p<0.001). Patients who scored 10 points in the renal domain had significantly higher renal damage score than those scored 8 points or 4

**Conclusions** In addition to disease classification, the EULAR/ACR SLE criteria may have a role in.

# Concurrent session 4: cytokines and cell signaling

## LO-012 THE INNATE IMMUNE CHECKPOINT NLRP12 REPRESSES IFN SIGNATURES AND ATTENUATES THE PROGRESSION OF LUPUS NEPHRITIS

[1]Szu-Ting Chen*, [1,2]Yen-Po Tsao, [3]Fang-Yu Tseng. *[1]Institute of Clinical Medicine, National Yang Ming Chiao Tung University, Taiwan; [2]Division of Allergy, Immunology and Rheumatology, Department of Medicine,, Taipei Veterans General Hospital, Taiwan; [3]Program in Molecular Medicine, National Yang Ming Chiao Tung University and Academia Sinica, Taiwan*

10.1136/lupus-2023-KCR.12

**Background** Signaling driven by nucleic acid sensors participates in interferonopathy-mediated autoimmune diseases. NLRP12, a pyrin-containing NLR protein, is a negative regulator of innate immune activation and type I interferon (IFN-I) production.

**Methods** SLE patients enrolled in this study will be analyzed the NLRP12 and IFNA expression in their Peripheral blood mononuclear cells (PBMCs), and their corresponding serological markers were recorded to determine the correlation between level of NLRP12 expression and serological markers. Regulation of NLRP12 expression was analyzed with the luciferase reporter assay, and the specific transcription factor on the NLRP12 promoter was determined with the chromatin immunoprecipitation assay (ChIP) in SLE PBMCs. The spontaneous activation of SLE PBMCs and the hyperresponsiveness of SLE PBMCs to nucleic acid stimulation toward cytokine production was analyzed. Nlrp12 deficient mouse was applied to confirm the role of NLRP12 in the pathogenesis of lupus progression.

**Results** PBMCs derived from systemic lupus erythematosus (SLE) patients expressed lower levels of NLRP12, with an inverse correlation with IFNA expression and high disease activity. NLRP12 expression was transcriptionally suppressed by runt-related transcription factor 1–dependent (RUNX1-dependent) epigenetic regulation under IFN-I treatment, which enhanced a negative feedback loop between low NLRP12 expression and IFN-I production. Reduced NLRP12 protein levels in SLE monocytes were linked to spontaneous activation of innate immune signaling and hyperresponsiveness to nucleic acid stimulations. Pristane-treated Nlrp12–/– mice exhibited augmented inflammation and immune responses; and substantial lymphoid hypertrophy was characterized in NLRP12-deficient lupus-prone mice. The NLRP12 deficiency mediated-increase of autoantibody production, intensive glomerular IgG deposition, monocyte recruitment, and the deterioration of kidney function were bound to IFN-I signature-dependent manner in the mouse models.

**Conclusions** These findings highlight a relationship between low NLRP12 expression and SLE progression with implications as a treatment target. We also suggest the level of NLRP12 expression on homeostasis and immune resilience.

## LO-013 NOVEL PATHOGENETIC MECHANISMS MEDIATED BY DYSREGULATION OF TRIM21-STING-TYPE I INTERFERON AXIS IN LUPUS

[1,2]Da Som Kim, [3]Youngjae Park*, [1]Mi-La Cho, [1,3]Seung-Ki Kwok. *[1]The Rheumatism Research Center, The Catholic University of Korea, Republic of Korea; [2]Department of Biomedicine and Health Sciences, College of Medicine, The Catholic University of Korea, Republic of Korea; [3]Department of Internal Medicine, Seoul St. Mary's hospital, The Catholic University of Korea, Republic of Korea*

10.1136/lupus-2023-KCR.13

**Background** Tripartite motif-containing protein (TRIM) 21 is an E3 ubiquitin-protein ligase, involved in the ubiquitin-dependent proteolysis pathway of various proteins including factors related to type I interferon pathways. Although the presence of autoantibodies against TRIM21 in various autoimmune diseases suggests potential pathogenetic roles, no studies have clarified its exact implications, especially in lupus. We aimed to elucidate the functions of TRIM21 in the dysregulation of type I interferon signals in lupus.

**Methods** To investigate the effects of TRIM21 dysfunction in lupus pathogenesis, two independent lupus animal models, the R848-induced model and the B6/lpr mice model were performed using TRIM21 knockout mice, and their phenotypes and immunological profiles were determined. In addition, we investigated the degree of TRIM21 dysfunction and therapeutic effects of in vivo delivery of TRIM21 in MRL/lpr mice. To evaluate the E3 ubiquitin ligase activity of TRIM21 for targeted proteins in type I interferon pathways, we performed a specialized immunoblot assay.

**Results** The R848 induced model and the B6/lpr model both presented with more severe lupus-like phenotypes such as nephritis, lymphadenopathies, and inflammatory immune cell profiles in TRIM21 knockout mice than in control mice. TRIM21 deficiency resulted in activation of intracellular factors related to type I interferon pathways such as STING, TBK1, and IRF3 in both models. MRL/lpr mice presented with activation of type I interferon pathways including STING, TBK1, and IRF3, and decreased expressions of TRIM21. Overexpression of TRIM21 attenuated the disease phenotypes in MRL/lpr mice. Using immunoblot assay, we observed E3 ubiquitin ligase activity of TRIM21 directly targeting STING via the proteasome pathway.

**Conclusions** TRIM21 dysfunction induces dysregulation of STING-type I interferon pathways and exacerbates the disease in lupus animal models. Targeting TRIM21-STING-type I interferon axis can be a novel therapeutic strategy in lupus treatment.

## LO-014 MECHANISTIC INTERROGATION OF STAT1 GAIN-OF-FUNCTION SYNDROME PROVIDES NEW INSIGHTS INTO HUMAN LUPUS PATHOGENESIS

[1]Andrea Largent, [2]Jane Buckner, [1,3]David Rawlings, [1,3]Shaun Jackson*. *[1]Center for Immunity and Immunotherapies, Seattle Children's Research Institute, USA; [2]Immunology, Benaroya Research Institute, USA; [3]Pediatrics, University of Washington, USA*

10.1136/lupus-2023-KCR.14

**Background** Heterozygous STAT1 gain-of-function (GOF) mutations result in a predisposition to early-onset humoral autoimmunity, including lupus-like disease. Since multiple STAT1-dependent cytokines are implicated in lupus pathogenesis, we hypothesized that insights into STAT1 GOF disease