Background Lupus nephritis (LN) is one of the most serious manifestations of systemic lupus erythematosus (SLE). Overactivation of type I interferon (IFN) signaling pathway is associated with LN pathogenesis, since overexpression of IFN stimulated genes (ISGs) has been found in the kidney of LN and deficiency of IFN receptor alleviates nephritis in lupus prone mice. Abnormal expression of microRNAs in renal tissues is linked to the pathogenesis of LN. However, the functions of these microRNAs and mechanisms for them to participate in the development of LN are largely unknown. In this study, we aimed to investigate the role of LN-associated renal microRNAs in the overactivation of IFN signaling pathway in the kidney of LN.

Methods microRNA expression was measured by Taqman assay. Interferon-stimulated response element (ISRE)-luciferase reporter assay and western blotting were used to investigate the function of candidate microRNAs in IFN signaling pathway. mRNA expression was measured by SYBR green assay. Gene expression profile was done by microarray. Agomir and antagonor (chemical modified microRNA mimics and inhibitors) of the candidate microRNA was used to perform gain and loss of function experiments. Pristane induced lupus mouse model and NZB/NZW F1 mice were used to investigate the in vivo function of the candidate microRNA.

Results Among revolutionary conserved differentially expressed renal microRNAs in LN, mir-127–3p, which was reduced in the kidney biopsies of LN patients, inhibited IFN induced ISRE mediated expression of luciferase reporter gene, as well as the phosphorylation of STAT1 and STAT2. By microarray, we revealed that most of the ISGs were inhibited by miR-127–3p in IFN stimulated Hela cells. Consistently, loss of function of miR-127–3p augmented IFN response in human primary renal mesangial cells, with enhanced ISRE mediated expression of reporter gene, phosphorylation of STAT2 and ISGs expression. Further, we identified JAK1, the upstream tyrosine kinase of STAT1 and STAT2, as a novel target of miR-127–3p. In vivo administration of miR-127–3p agomir reduced ISGs expression and alleviated pulmonary hemorrhage induced by pristane in B6 mice and proteinuria in NZB/NZW F1 mice.

Conclusions Our study shows miR-127–3p can inhibit IFN signaling by targeting JAK1. Decreased expression of miR-127–3p in the kidney contributes to the overactivated IFN response in LN. Subsequent mouse model studies indicate the therapeutic potential of miR-127–3p in treating lupus associated organ damage.

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