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MiR-125a Is Critical Regulator for Controlling Autoimmunity in Multiple Autoimmune Diseases through Stabilizing Treg Mediated Immune Homeostasis

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Background/Purpose

Although different autoimmune diseases show distinct clinical phenotypes, common cellular and molecular immune pathways have been shown to be intimately involved in the autoimmune pathogenesis. Treg cells suppress inflammation and maintain immune homeostasis. Impairment of the development and function of Treg cells is a common immune defect that contributes to the development of multiple autoimmune diseases. MicroRNAs as novel epigenetic regulator of immune response play critical role on T cell mediated immune regulation. In this study we focus on defining the cellular and molecular mechanisms underlying microRNA(miR) mediated dysregulation of Treg cells on multiple autoimmune diseases and explore therapeutic potentials of miRs based intervention for re-program immune homeostasis on these disease relevant mouse models.

Methods

miR profiling for CD4+ T cells of multiple autoimmune diseases and their relevant mouse models were done by ABI miR array. miR125a KO and transgenic mice have been generated for testing Treg cell phenotype and function. EAE and T-cell mediated colitis models were conducted on both genetically modified mice and B6 controls mice for evaluating role of miR125a on Treg cell mediated tissue inflammation. mRNA profiling ,IPA bioinformatics tool and several microRNA databases were used for miR targets predication . 3UTR report gene assay ,western blot and FACS were used for miR125a targets's validation. We administrated miR 125a agomir(chemical modified miRNA mimics) into EAE and Lpr/MRL mice for evaluating its efficacy .

Results

Frist we identified a commonly down-regulated miRNA, miR-125a, in peripheral CD4+ T cells of multiple autoimmune diseases including systemic lupus erythematosus ,multiple sclerosis, and Crohn's diseases, as well as their relevant mouse models. Although the common dysregulation implied a shared mechanism of autoimmune pathogenesis, a function for miR-125a in either driving

or constraining autoimmune pathology was still unclear. By using miR-125a deficient mice, we identified miR-125a as a key regulator that stabilizes the commitment and immunosuppressive capacity of Treg cells by restraining the differentiation programs of effector lineages, thus contributing to the suppression of inflammation, as well as the maintenance of immune homeostasis. Deficiency of miR-125a may ultimately result in more severe pathogenic consequences of T-cell mediated colitis and EAE development. Analysis of the genome-wide targets of miR-125a revealed that it suppressed several effector T cell factors that are detrimental to Treg cell differentiation, including Stat3, Il13 and Ifng. Moreover, manipulation of miR-125a level by chemically synthesized analogue of miR-125a showed therapeutic potentials to re-program the immune homeostasis and contributed to certain disease prevention or treatment in clinically-relevant animal models.

Conclusion

Our finding identify miR-125a as a commonly down-regulated miRNA critical for controlling autoimmune diseases through stabilizing Treg mediated immune homeostasis by repressing effector programs. miR-125a could be promsining therapeutic traget for treating multiple Treg cells mediated autoimmune diseases

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Disclosure:

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None;

D. Dai,
None;

J. Harley,
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