IFIT3 produced an opposite effect. Mechanistically, IFIT3 protein was found to interact both with STING and TBK1.

Conclusions We proposed that cGAS-STING signalling pathway was hyperactive in monocytes of SLE. IFIT3 is one of the important genes which contributed to the over-activation of cGAS-STING signalling pathway and over-produced IFN in SLE pathogenesis.

Background and aims Autoantibodies directed against the 60-kD Ro (Ro60)/SSA ribonucleoprotein particle are the major target of humoral autoimmunity in patients with systemic lupus erythematosus (SLE) and primary Sjögren’s syndrome (SS). However, little is known of the anti-Ro60 immunoglobulin variable-region (IgV) repertoire in terms of clonality and IgV gene usage at the level of the serum proteome.

Methods We used high-resolution mass spectrometry to sequence precipitating anti-Ro60 proteomes from sera of patients with SLE and primary SS and compared IgV peptide signatures in Ro/La autoantibody subsets. Anti-Ro60 were purified by elution from native Ro60-coated ELISA plates and subjected to combined de novo amino acid sequencing and database matching. Additionally, Ro60 precipitins from counterimmunoelectrophoresis gels were excised, digested and sequenced directly by mass spectrometry.

Results Anti-Ro60 IgGs purified from ELISA plates and Ro60 precipitins were comprised dominant public sets of IgG1 kappa and lambda restricted heavy and light chains (with sharing of IGHV3-23, IGHV3-74 and IGHV1-18; IGKV3-20, IGKV1-5 and IGLV3-19). Significantly, mass spectrometric sequencing of purified anti-Ro60 IgGs from SLE patients showed the same convergence of autoimmune repertoire as primary SS, apart from one SLE patient who lacked IGHV3-74, suggesting that humoral anti-Ro60 molecular signatures are conserved across these two systemic autoimmune diseases. Specific IgV amino acid substitutions stratified anti-Ro60 from anti-Ro60 plus anti-La responses, providing a molecular fingerprint of Ro60/La determinant spreading.

Conclusions Unique anti-Ro60 IgV peptide signatures provide insights into mechanisms of autoantibody production as well as holding promise as serum-based molecular markers for clinical syndromes linked to Ro60 autoimmunity.

Background and aims Systemic lupus erythematosus (SLE) is an autoimmune disease with great heterogeneity in pathogenesis and clinical symptoms. To better categorise SLE subtypes we determined the dominant cytokines based on RF+IgE+ (both RF and IgE were positive) familial SLE.

Methods RF, IgE and multiple cytokines (i.e., IL-1β, IL-6, IL-8, IL-10, IL-17, IFN-γ, IP-10, MCP-1 and MIP-1β) were measured in sera of familial SLE (n=3), non-inherited SLE (n=108) and healthy controls (n=80).

Results Three SLE patients in family and 5 out of 108 non-inherited patients featured with RF+IgE+. These RF+IgE+SLE patients expressed significantly higher levels of IL-1β and IL-6 than the other SLE patients (p<0.05). IL-6 correlated with both IgE and IL-1β levels in RF+IgE+SLE patients ($r^2=0.583, p=0.027$; $r^2=0.847, p=0.001$).

Conclusions Both IL-1β and IL-6 are highly expressed cytokines in RF+IgE+SLE subtype which may be related to the pathogenesis of this special SLE subtype.
IN VIVO THERAPEUTIC SUCCESS OF MICRORNA-155 (MIR-155) ANTAGOMIR IN A MOUSE MODEL OF LUPUS ALVEOLAR HAEMORRHAGE

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Background and aims Diffuse alveolar haemorrhage (DAH) is a rare but life-threatening complication of systemic lupus erythematosus (SLE). Pristane-treated B6 mice develop severe DAH within 2 weeks of treatment. MicroRNA-155 (miR-155) is a pleiotropic microRNA that plays a crucial role in the regulation of immune responses. The purpose of this study was to examine the role of miR-155 in the development of DAH in pristane-induced lupus using miR-155-knockout (miR-155/-) mice and miR-155 antagonir to silence miR-155.

Methods DAH was induced by an intraperitoneal injection of 0.5 mL of pristane. MiR-155 antagonir was intravenously administrated to silence miR-155 expression. Lung tissues were collected for RNA extraction and were embedded in paraffin for sectioning. Gene expression profiling data were analysed using Ingenuity Pathway Analysis. Real time q-PCR was used for single validation. Luciferase reporter assay and RNA-Ago2 immunoprecipitation were performed for target validation.

Results MiR-155 expression was significantly increased in the development of DAH. Disease progression was reduced in miR-155/- mice and by in vivo silencing of miR-155 using miR-155 antagonir. MiR-155 silencing dampened pristane-induced ectopic activation of multiple inflammatory pathways, and reduced the expression of pro-inflammatory cytokines. Several negative regulators of nuclear factor (NF)-κB signalling were inhibited by pristane, and were re-activated in miR-155/- mice. In particular, the anti-inflammatory factor peroxisome proliferator-activated receptor-α was identified as a direct target of miR-155.

Conclusions MiR-155 promotes pristane-induced lung inflammation. MiR-155 contributes to ectopic activation of NF-κB signalling pathways by targeting multiple negative regulators. MiR-155 antagonir may be a promising therapeutic strategy for treating acute lung inflammation in lupus.

MICRORNA-21 IS A CRITICAL REGULATOR OF AUTOIMMUNITY THROUGH PROMOTING EFFECTOR AND METABOLIC FUNCTION OF PATHOGENIC TH17 CELLS

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Background and aims Systemic lupus erythematosus is a prototypical autoimmune disease that causes mortality and morbidity worldwide. Recent studies suggest proinflammatory TH17 cells are key pathogenic factors that contribute to lupus nephritis. Our group previously demonstrate that microRNA-21 was highly upregulated in CD4+ T cells from both lupus patients and lupus-prone mice. However, the role of microRNA-21 in pathogenic TH17 cells and they-mediated autoimmune diseases is still unclear. In this study, we systemically dissect the role of microRNA-21 in the differentiation and effector function of pathogenic TH17 cells.

Methods MicroRNA-21 knockout and conditional knockout mice were generated. EAE was induced to study the role of microRNA-21 in pathogenic TH17 cell-mediated autoimmune diseases. RNA-seq, RIP-seq and DAVID bioinformatic analysis were conducted to find key microRNA-21 regulated pathway and molecular targets in pathogenic TH17 cells. Metabolic assays were done to study the glycolytic activity of microRNA-21-deficient pathogenic TH17 cells.

Results In this study, we demonstrate that IL-6-STAT3 signaling induced microRNA-21 is essential for the late stage commitment and maintenance of pathogenic TH17 cells by targeting key regulators. MicroRNA-21-deficient TH17 cells express less pathogenic TH17 signature genes and show less glycolytic activity. Conditional deletion of microRNA-21 in CD4+ T cells protects mice from EAE while loss of microRNA-21 expression by dendritic cells and myeloid cells do not.

Conclusions These findings suggest that microRNA-21 is a novel cell-intrinsic regulator of the commitment and metabolic function of pathogenic TH17 cells. It may be a potential therapeutic candidate with which to reprogram the immune system and help prevent and treat autoimmune diseases.