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 antagonist to silence miR-155.

Methods DAH was induced by an intraperitoneal injection of 0.5 mL of pristane. MiR-155 antagonist 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 antagonist. 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 antagonist may be a promising therapeutic strategy for treating acute lung inflammation in lupus.

MICRORNA-21 IS A CRITICAL REGULATOR OF AUTOIMMUNITY THROUGH PROMOTING EFFECCTOR 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 demonstrated 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.