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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 antagomir to silence miR-155.

Methods DAH was induced by an intraperitoneal injection of 0.5 mL of pristane. MiR-155 antagomir was intravenously administered 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 antagomir. 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)- κ B 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- κ B signalling pathways by targeting multiple negative regulators. MiR-155 antagomir may be a promising therapeutic strategy for treating acute lung inflammation in lupus.

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SERUM IL-18 AS BIOMARKER IN PREDICTING LONG-TERM RENAL OUTCOME AMONG PEDIATRIC-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS

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Background and Aims An urge of biomarker identification is needed to better monitor lupus nephritis (LN) disease activity, guide clinical treatment, and predict patient's long-term outcome. With the proinflammatory effect and its association with inflammasomes, the significance of interleukin-18 (IL-18) among pediatric-onset systemic lupus erythematosus (pSLE) patient.

Methods In a pSLE cohort of 96 patients with an average follow-up period of 10.39 \pm 3.31 years, clinical data and laboratory workups including serum IL-18 were collected at time of disease onset and 6 months after treatment despite their initial

renal status. Through Cox regression analysis, the parameters at baseline and at 6 months posttreatment were carefully analysed.

Results Average age of all cases was 12.74 \pm 3.01 years old and 65 of them underwent renal biopsy at the time of diagnosis. Nine (9.38%) progressed to end-stage renal disease (ESRD) and 2 (2.08%) died during follow-up. Through multivariate analysis, serum IL-18 level 6 months posttreatment was found to be the most unfavourable factor associating poor clinical outcome despite patient's initial renal status. The presentation of serum IL-18 in its correlation with SLE global disease activity as well as the presence and severity of LN were all significant ($p < 0.001$, $p = 0.03$, and $p = 0.02$, respectively). The histological classification of LN was not associated with the level of IL-18 among the pSLE patients ($p = 0.64$).

Conclusions The role of serum IL-18 as biomarker representing global disease activity and status of renal flares among pSLE population was shown for the first time. Additionally, we have identified IL-18 at 6 months posttreatment a novel marker for long-term renal outcome prediction.

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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 signalling 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.