AUTOIMMUNE CONNECTIVE TISSUE DISEASES

MICRORNA-3926 CONTRIBUTES TO CD4+ T CELL APOPTOSIS AND AUTOREACTIVITY IN HUMAN SLE THROUGH INHIBITING AUTOPHAGY BY TARGETING ATG12-5/16L1

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Introduction: Systemic lupus erythematosus (SLE) is characterized by impaired T lymphocyte homeostasis, resulting in increased apoptosis and T cell hyperactivation.

Objective: Autophagy is recognized as a crucial pathogenic factor in SLE; however, little information is available regarding the mechanisms governing the regulation of autophagy and apoptosis in SLE. This study was undertaken to investigate the role of MicroRNA-3926 (miR-3926) in the etiology of SLE.

Materials and Methods: MiR-3926 expression was determined by quantitative reverse transcription PCR. Potential target genes were verified using luciferase reporter assays. MiR-3926 mimics or inhibitor were transfected into cells to modify miRNA levels. Autophagy levels were measured by Western blotting, immunofluorescent labeling of LC3 and Cyto-ID dye incorporation. Apoptosis levels were evaluated by flow cytometry and Western blotting.

Results: Compared with those in healthy donors, miR-3926 was significantly upregulated in SLE CD4+ T cells, whereas autophagy related 5 (ATG5), autophagy related 12 (ATG12) and autophagy related 16 like 1 (ATG16L1) expression was downregulated. Luciferase reporter assays demonstrated that miR-3926 directly targeted ATG5, ATG12 and ATG16L1 mRNA. Furthermore, in SLE CD4+ T cells, there was an inverse correlation between levels of miR-3926 and those of ATG5/12/16L1. Moreover, autophagy inhibition through miR-3926 mimics transfection promoted cell apoptosis, whereas autophagy inducer rapamycin inhibited miR-3926-induced apoptosis. Autophagy induction through miR-3926 inhibitor transfection reduced cell apoptosis, whereas autophagy inhibitor 3-MA reversed this effect. In normal CD4+ T cells, overexpression of miR-3926 inhibited autophagy activity by down-regulating ATG12-5/16L1 expression, leading to increased caspase-mediated apoptosis and increased CD4+ T cell activation observed in SLE. However, inhibition of miR-3926 induced completely opposite effect in SLE CD4+ T cells.

Conclusions: The results of this study revealed that miR-3926 promotes apoptosis and T cell autoreactivity through inhibiting autophagy by directly targeting ATG12-5/16L1 in SLE

CD4+ T cells, providing potential novel strategies for therapeutic intervention in SLE.