and IL-6 protein production were measured using realtime PCR and ELISA at day 2/7/14 of OD.
Results: H19 up-regulation in MSCs during OD could be confirmed in a time dependent manner. Visfatin-stimulation of MSC during OD increased matrix mineralization over time as well as IL-6 production (day 7, 14, 21: 46-, 93-, 78-fold). Visfatin stimulation down-regulated H19 expression up to 10-fold over the course of OD compared to non-stimulated control. The effect was significant in phMSCs in 2/3 measured time points (day 7, p=0.03; day 14, p=0.002, n=3) and in hMSCs on day 14 (p=0.0003, n=4).
Conclusions: During osteogenic differentiation of MSCs, visfatin showed pro-inflammatory and mineralization promoting effects. However, H19 was significantly down-regulated by visfatin during osteogenic differentiation. This may contribute to the loss of osteogenic potency of MSCs in inflamed tissues with increased visfatin concentration as observed in affected areas of destructive bone disease. Further research to understand the H19 effector mechanisms on osteogenic differentiation and osteogenic potency of MSCs are in progress.

REFERENCES:

[1] Wang L. Differential expression of long noncoding ribonucleic acids during osteogenic differentiation of human bone marrow mesenchymal stem cells. Int. Orthop 2015;39:1013–1019.
[2] Huang Y. Long Noncoding RNA H19 Promotes Osteoblast Differentiation Via TGF-?1/Smad3/HDAC Signaling Pathway by Deriving miR-675. Stem Cells 2015;33:3481–3492.
[3] Liang W-C. H19 activates Wnt signaling and promotes osteoblast differentiation by functioning as a competing endogenous RNA. Sci. Rep 2016;6;20121.

Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2018-eular.6291

SAT0031 INTERLEUKIN 29 INHIBITS OSTEOCLAST DIFFERENTIATION AND FUNCTION IN RANKL-INDUCED OSTEOCLASTOGENESIS

F. Wang, A. Luo, Q. Wu, Z. Zhou, Q. Peng, W. Xuan, W. Tan. *The First Affiliated Hospital of Nanjing Medical University, Nanjing, China*

Background: Interleukin-29 (IL-29) is a new member of the recently discovered interferon (IFN) λ family and known to modulate immune functions of monocyte or macrophage. We have demonstrated that IL-29 is dysregulated in patients with rheumatoid arthritis (RA) and contributes to RA pathogenesis via inducing proinflammatory cytokines, chemokines or matrix metalloproteinases production in synovial fibroblasts,[1, 2] as well as stimulating inflammation and cartilage degradation in osteoarthritis disease.[3] However, the role of IL-29 in bone resorption is unclear.
Objectives: Bone erosion in RA is associated with increased production of pro-inflammatory cytokines and accelerated osteoclastogenesis in affected joints.[4] IL-29 is an important proinflammatory cytokine in RA. We investigated the effect of IL-29 on receptor activator of nuclear factor κB ligand (RANKL)-induced osteoclastogenesis *in vitro* to determine whether IL-29 can stimulate or attenuate osteoclast-mediated bone resorption that is a hallmark of RA.
Methods: The viability and apoptosis of RAW264.7 cells after IL-29 different treatment were assessed by Cell Counting Kit-8 and flow cytometry, respectively. Osteoclasts were generated from RAW264.7 cells, bone-marrow-derived monocyte/macrophage precursor cells (BMMs) and blood-derived human PBMC cells. The effects of IL-29 on osteoclast formation were evaluated by tartrate-resistant acid phosphatase (TRAP) staining and counting the number of TRAP +multinucleated cells. Bone resorption experiment was assessed by pit formation. The expression of key molecules implicated in osteoclastogenesis (TRAP, CTSK, MMP-9, NFATC1 and c-Fos) was measured by real time RT-PCR.
Results: Although IL-29 did not show significant effect on the viability and apoptosis of RAW264.7 cells, it inhibited multinucleated cells in the differentiation of murine and human osteoclastogenesis, the bone-resorbing activity of mature osteoclasts. In addition, IL-29 downregulated osteoclastic specific genes expression of TRAP, CTSK, MMP-9, NFATC1 and c-Fos.
Conclusions: IL-29 inhibits murine and human osteoclastogenesis by a direct mechanism suppressing responses of osteoclast precursors to RANKL. Our findings suggest that IL-29 may play a previously unrecognised role in the osteoclast formation.

REFERENCES:

[1] Wang F, Xu L, Feng X, Guo D, Tan W, Zhang M. Interleukin-29 modulates proinflammatory cytokine production in synovial inflammation of rheumatoid arthritis. Arthritis Res Ther 2012;14;R228.
[2] Xu L, Feng X, Tan W, Gu W, Guo D, Zhang M, Wang F. IL-29 enhances Toll-like receptor-mediated IL-6 and IL-8 production by the synovial fibroblasts from rheumatoid arthritis patients. Arthritis Res Ther 2013;15:R170.
[3] Xu L, Peng Q, Xuan W, Feng X, Kong X, Zhang M, Tan W, Xue M, Wang F. Interleukin-29 Enhances Synovial Inflammation and Cartilage Degradation in Osteoarthritis. Mediators Inflamm 2016;2016:9631510.
[4] Schett G, Gravallese E. Bone erosion in rheumatoid arthritis: mechanisms, diagnosis and treatment. Nat Rev Rheumatol 2012;8:656–664.

Acknowledgements: This project was sponsored by the grants from the National Natural Science Foundation of China (No. 81671610, 81471610, 81471611, 81401352, 81172845, 81671615, and bk20141021).
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2018-eular.6218

SAT0032 MESENCHYMAL STEM CELLS ALLEVIATE EXPERIMENTAL AUTOIMMUNE CHOLANGITIS THROUGH IMMUNOSUPPRESSION MEDIATED BY GALECTIN-9

J. Fan, X. Tang, H. Chen, L. Sun, Q. Wang. *Department of Rheumatology and Immunology, The Affiliated Drum Tower Hospital of Nanjing University Medical School, nanjing, China*

Background: Mesenchymal stem cells (MSCs) play anti-inflammatory role by secreting some kinds of bioactive molecules. However, the effect of MSCs on chronic autoimmune liver disease, such as primary biliary cholangitis (PBC) and its underlying mechanism remains elusive.
Objectives: The aim of this study was to assess the efficacy of UC-MSCs treatment (UC-MSCT) in 2OA-BSA-induced murine autoimmune cholangitis and explore its underlying mechanisms.
Methods: UC-MSCs were transplanted into experimental autoimmune cholangitis mice. Biochemical and histological analysis were performed based on the blood and liver tissues. The immunomodulatory effects of UC-MSCs and its cytoprotective function were also investigated.
Results: We found that UC-MSCT significantly ameliorated liver inflammation in 2OA-BSA induced autoimmune cholangitis mice, primarily by diminishing Th1 and Th17 responses, and modifying liver chemokine activity. We also found that UC-MSCs significantly repressed the proliferation of CD4 +T cells and suppressed the differentiation of Th1 and Th17 cells, both of which were dependent on galectin-9 (Gal-9). Furthermore, we determined the signal transducer and activator of transcription (STAT) and c-Jun N-terminal kinase (JNK) signalling pathways were involved in the production of Gal-9 in MSCs.
Conclusions: The present study shows that UC-MSCs exert profound inhibitory effects on inflammatory responses and that they ultimately alleviate the liver injury in experimental autoimmune cholangitis mice. Further, we demonstrate that UC-MSCs inhibit Th1 and Th17 cell responses as well as aberrant chemokine activity through Gal-9 mediated immunosuppression. Additionally, our research reveals that the induction of Gal-9 in MSCs is mediated by the involvement of the STAT and JNK signalling pathways. These findings may help in the development of stem cell therapies for the treatment of PBC.

Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2018-eular.4439

SAT0033 TIME-DEPENDENT RELATIONSHIPS BETWEEN BIOLOGICAL PARAMETERS AND DISEASE ACTIVITY IN SYSTEMIC LUPUS ERYTHEMATOSUS

K. Connelly[1], H. Nim[2], F. Vincent[1], F. Petitjean[2], A. Hoi[1], R. Kohlmeyer[1], S. Boyd [2], E. Morand[1]. [1]*Centre for Inflammatory Diseases*; [2]*Faculty of Information Technology, Monash University, Clayton, Australia*

Background: Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterised by high inter-patient variability of clinical features, pathology, and disease time-course. Relationships between biomarkers and disease remission/relapse cycles are especially complex and poorly understood.
Objectives: To investigate the relationship between disease activity and biomarker expression in a longitudinally-followed SLE cohort.
Methods: We measured 4 candidate protein biomarkers implicated in SLE (MIF, CCL2, CCL19 and CXCL10) and 13 routinely collected serum and urine biological parameters, and assessed disease activity (SLEDAI-2k) on each clinic visit. We analysed these data by first focusing on the magnitude of expression levels of the 17 biological markers and then on the temporal dimension, to untangle their relationship to disease activity.
Results: Data from 843 visits in 110 SLE patients (median age 47, 83% female, 49% Asian ethnicity) were analysed. We demonstrated highly heterogeneous time-dependent relationships between disease activity and the measured

biological markers. Using unbiased magnitude-based hierarchical clustering of biomarker expression levels, we isolated a patient subset (n=9) with distinctively heterogeneous patterns of expression of the 17 biological parameters, compared to the other (n=101) patients who were more homogeneous. The smaller subgroup had significantly higher levels of MIF, CCL2, CCL19 and CXCL10, but the larger subgroup had stronger associations between biological parameters and SLEDAI-2k, based on leave-one-out cross-validated regression analysis. In this subgroup, when we constructed a time-dependent regression model, compared to the equivalent time-agnostic regression model, the biological parameters had significantly stronger predictive power for disease activity, suggesting a time-dependent relationship. To disentangle the effect of magnitude versus temporal correlation, we used dynamic time-warping analysis to align longitudinal clinical and laboratory profiles. This revealed a further subset (n=69) in whom a time-dependent regression model showed significantly stronger associations between biological parameters and disease activity, despite no significant difference in simple magnitude. This subgroup was characterised by lower rates of flare, lower disease activity and lower damage scores, suggesting that this patient cluster is highly clinically meaningful.

Conclusions: Using aggregated longitudinal clinical data and samples, we demonstrated significant subgroups of time-dependent relationships between disease activity and biological markers among patients with SLE. These results imply the association between biological parameters and disease activity may exist in a multi-dimensional time-dependent pattern. Longitudinal SLE data presents potential opportunities to identify patient-stratifying biomarker patterns that are concealed when time is not considered. This finding has significant implications for the design of SLE biomarker studies.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.2034

SAT0034 POSSIBLE INVOLVEMENT OF BAFF AND MATRIXMETALLOPROTEINASE-9 IN THE ACTIVATION OF MONOCYTES OF PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME

K. Yoshimoto, K. Suzuki, T. Takeuchi. *Keio University School of Medicine, Tokyo, Japan*

Background: B cell activating factor belonging to TNF family (BAFF) is well known as a factor which regulates proliferation, differentiation and survival of B cells, and plays a pivotal role in the pathogenesis of primary Sjögren's syndrome (pSS). In our previous study, we found that BAFF significantly enhanced IL-6 production by pSS monocytes and the amount of IL-6 produced by BAFF-stimulated monocytes was positively and significantly correlated with the expression level of a BAFF receptor (BR3). These data collectively suggest that the BAFF signalling through BR3 is involved in activation of monocytes to promote production of inflammatory cytokines, such as IL-6. Matrix metalloproteinase-9 (MMP-9) is well known as one of the enzymes involved in degradation of extracellular matrix (ECM) and mainly produced by activated T cells and monocytes. It has been reported that the concentration of MMP-9 in saliva was significantly higher in pSS patients as compared to healthy controls (HC). Therefore, it is conceivable that MMP-9 is involved in the pathogenesis of pSS through degradation of ECM of salivary glands, which consequently results in decrease in saliva, one of the clinical manifestations of pSS.

Objectives: To explored the relationship between BAFF and MMP-9 in the pathogenesis of pSS.

Methods: Peripheral monocytes from pSS patients (n=37) and HC (n=19) were prepared by using CD14 +microbeads and cultured *in vitro* in the presence or absence of recombinant human soluble BAFF (rhsBAFF) for 96 hours. The amounts of IL-6 and MMP-9 in the culture supernatants were measured by ELISA. Signal transduction pathways were investigated by exposing rhsBAFF-stimulated pSS monocytes to several inhibitors against NF-κB (BAY11–7082 and BAY11–7085) and PI3 kinase (LY294002). FACS analysis of whole blood samples was performed to investigate the expression levels of BR3 and MMP-9 in monocytes. The expression level of MMP-9 was also analysed by quantitative RT-PCR (qPCR). Serum levels of BAFF and MMP-9 were measured by an electrochemiluminescence assay.

Results: Serum levels of BAFF and MMP-9 in pSS patients were significantly higher than those of HC, and the levels showed positive and significant correlation. FACS analysis of whole blood samples demonstrated that MMP-9 was mainly expressed in monocytes and that the expression level was significantly higher in pSS than in HC. ELISA and qPCR revealed that stimulation of pSS moncytes with rhsBAFF drastically enhanced the expression of MMP-9 as compared to normal monocytes. Remarkably, the amount of MMP-9 produced by the cells was positively and significantly correlated with the expression level of BR3 in pSS monocytes, suggesting that BAFF-signalling is involved in the production of MMP-9 by the cells. Moreover, the elevated production of MMP-9 was significantly suppressed by specific inhibitors against NF-κB and PI3 kinase in a dose dependent manner.

Conclusions: The present study suggests that BAFF stimulates monocytes through BR3 to promote MMP9 production and may contribute to ECM degradation. Our study also suggests that NF-κB and PI3 kinase are involved in the pathway.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.4149

SAT0035 THE EFFECTS OF VISFATIN, RESISTIN AND IL-17 ON SYNOVIAL FIBROBLASTS FROM DIFFERENT RHEUMATIC DISEASE BACKGROUNDS

K. Frommer[1], S. Rehart[2], M. Sauerbier[3], U. Müller-Ladner[1], E. Neumann[1]. *[1]Dept. of Rheumatology and Clinical Immunology, Campus Kerckhoff-Klinik, Justus-Liebig-University Giessen, Bad Nauheim; [2]Dept. of Orthopaedics and Trauma Surgery, Agaplesion Markus Hospital; [3]Dept. of Plastic, Hand and Reconstructive Surgery, BGU Frankfurt, Frankfurt, Germany*

Background: Although rheumatoid arthritis (RA) and psoriatic arthritis (PsA) have several features in common, they also possess distinct differences. We hypothesised that RA and PsA synovial fibroblasts (SF), known key effector cells in the pathophysiology of inflammatory arthritis, differentially respond to various stimuli including adipokines and cytokines and that this may contribute to those differences. For example, IL-17 (also found in synovial tissue) is of particular therapeutic significance in PsA but not as effective in RA. Thus far, IL-17 in its isoform IL-17A has been the major therapeutic target in PsA but IL-17F also plays a role in the IL-23/IL-17 axis of inflammatory diseases.

Objectives: Therefore, we analysed the responses of SF from patients with PsA, RA or no rheumatic disease to IL-17A/F±TNF-α and the adipokines visfatin and resistin, which show strong expression in the synovium of inflammatory arthritis.

Methods: SF were isolated from patients with PsA, RA or non-rheumatic disease controls (N), each undergoing joint surgery. PsASF, RASF and NSF were stimulated with human recombinant IL-17A/F, TNF-α, visfatin, and resistin. A neutralising anti-IL-17A antibody was used to verify specificity of the IL-17A effects. Secretion of the proinflammatory cytokine IL-6 was used as the initial readout parameter and was quantified using a commercial immunoassay.

Results: Stimulation with visfatin caused a strong increase in IL-6 secretion in all SF types (n=3 each), while resistin had no effect. Differences in responses were not statistically significant between the SF types studied. IL-17A at concentrations found in serum or synovial fluid did not induce IL-6 secretion in any of the SF. Dose-response curve analysis showed that considerably higher concentrations of IL–17A, which may occur locally in tissue, are required for the induction of IL-6 secretion. An anti-IL–17A antibody abolished the effect, thus showing that the effect is specific for IL-17A. The effects of IL-17A and IL–17F on IL-6 secretion by PsASF could be strongly amplified by a co–stimulation with TNF-a (IL-17A: 5-fold vs 113-fold; IL-17F: 1.7-fold vs 39-fold; TNF-α alone: 12-fold). The effects were stronger for IL-17A than for IL–17F with or without TNF co–stimulation. No effect of IL–17F alone was observed on NSF (n=1).

Conclusions: SF from RA and PsA patients were not differentially affected by the adipokines visfatin and resistin or IL-17A when used at serum or synovial fluid concentrations suggesting inflammatory cells to be the primary target of anti-IL-17 therapy. In its use as a therapeutic target, the attribute of IL-17F affecting PsASF would potentially increase the beneficial effects.

Acknowledgements: This work was supported by an unrestricted educational grant from Celgene GmbH.

Disclosure of Interest: K. Frommer Grant/research support from: unrestricted educational grant from Celgene GmbH, S. Rehart: None declared, M. Sauerbier: None declared, U. Müller-Ladner: None declared, E. Neumann: None declared

DOI: 10.1136/annrheumdis-2018-eular.2691

SAT0036 NICOTINE PROMOTES MMP-3 AND RANKL SECRETION THROUGH OVEREXPRESSED NICOTINIC ACETYLCHOLINE RECEPTOR A7 IN RHEUMATOID ARTHRITIS FIBROBLAST-LIKE SYNOVIOCYTES

J.-D. Ma[1], Y.-S. Mou[2], T. Yan[2], J. Jing[1], Y.-Q. Mo[1], Y.-L. Chen[1], L. Dai[1]. *[1]Rheumatology, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University; [2]Zhongshan School of Medicine, Sun Yat-Sen University, Guangzhou, China*

Background: Smoking has been reported not only an established environmental risk factor for developing rheumatoid arthritis (RA), but also a predictor of radiographic progression. Nicotine, the major constituent of cigarette smoke, has been demonstrated inhibitory effect on proinflammatory cytokines through its receptor nicotinic acetylcholine receptor α7 (AChRα7) in RA fibroblast-like synoviocytes (FLS). However, its effects on other function of RA-FLS remain elusive.