coding small RNAs, ranging from 18 to 25 nucleotides in length. MiRNAs are essential in regulating gene expression, cell development, differentiation and function. Dysregulation in miRNAs expression may contribute to the development of autoimmunity. However, a given miRNA may have hundreds of different mRNA targets and a target might be regulated by multiple miRNAs, thus the characterisation of dysregulated miRNA expression profiles could give a better insight into the development of immunological disturbances in autoimmune diseases.

Objectives: The aim of our study was to examine the changes in miRNA expression profiles in patients with primary Sjögren's syndrome (pSS) and systemic lupus erythematosus (SLE).

Methods: Eight pSS patients, 8 SLE patients and 7 healthy control subjects were enrolled in the investigation. MiRNAs were isolated from peripheral blood mononuclear cells, and expression patterns were determined with Illumina next-generation sequencing technology. Since the immunopathogenesis of pSS and SLE encompasses pronounced B cell hyperactivity along with specific autoantibody production, we paid a special attention on the association between miRNA expression levels and altered peripheral B cell distribution.

Results: In SLE patients 135, while in pSS patients 26 miRNAs showed altered expression. Interestingly, the 25 miRNAs including miR-146a, miR-16 and miR-21, which were over-expressed in pSS patients, were found to be elevated in SLE group, as well. On the contrary, we observed the down-regulation of miR-150–5p, which is a novel and unique finding in pSS. Levels of several miRNAs over-expressed in SLE, were not changed in pSS, such as miR-148a-3p, miR-152, miR-155, miR-223, miR-224, miR-326 and miR-342. Expression levels of miR-223–5p, miR-150–5p, miR-155–5p and miR-342–3p, which miRNAs are potentially linked to B cell functions, showed associations with the B cell proportions within peripheral blood mononuclear cells.

Conclusions: The observed differences in miRNA expression profiles and the better understanding of immune regulatory mechanisms of miRNAs may help to elucidate the pathogenesis of pSS and SLE.

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Disclosure of Interest: None declared

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AB0138 INTERFERON-GAMMA CHALLENGE OF PBMC FROM PATIENTS WITH LUPUS NEPHRITIS IN REMISSION DECREASES SUPPRESSOR OF CYTOKINE SIGNALING 1 (SOCS1) AND REGULATORY T CELLS (TREGS) AND PROMOTES IMMUNE ACTIVATION

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Background: Interferon-gamma (IFN-γ) plays an important role in the development of lupus nephritis (LN). Regulation of IFN-γ signaling that occurs in disease remission and in active LN is herein addressed.

Objectives: To study the impact of IFN-γ on PBMC obtained from patients with LN in remission as compared to active LN.

Methods: Sixteen patients fulfilling the ACR classification criteria for systemic lupus erythematosus were recruited. All patients had a history of LN of whom 10 were in remission (as defined by EULAR criteria) and 6 had active LN (as defined by SLEDAI-2K or BILAG). Healthy subjects (n=10) were included as a control group. Sera and PBMC were obtained from each individual. Flow cytometry, western blots and real time RT-PCR were used in processing and detection of cell subtypes, protein and mRNA levels. Recombinant human IFN-γ (rhIFN-γ) and anti-IFN-γ neutralizing antibody were used in vitro. Mann-Whitney and student t-tests were used for statistical analysis.

Results: In active LN there was a significant 2-fold increase in $CD4^+CD69^+$ activated T cells as compared to healthy subjects and patients in remission. Reactivity to interferon-gamma receptor was determined by the phosphorylation of its predominant transcription factor, signal transducer and activator of transcription 1 (STAT1) in the cells that were incubated with rhIFN-γ or with media alone. In active LN, 3- and 6-fold increase in pSTAT1 occurred with rhIFN-γ incubation during 24h and 48h, respectively, and healthy subjects responded likewise. In patients in remission, pSTAT1 increase was even higher (by 8- and 10-fold at 24h and 48h, respectively). After 24h incubation with rhIFN-g all groups had elevated (mRNA) expression of SOCS1, but at 48h, it significantly decreased in healthy subjects and in patients in remission by 34% and 50%, respectively. Further, at 24h the frequency of $CD4^+CD127^{low}FoxP3^+$ regulatory T cells (e.g. Tregs) increased by 27–30% in active LN and in healthy subjects, and in remission it was minimally changed. At 48h, the frequency of Tregs significantly decreased in healthy subjects (to baseline levels before rhIFN-γ challenge) and in patients in remission (by 24%, p=0.003). A challenge of PBMC from LN patients in remission with sera (at 1% concentration) derived from patients with active LN resulted in 7.5-fold increase in pSTAT1 expression and 20–30% decrease in Tregs, however, combination of sera and anti-IFN-g neutralizing antibody resulted in 5-fold decrease in pSTAT1 expression and significantly diminished the decrease in Tregs.

Conclusions: In LN in remission a challenge with IFN-γ could lead to immune activation and a risk of flare-up, as it results in a decrease in both SOCS1 and Tregs and a robust STAT1 phosphorylation. In active LN, STAT1 phosphorylation is less diminishing, as both SOCS1 and Tregs are saturated, which could affect their suppressive effectiveness.

Disclosure of Interest: None declared

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AB0139 ROLE OF MUCOSAL-ASSOCIATED INVARIANT T (MAIT) CELLS IN A LUPUS MODEL

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Background: Mucosal-associated invariant T (MAIT) cells are innate T cells that are restricted by MHC-related molecule-1 (MR1) and express a semi-invariant TCRα chain: Vα7.2-Jα33 in humans and Vα19-Jα33 in mice. Previously, we have demonstrated that MAIT cells played a protective role against experimental autoimmune encephalomyelitis, an animal model of human multiple sclerosis. We found that MAIT cells are activated in patients with systemic lupus erythematosus (SLE) and that the activation state of MAIT cells correlated with SLE disease activity index (SLEDAI) score, suggesting their association in lupus pathology.

Objectives: We set out to clarify functions of MAIT cells in a lupus model by using $Fc\gamma RIIB^{-/-}$ Yaa mice.

Methods: $Fc\gamma RIIB^{-/-}$ Yaa mice were crossed to MR1 deficient mice lacking MAIT cells, and disease progression was compared between $MR1^{-/-}$ $Fc\gamma RIIB^{-/-}$ Yaa and $MR1^{+/+}Fc\gamma RIIB^{-/-}$ Yaa mice at 1–4 months of age. Serum anti-dsDNA antibody levels were measured and urinary microalbumin were evaluated. At the time of sacrifice, at 4 months of age, the severity of nephritis and dermatitis were assessed by histologically and IgG deposition in skin and glomeruli was measured.

Results: Survival rate was significantly reduced in $MR1^{-/-}$ $Fc\gamma RIIb^{-/-}$ Yaa mice compared with $MR1^{+/+}$ $Fc\gamma RIIb^{-/-}$ Yaa mice. Anti-dsDNA antibody levels were remarkably higher in $MR1^{+/+}$ than $MR1^{-/-}$ $Fc\gamma RIIb^{-/-}$ Yaa mice at 4 months of age. Even though Glomeruli were significantly enlarged both in $MR1^{+/+}$ and $MR1^{-/-}$ $Fc\gamma RIIb^{-/-}$ Yaa mice due to a marked cellular proliferation in glomeruli, the glomerulonephritis score tended to be lower in $MR1^{-/-}$ $Fc\gamma RIIb^{-/-}$ Yaa mice compared with $MR1^{+/+}$ $Fc\gamma RIIb^{-/-}$ Yaa mice. A larger amount of IgG deposition was observed in mesangial area and along glomerular capillary walls in $MR1^{-/-}$ than $MR1^{+/+}$ $Fc\gamma RIIb^{-/-}$ Yaa mice. However, $MR1^{-/-}$ $Fc\gamma RIIB^{-/-}$ Yaa mice showed exacerbated inflammation in the skin lesions. There was a high degree of inflammatory cells infiltration into the skin and a significant worsening of dermatitis score in $MR1^{-/-}$ $Fc\gamma RIIb^{-/-}$ Yaa mice compared to $MR1^{+/+}Fc\gamma RIIb^{-/-}$ Yaa mice.

Conclusions: These data suggests that MAIT cells exhibit dual roles in lupus pathogenesis. MAIT cells enhance autoantibody production and the disease severity of nephritis, but have a suppressive effect on dermatitis. Further studies are under going to uncover the mechanisms by which MAIT cells are involved in each target tissues.

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AB0140 LUPUS-PRONE SLAM HAPLOTYPE EXERTS MONOCYTOSIS AND DEVELOPS SPECIFIC PHENOTYPE OF AUTOIMMUNE DISEASE INTRODUCED BY YAA MUTATION

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Background: We previously obtained a 129-derive FcγRIIB-deficient C57BL/6 (B6) congenic strain of mice, which spontaneously developed severe rheumatoid arthritis (RA)[1]. The introduction of the *Yaa* (Y-linked autoimmune acceleration) mutation, which is a consequence of a translocation from the telomeric end of the X chromosome containing the *Tlr7* gene onto the Y chromosome, to the FcγRIIB-deficient B6 mice (B6.FcγRIIB-/-. *Yaa*) developed lupus like nephritis but not RA[2].

Objectives: By extensively backcrossing 129-based FcγRIIB-deficient mice to B6 mice, we established wildtype FcγRIIB and 129-derive autoimmune-prone SLAM haplotype ($Slam^{129}$). We examined the phenotype of $Slam^{129}$ mice, and also $Slam^{129}$.*Yaa* mice by introducing *Yaa* mutation to these mice.

Methods: We analyzed peripheral blood monocyte subset and also serum autoantibodies as well as immunohistopathological findings of kidneys and lungs.

Results: $Slam^{129}$ mice showed age-associated monocytosis with marked expan-

sion of Gr-1 negative monocytes, also perivascular inflammatory cell infiltration in lungs. But they did not show any pathogenic autoantibodies. When introducing *Yaa* mutation, *Slam*^{129}.*Yaa* mice showed significant increase the serum levels of anti-RNP antibodies and anti-Sm antibodies. Although they showed significant increase of serum levels of IgM class anti-dsDNA antibodies, they did not show the elevation of IgG class anti-dsDNA antibodies. Also they developed nephritis but the pathological score was significantly lower than B6.FcγRIIB-/-.*Yaa* mice.
Conclusions: Autoimmune-prone SLAM haplotype plays a role for Gr-1 negative monocytosis and *Slam*^{129}.*Yaa* mice developed specific lupus phenotype with elevation of anti-RNP and anti-Sm autoantibodies.
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AB0141 LOW DOSE IL-2 CIRCUMVENTED MTOR SIGNALING IN T CELLS IN THE TREATMENT OF SLE

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Background: mTOR signaling is proved to be one of the most important pathway in the pathogenesis in SLE. However, in patients with SLE, whether mTOR pathway can be activated by low-dose IL-2 remained unclear.
Objectives: To clarify the effects of low-dose IL-2 therapy on mTOR signaling in the treatment of SLE.
Methods: Eight patients with active SLE were treated with 1 million IU IL-2. Phophrylation of S6 ribosomal protein (S6RP), AKT and pSTAT5 were measured before and after the first 2 week of low-dose rhIL-2 administration. C57BL/6 mice (male, 8–12 weeks old) were intraperitoneally immunized with SRB and followed by administration of different doses (low:10,000 IU and hight:300,000 IU) of rhIL-2 or PBS from day 3 to day 9. The ratio of Th1, Th2, Tfh, Th17, Tfh and Treg as well as the level of S6RP, AKT and pSTAT5 were assayed by flow cytometry
Results: Low-dose IL-2 was efficient and well tolerated in active SLE, and was associated with expansion of Treg cells ($p<0.001$) and reductions of Tfh and Th17 cells ($p\leq0.001$). No significant change of pS6RP and pAKT was observed. On the other hand, there was a signficiant induction of the activation of STAT5. In mouse studies, low-dose IL-2 inhibited the differentiation of Th17 cells and Tfh cells. Comparing with high dose IL-2 group, there was no significantly increased mTOR activity after low-dose IL-2 administration.
Conclusions: Low-dose IL-2 might circumvent mTOR pathway and play a regulatory role in the T cells in lupus
Disclosure of Interest: None declared
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AB0142 IGM ANTIBODIES AGAINST PHOSPHORYLCHOLINE PROMOTE POLARIZATION OF T REGULATORY CELLS FROM PATIENTS WITH ATHEROSCLEROTIC PLAQUES, SYSTEMIC LUPUS ERYTHEMATOSUS AND HEALTHY DONORS: A NOVEL IMMUNOLOGICAL CONCEPT

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Background: IgM antibodies against Phosphorylcholine (anti-PC) are negatively associated with atherosclerosis, cardiovascular disease (CVD) and systemic lupus erythematosus (SLE) where the risk of CVD and atherosclerosis is very high. We here study effects of IgM anti-PC on Th17 and T regulatory cells (Tregs).
Objectives: Immunomodulation in atherosclerosis and SLE could have a huge impact on disease prevention and treatment.
Methods: Mononuclear leukocytes were isolated from peripheral blood (PBMC) obtained from healthy blood donors, from six SLE patients with age- and sex-matched controls and from symptom-giving human atherosclerotic plaques. The proportion of Th17 ($CD4^+CCR6^+$) and Treg ($CD4^+CD25^+CD127^{dim/-}$) cells were determined by flow cytometry in $CD4^+$T cells after 6 days culture with Th17 or Treg-polarizing cytokines, with PMA and Ionomycin stimulation. IgM anti-PC were extracted from total IgM, with flow-through IgM as controls. Dendritic cells (DC) were differentiated from PBMC. Antibody peptide/protein characterization was done by a proteomics de novo sequencing approach.
Results: IgM anti-PC increased significantly the proportion of Tregs from healthy donors, SLE patients and from atherosclerotic plaque cells while control antibodies did not. T cells from SLE patients had a significantly lower proportion of Tregs and higher proportion of Th17 cells as compared to matched controls. IgM anti-PC but not control antibodies significantly reduced production of IL-17 and TNF-alpha in cell culture from SLE patients and from atherosclerotic plaque cells. IgM anti-PC interacted with CD40 and kept DCs in an immature stage potentially being tolerogenic. We identify differences on the IgM peptide expression level in anti-PC compared to control antibodies.
Conclusions: IgM anti-PC increase Tregs and having low levels could contribute to both SLE and atherosclerosis (and CVD) and could thus represent a novel underlying mechanism in these conditions. This finding could also have therapeutic implications.
Disclosure of Interest: None declared
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AB0143 IMMUNOMODULATION FOLLOWED BY QUANTITATIVE TRANSCRIPTIONAL PROFILING TO CHARACTERIZE THE FUNCTIONAL ROLE OF THE SJÖGREN'S-ASSOCIATED NCRNA AC092580.4

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Background: Despite concerted efforts to characterize dysregulated transcriptional responses observed in Sjögren's syndrome and related autoimmune disorders (both in whole blood and target tissues), the functional roles of non-coding RNAs (ncRNAs), many of which have been identified as critical players in transcriptional regulation of disease, remain poorly defined.
Objectives: In the present study, we describe ongoing efforts to functionally characterize the upregulated ncRNA identified by RNA-seq and *in silico* approaches, *AC092580.4* (FC=2.54), which we hypothesize plays a role in T and NK cell responses.
Methods: To study the immunomodulation of the ncRNA *AC092580.4*, we carried out a time-course experiment (0–36 hrs) using either PMA/I (500x dil) or universal Type I Interferon. Relative gene expression changes were determined using the Livak method by qPCR using optimized primers for *GZMA* and *AC092580.4* normalized to *GAPD*. Healthy PBMCs were subjected to stimulation by PHA (1mg/mL; 3 days), PMA/I (500x dil; 3 days), or anti-CD3/CD28 ($50uL/1x10^6$cells; 1 day). An average 150-bp RNA-seq reads were generated for each sample; alignment was carried out using STAR (hg38) and comparisions of stimulated vs unstimulated cells were done using DEseq. Pearson's correlation (r) was calculated for all 3,748 differentially expressed (DE) transcripts to identify transcripts co-expressed with *AC092580.4*.
Results: Of the transcripts showing DE in our SS RNA-seq study, we identified 8 as having significantly correlated expression with *AC092580.4* in the SS^{Ro-} expression matrix ($r>0.70$ or <-0.65). To understand the possible effects of immunomodulation on relevant cells, we stimulated HSB-2 cells with PMA/I at various time points and assessed *AC092580.4* expression by. We observed downregulation of *AC092580.4* and the co-expressed transcript *GZMA* by PMA/I (trough: 12–16hrs; FC=0.09) followed by slow recovery at 36hrs (FC=0.59). To characterize these transcriptional changes further, we performed RNA-seq using healthy PBMCs exposed to various T cell stimulants. We observed marked upregulation of both *AC092580.4* and *GZMA* at 24/36hrs by all stimulants (FC=4.89–5.98). Other transcripts showed variable responses. *CAV2* is upregulated by PMA/I, but downregulated by CD3/CD28 and PHA. Stimulation by PHA leads to upregulation of *CD3D* (FC=1.56) and *SNRPD1* (FC=3.28) with little change in *RPL36A* (FC=1.09). Stimulation by CD3/CD28 similarly leads to upregulation of *CD3D* (FC=2.85) and *SNRPD1* (FC=10.04), but clear downregulation of *RPL36A (*FC=0.64*)*. We assessed *AC092580.4* expression in HSB-2 cells exposed to I IFN and observed initial upregulation (6hrs, FC=1.46) followed by gradual downregulation (36hrs, FC=0.18).
Conclusions: In the present study, we have initiated stimulation studies with to understand the immune relevance of *AC092580.4* and co-expressed targets. *AC092580.4* shows transcriptional induction by potent inducers of T cell responses (PMA/I, PHA, CD3/CD28) but is downregulated by type I IFN. Transcripts showing co-expressed with *AC092580.4* by whole-blood RNA-seq show divergent expression patterns according to the specific stimulus, suggesting a complex regulatory network governing dysregulated T and NK responses.
Disclosure of Interest: None declared
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AB0144 PREGNANCY OUTCOMES IN IMMUNE-MEDIATED RHEUMATIC DISEASES: A RETROSPECTIVE LONGITUDINAL STUDY IN A TERTIARY HOSPITAL

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Background: Autoimmune rheumatic diseases such as systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome (APS) and Sjögren's syndrome (SS) are part of a clinical spectrum eligible to affect women in child-bearing ages, increasing pregnancy morbidity and affecting neonatal outcomes. Pregnancy complications include the teratogenic risk from immunosuppressive drugs, pregnancy-related disease flares, recurrent pregnancy loss, premature