through endosomal TLR inhibition effectively blocks IFN- α , is standard of care. However, few patients experience complete remission.

Objectives: We asked how an IL-1 receptor associated kinase 4 (IRAK-4) inhibitor I92 (ND-2158, Nimbus Discovery),¹ acting downstream of TLR 7/9, affects RNA-IC-induced cytokine production compared to hydroxychloroquine (HCQ).

Methods: Plasmacytoid dendritic cells (pDCs) and natural killer (NK) cells were isolated from peripheral blood mononuclear cells (PBMCs) of healthy individuals. PBMCs from 15 SLE patients were depleted of monocytes. Cells were stimulated with RNA-IC, consisting of IgG from SLE patient sera and U1snRNP particles, in the presence or absence of I92 or HCQ. Cytokines were measured by immunoassays or flow cytometry. RNA-sequencing was performed on RNA-IC stimulated pDCs from four healthy individuals and the effect of I92 and HCQ was assessed.

Results: RNA-IC induced IFN- α , TNF- α , IL-6, IL-8, IFN- γ , MIP1- α and MIP1- β production in pDC and NK cell co-cultures. I92 reduced the pDC and NK cell derived cytokine production by 74.95%. HCQ interfered with cytokine production in pDCs, but not in NK cells. In monocyte-depleted SLE PBMCs I92 blocked TNF- α , IFN- γ , MIP1- α and MIP1- β production more efficiently than HCQ. IL-8 production was high in monocyte depleted PBMC from SLE patients, and not blocked by neither drug, despite significant inhibition of IL-8 in pDC-NK co-cultures from healthy individuals. Following RNA-IC activation of pDCs, 975 differentially expressed genes were observed (FDR<0.05), many connected to cytokine pathways, cell regulation and apoptosis. The IRAK4 inhibitor significantly changed more RNA-IC induced genes than HCQ (492 vs. 65 genes). Several top upregulated genes were reversed by both I92 and HCQ, including *IFNA2*, *IFIT2-3*, *OASL*, *CXCL10*, *CD274*, *TNFSF10*, *APOL6*. Genes such as *DKK4*, *LAD1* and *EAF2* were significantly more downregulated by I92 than by HCQ.

Conclusions: Whereas both HCQ and the IRAK4 inhibitor block important pro-inflammatory cytokines, the IRAK4i I92 exhibits a broader inhibitory effect than HCQ on pathways triggered by RNA-IC, which suggests that IRAK4 inhibition could be a future therapeutic option in SLE and possibly other systemic autoimmune diseases characterized by the presence of ICs containing nucleic acid.

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AB0160 LOSS OF LET-7 MICRORNA UPREGULATES IL-6 IN BONE MARROW-DERIVED MESENCHYMAL STEM CELLS TRIGGERING TREG/TH17 IMBALANCE IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Systemic lupus erythematosus (SLE) patients exist an imbalance between CD4⁺CD25⁺FoxP3⁺ T regulatory (Treg) and IL-17-producing cells (Th17). Correction of this Treg/Th17 imbalance may have therapeutic impact for SLE patients. Our previous study demonstrated that bone marrow derived mesenchymal stem cells (BMSCs) from SLE patients are defective in immune modulation, which might be involved in Treg/Th17 imbalance and disease onset, but the mechanisms are not clear yet. The expression imbalance of microRNAs (miRNAs) can cause cell dysfunction, which participates in a variety of diseases development. As an important computer predicted target of let-7, interlukin-6 (IL-6) is an important negative immune regulatory factors secreted by BMSCs. Our previous experiments found that the expressions of let-7 are markedly down-regulated in SLE BMSCs by microRNA array analysis, and the synthesis of IL-6 is significantly higher in SLE BMSCs compared to normal controls.

Objectives: To investigate whether loss of let-7 could play its role in SLE BMSCs immune modulation defects by directly up-regulating IL-6 mRNA, which might contribute to Treg/Th17 imbalance in PBMCs from SLE patients, to further understand the pathogenesis of SLE.

Methods: BMSCs were isolated, cultured and expanded from iliac crest bone marrow of four healthy donors and four SLE patients. Real-time PCR was used to further determine the let-7 expression and IL-6 mRNA level in BMSCs from healthy controls and SLE patients. The important computer predicted target of let-7, IL-6 was determined using the luciferase reporter assay. Let-7-mimics, let-7-inhibitor, and let-7-negative control were transfected to BMSCs with using Lipofectamine 2000. BMSCs from healthy controls and SLE patients were co-cultured

with PBMCs from SLE patients for 72 hours to detect their effect on the ratio of Treg/Th17.

Results: Compared to normal controls, the expression of let-7 was markedly down-regulated in BMSCs from SLE patients by RT-PCR, and the synthesis of IL-6 mRNA and protein levels were significantly higher in BMSCs from SLE patients. Compared to let-7-negative controls, transfection of BMSCs with let-7-mimics markedly lower synthesis of TGF- β 1 mRNA, and let-7-inhibitor led to an opposite effect. The mean value of Treg/Th17 was significantly decreased in PBMCs from SLE patients compared to normal controls. Transfection of normal BMSCs with let-7-inhibitor caused significant downregulation of Treg/Th17 compared to let-7-negative controls, while transfection with let-7-mimics led to an opposite effect.

Conclusions: SLE patients exist an imbalance between Treg and Th17 cells, which might be associated with up-regulation of IL-6 secretion of BMSCs by loss of let-7.

Disclosure of Interest: None declared

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AB0161 INTERLEUKIN-37: A THERAPEUTIC FOR LUPUS NEPHRITIS IN MRL-FASLPR MICE

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Background: Systemic lupus erythematosus (SLE) is a serious and noticed autoimmune disease, and lupus nephritis (LN) as one of its major complications without effective treatment. IL-37 has been identified as a natural inhibitor of innate immunity. Although increasing evidence shown that serum IL-37 correlated with SLEDAI and nephritis activity, However, it is still unclear that the therapeutic effect of IL-37 on lupus mice *in vivo*.

Objectives: This study aims to determine the inhibitory effect of IL-37 in lupus mice and lupus nephritis *in vivo*, and to expose the IL-37 related mechanisms of cell and molecules that inhibits the inflammation in lupus nephritis.

Methods: MRL-Fas^{lpr} mice with mild and advanced disease were treated with lentiviral vector pLVX-IL-37b. The protein levels of IL-37b in serum and tissue, IL-17, IL-6, IL-10 and TGF β -3 produced by cell culture from spleen and kidney of mice were measured by ELISA, the relative mRNA expression of these cytokines in PBMCs was detected by RT-PCR, and the frequency of Th17 and Treg cells in splenocyte were determined by FACS.

Results: Our results show that IL-37 was highly effective in prolonging survival, alleviating the pathologic characteristics of lupus nephritis (LN) in MRL-Fas^{lpr} mice by reducing the autoimmune complex deposition such as IgM, IgG and C3, decreasing the production of inflammatory cytokines such as IL-17, IL-6 and promoting the anti-inflammatory cytokines IL-10 and TGF β -3. We also found that IL-37 protect lupus mice from LN associated with increasing the frequency of Treg cells and reducing the frequency of Th17 cells.

Conclusions: These results indicate the protective action of IL-37 in LN, and strengthen the support for IL-37 as a new target for therapy of SLE.

Disclosure of Interest: None declared

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AB0162 KLRG1 EXPRESSION IS REDUCED ON NK CELLS FROM SLE PATIENTS AND INVERSELY CORRELATES WITH DISEASE ACTIVITY AND CLINICAL FEATURES

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Background: Systemic Lupus Erythematosus (SLE) is a multifactorial autoimmune disease, with different immunological alterations and clinical phenotypes. Natural killer (NK) cells participate in the regulation of several immune responses but their function in SLE is not well understood.¹ KLRG1 (killer cell lectin like receptor G1) is a trans-membrane protein expressed in humans especially on NK cells, working as an inhibitory receptor of their cytotoxic activity. Thus, KLRG1-mediated signal might have a role in preventing autoimmunity, increasing the activation threshold of NK cells.² KLRG1 gene also, emerged as a disease susceptibility gene for SLE in four different ethnic groups.³

Objectives: The aim of this study was to characterize KLRG1 expression on NK cells (both CD56^{dim} and CD56^{bright}) from SLE patients compared to healthy subjects (HS) and to investigate its possible correlations with clinical features, including SLE disease activity.

Methods: We enrolled 14 patients (14F, mean age $\pm$ SD 37 $\pm$ 10.7 years, mean disease duration $\pm$ SD 10.5 $\pm$ 7.9 years) affected by SLE according to the 1997 ACR criteria, and 7 HS (7F, mean age $\pm$ SD 33 $\pm$ 5.5 years). Disease activity was measured by SLEDAI-2K. Peripheral blood mononuclear cells (PBMCs) were purified