion has no effect on trabecular and cortical bone density parameters in mouse tibiae under resting

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

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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-synovio-cytes (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 ($p < 0.0001$),