OR=2.812; 1.2 vs. 1.1; OR=2.252). Genotype and allele frequencies of rs3212227 polymorphism of the IL12B were similar in cases and controls. The mean ($\pm$ SEM) levels of IL-12p40 and IL-23 in AS patients (176.5 $\pm$ 20.7 pg/ml; 26.98 $\pm$ 3.4 pg/ml, respectively) was significantly higher than in controls (88.8 $\pm$ 9.6 pg/ml; 12.1 $\pm$ 1.5; respectively) ($p < 0.001$). Stratification based on IL12Bpro revealed significantly higher serum levels of IL-12p40 in AS patients with IL12Bpro 1.1 and 1.2 genotypes than controls. Highest IL-23 serum levels were associated with IL12Bpro 2.2 genotype. With regard of polymorphic variability of IL12B 3' UTR, AC genotype in AS has been linked to a higher IL-12p40 production and lower one of IL-23.

Conclusions: Allelic variants in the IL12B genes have the potential to alter the expression of both IL-12p40 and IL-23 cytokines in specific manner for AS patients. Carriage of the IL12Bpro variant 1-allele and of the 3'-UTR A-allele in the genotype regardless of homo- or heterozygosity could enhance systemic IL-12p40 and IL-23 levels.

Disclosure of Interest: None declared

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SAT0021

INNATE LYMPHOID CELLS ARE NOT A MAIN SOURCE OF IL-17A IN THE INFLAMED SPONDYLOARTHRITIS JOINT

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Background: Clinical trials of the anti-IL-17A antibody secukinumab demonstrated the crucial role of IL-17A cytokine in the pathogenesis of spondyloarthritis (SpA), however, its cellular source in this condition remains controversial. Group 3 innate lymphoid cells (ILC3s) have been recently identified in a number of different tissues as potent producers of proinflammatory cytokines, including IL-17A and IL-22.

Objectives: In this study we set out to characterise the presence and composition of ILCs and investigate whether these cells are the important source of IL-17A in the synovial tissue of patients with SpA.

Methods: Matched synovial tissue (ST), synovial fluid (SF) and peripheral blood (PB) were obtained from SpA and rheumatoid arthritis (RA) patients with actively inflamed knee joints. ILCs subsets were characterised by flow cytometry. Gene expression analysis at the single-cell level was performed directly *ex vivo* and after stimulation with PMA ionomycin. IL-17A ELISPOT assay was used to detect IL-17A-secreting cells.

Results: Analysis revealed that ILCs, and particularly NKp44-positive ILC3s, are expanded in the inflamed arthritic joint. Single cell expression analysis revealed that ST ILCs are clearly distinguishable from ST T cells and from their PB counterparts. We detected expression of Th17 signature transcripts *RORC*, *AHR* and *IL-23R* in the notable fraction of ST ILC3s. Furthermore these cells were capable to induce IL-22, but not IL-17A expression in response to *in vitro* re-stimulation

Conclusions: We demonstrate in this study that ILC3s are absolutely and relatively enriched in the synovial joint of patients with SpA, however these cells are not a significant source of IL-17A cytokine in this pathology.

Disclosure of Interest: None declared

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SAT0022

MIR-15A/16 SUPPRESS INFLAMMATORY RESPONSE AND CELL INVASION AND MIGRATION IN FIBROBLAST-LIKE SYNOVIOCYTES IN RHEUMATOID ARTHRITIS VIA TARGETING SOX5

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Background: Aberrant expressions of miRNAs play a critical role in the inflammatory and immune response in rheumatoid arthritis (RA). The microRNA cluster which encodes for miR-15a and miR-16, located at 13q14.3. Both these microRNAs have been implicated in the pathogenesis of many diseases, but little is known of their role in RA.

Objectives: In this study, we aim to investigate the underlying molecular mechanisms of MiR-15a/16 in RA, which will provide new insight into understanding the pathogenesis of RA and identifying novel therapeutics targets for this disease.

Methods: The expression of MiR-15a/16 in the peripheral blood mononuclear cell (PBMC) and synovium from RA, osteoarthritis (OA) and healthy controls (HC) was determined by RT-qPCR and Western blotting. Mimics of MiR-15a/16 were

transfected into the human rheumatoid fibroblast-like synoviocytes (FLS) MH7A cell line. The effect of MiR-15a/16 on proinflammatory cytokines expression, migration and invasion of FLS was detected by RT-qPCR, transwell and F-actin staining. The potentially target gene of miR-15a/16 was predicted by bioinformatics analysis. The 3'UTR of Sox5 containing wild-type or mutated miR-15a/16 binding sites was cloned to the downstream of a luciferase vector and transfected into MH7A, respectively.

Results: There is no significant difference of MiR-15a/16 expression in PBMC in RA and HC at baseline. However, the MiR-15a/16 expression is lower in PBMC from non-responders (defined DAS28 changes < 1.2 after 3 months DMARDs therapy) than those in responders after 3 months DMARDs therapy. The levels of MiR-15a/16 expression were significant decreased in the synovium from RA patients, as compared with OA patients. Transfection of MH7A with MiR-15a and 16 mimic suppressed IL-1b, TNFa, IL-17 expression, decreased cell migration and invasion and affected the cytoskeletal reorganisation in RA-FLS. We co-transfected MH7A with luciferase-reporter constructs with either wild-type or mutated miR-132 or miR-15a/16 mimics. Luciferase assay showed that either miR-15a or 16 reduced the luciferase intensity of Sox5 3'UTR. However, mutated miR-15a/16 alleviated the inhibitory effect of miR-15a/16 on the intensity of Sox5 3'UTR. To determine whether Sox5 mediates the roles of miR-15a/16 in cell migration and invasion, we constructed recombinant Adenovirus SOX5 recombinant Adenovirus SOX5 overexpressing vector. We then found that overexpression of Sox5 restored the cell invasion, and migration in MH7A that were inhibited by and miR-15a/16.

Conclusions: In conclusion, our data indicate that MiR-15a/16 play an important role in inflammatory response and cell invasion and migration in RA-FLS by directly targeting Sox5, and imply that these miRNAs have potential as therapeutic targets for RA.

Disclosure of Interest: None declared

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SAT0023

CONTROL OF CYTOKINE MRNA DEGRADATION BY THE HISTONE DEACETYLASE INHIBITOR ITF2357 IN RHEUMATOID ARTHRITIS FIBROBLAST-LIKE SYNOVIOCYTES

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Background: Control of cytokine mRNA degradation acts as an essential checkpoint to limit the overproduction of inflammatory proteins.¹ In rheumatoid arthritis (RA), altered expression of the mRNA-degrading protein TTP (tristetraprolin, ZFP36) has been recently reported in synovial tissue, possibly contributing to the perpetuating inflammatory loop in the synovium.² Histone deacetylase inhibitors (HDACi) are small molecule drugs suppressing cytokine production *in vitro* and *in vivo* and displaying initial safety and efficacy in the treatment of systemic onset juvenile idiopathic arthritis.^{3,4} However, their transcriptional and post-transcriptional mechanisms of action are not yet completely characterised.

Objectives: We aimed to investigate the mRNA degrading properties of the HDACi ITF2357 on a panel of inflammatory mediators in RA fibroblast-like synoviocytes (FLS).

Methods: The effects of ITF2357 on the expression and mRNA stability of IL-1 β -inducible genes in FLS were analysed using array-based qPCRs and Luminescence. The expression of primary and mature cytokines transcripts, the mRNA levels of TTP and other AU-rich element binding proteins (ARE-BP) and the cytokine profile of fibroblasts derived from ZFP36^{+/+} and ZFP36^{-/-} mice was measured by qPCR. ARE-BP silencing was performed by siRNA-mediated knockdown, and TTP post-translational modifications analysed by immunoblotting.

Results: ITF2357 reduced the expression of 85% of the analysed IL-1 β -inducible transcripts, including cytokines (IL6, IL8), chemokines (CXCL2, CXCL5, CXCL6, CXCL10), matrix-degrading enzymes (MMP1, ADAMTS1) and other inflammatory mediators. Analyses of mRNA stability demonstrated that ITF2357 accelerates IL6, IL8, PTGS2, and CXCL2 mRNA degradation, a phenomenon associated with the enhanced transcription of TTP, but not other ARE-BP, and the altered post-translational status of TTP protein. TTP knockdown potentiated cytokine production in RA FLS and murine fibroblasts.

Conclusions: Our study identifies that regulation of cytokine mRNA stability is a predominant mechanism underlying ITF2357 anti-inflammatory properties, occurring via regulation of TTP. These results highlight the therapeutic potential of ITF2357 in the treatment of RA.