SUPPRESSOR OF CYTOKINE SIGNALING-1/STAT1 REGULATES RENAL INFLAMMATION IN MESANGIAL PROLIFERATIVE GLOMERULONEPHRITIS MODELS

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INTRODUCTION AND AIMS: Glomerulonephritis (GN) is characterized by intraglomerular inflammation and is a major cause of end-stage renal disease (ESRD). Inflammation plays a crucial role in the progress of mesangial proliferative glomerulonephritis (MsGN). The suppressor of cytokine signaling (SOCS) proteins which are inhibitors of cytokine signaling pathways unveiled an important mechanism for the negative regulation of the cytokine-induced JAK/STAT pathway. SOCS1 participates in renal fibrosis by downregulating JAK2/STAT1-mediated cytokine signaling in LN and Diabetic Nephropathy. This study examined whether SOCS1 can regulate renal inflammation in MsGN models.

METHODS: In Vivo: Rat (Thy 1.1 GN) and mouse (Habu GN) mesangial proliferative nephritis models were established. The expression of SOCS1, MHC class II, STAT1, inflammatory cells and cytokines were analyzed in MsGN models. In Vitro: IFN-γ-stimulated mouse mesangial cells (MMCs) were transfected with SOCS1 plasmids. Meanwhile, we used STAT1 inhibitor fludarabine in IFN-γ-treated MMCs. The expression of MHC class II, STAT1 and cytokines were analyzed.

RESULTS: The number of macrophages and CD4 T cells increased significantly in glomeruli of MsGN models. Expression of IFN-γ, TNF-α, IL-12A and IL-12B increased significantly in the course of Thy 1.1 and Habu nephritis. MHC class II is expressed in mesangial cells of MsGN models. SOCS1 protein also showed a significant decrease and P-STAT1 increased significantly at early stage in MsGN models. The overexpression of SOCS1 repress MHC class II and STAT1 phosphorylation which is induced by IFN-γ in mesangial cells. STAT-1 inhibitor could inhibit IFN-γ-induced CIITA promoter activity and MHC class II significantly.

CONCLUSIONS: This study emphasizes the pivotal role of the SOCS1/STAT1 axis in regulating inflammation in mesangial proliferative glomerulonephritis. In addition, it demonstrates that SOCS1 is a critical regulator of cellular sensitivity to IFN-γ-induced CIITA and MHC class II expression in mesangial cells. The negative feedback between the expression of SOCS1 and inflammation may play an important role in the mesangial proliferative glomerulonephritis.