receptor the anti-inflammatory response might be impaired and hence enhance cytokine release by the synovium, but this was not observed. The level of sMER and sAXL was either not high enough to suppress the innate immune response or efferocytosis did not play a major role in these RA patients with end stage disease. The putative effect of sMER on the adaptive immune response remains to be investigated and this might contribute to the pathogenesis of RA.

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Disclosure of Interest None declared.

P077

DYSREGULATED MIR-125A PROMOTES JOINT ANGIOGENESIS THROUGH ENHANCED GLYCOLYSIS

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

Introduction Psoriatic arthritis (PsA) is characterised by an early vascular phase essential for pannus growth, immune responses and disease progression. Recently, numerous studies have highlighted the emerging importance of endothelial cell (EC) metabolism in disease. Herein, we propose microRNA, miR-125, modulates EC bioenergetics and orchestrates joint angiogenesis as characterised by *ex-vivo* associations, *in-vitro* assays and novel CRISPR/cas9 *in-vivo* zebrafish models.

Objectives To elucidate the role of miR-125a and endothelial cell metabolism in dysfunctional angiogenesis in PsA.

Methods MiRNA levels were quantified in synovial tissue and compared to macroscopic synovial vascularity. HUVECs were transfected with anti-miR-125a for 24 hour and tube formation assays, transwell invasion, wound repair and gene expression analysis performed. Real-time analysis of anti-miR-125 treated ECs metabolism was assessed using the XF-24 Extracellular Flux Analyzer (Seahorse Bioscience). Metabolism markers (GAPDH/PKM2/GLUT1/ATP) were assessed *ex vivo* by immunohistochemistry. *In vivo*, miR-125a CRISPR/Cas9-based knock-out zebrafish were generated and vascular development monitored. Finally, miR-125a^{-/-} ECs and zebrafish embryos were treated with an inhibitor of PFKFB3, 3PO.

Results Synovial expression of miR-125 was significantly decreased in PsA versus OA synovial tissue, levels of which were associated with macroscopic and microscopic synovial vascularity. Decreased expression of miR-125a in HMVEC resulted in increased tube formation, invasion and migration properties. Inhibition of miR-125 promoted a metabolic shift towards glycolysis with parallel changes at the gene level. *Ex vivo*, increased vascular expression of glycolytic markers was observed in PsA versus OA synovial tissue. *In vivo*, miR-125a knockout zebrafish displayed increased vascular sprouting similar to the irregular nature of the vasculature within the PsA synovium. Finally, 3PO significantly inhibited anti-miR-125a-induced mechanism whilst normalising the vascular development of miR-125a^{-/-} embryos.

Conclusions Decreased expression of miR-125 in PsA synovium and *in-vivo* models was strongly associated pro-angiogenic mechanisms. Elevated glycolysis following miR-125 inhibition enabled ECs to meet the increased energy demands for new vessel formation. Correcting these miRNA deficiencies and their resulting metabolic shift, either by conventional pharmacological or as novel drug targets, may provide therapeutic benefit, especially in early disease.

Disclosure of Interest None declared.

P078

TRANSFORMING GROWTH FACTOR-BETA DAMPENS PRO-INFLAMMATORY INTERLEUKIN-6 SIGNALING IN CHONDROCYTES BY DECREASING THE INTERLEUKIN-6 RECEPTOR

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Career situation of first and presenting author Young investigator

Introduction The pro-inflammatory cytokine interleukin-6 (IL-6) is present in high levels in arthritic diseases and has been implicated in cartilage degeneration. In contrast, transforming growth factor- β (TGF- β) is a homeostatic regulator of cartilage that decreases the catabolic effects of pro-inflammatory cytokines in chondrocytes. In tissues other than cartilage, multiple mechanisms of cross-talk between TGF- β and IL-6 are reported.

Objectives In this study, we investigated whether TGF- β is able to control IL-6 signaling in chondrocytes.

Methods Human primary chondrocytes and the human G6 chondrocyte cell line were stimulated with rhTGF- β 1 (1.0 ng/ml). We determined mRNA expression levels of IL-6 and IL-6 receptor (IL-6R) using qPCR, measured IL-6 protein release using Luminex technology and IL-6R protein levels by Western Blot. rhIL-1 β was used as a positive control for IL-6 induction. Induction of signal transducer and activator of transcription (STAT)3 phosphorylation by TGF- β was determined using Western Blot in presence of the IL-6R inhibitor Tocilizumab. Induction of suppressor of cytokine signaling (SOCS)3 gene expression was used as a read-out for IL-6/STAT3 mediated transcriptional activity.

Results TGF- β increased both IL-6 mRNA expression and protein release in G6 and primary chondrocytes. Moreover, we observed activation of the main IL-6R downstream signaling protein STAT3 after TGF- β exposure, which could be completely prevented by blockade of the IL-6R, suggesting IL-6 dependency. Surprisingly however, TGF- β did not increase expression of the well known IL-6 target gene SOCS3, despite the increased levels of IL-6 and p-STAT3 we observed in these cells. Moreover, the effect of exogenously added rhIL-6 was markedly inhibited by TGF- β , as 6h pre-treatment prevented rhIL-6-mediated induction of both SOCS3 and p-STAT3. Interestingly, we observed decreased expression of the IL-6R in both primary and G6 chondrocytes after exposure to TGF- β , which might explain the decreased intracellular IL-6 signaling. This effect was not dependent on IL-6 itself, as IL-1 β did not affect IL-6R expression, despite being a strong inducer of IL-6. Finally, we showed that rescuing IL-6R levels using soluble IL-6R dose-dependently restored induction of SOCS3 and p-STAT3 by rhIL-6 in the presence of TGF- β .