

Abstract Submission No.: A-0505

Tmem30a Protects Against Podocyte Injury Through Suppression of Pyroptosis

Yanpei Hou, Li Wang, Yi Li, Guisen Li

Department of Nephrology, Sichuan Provincial People's Hospital,

Objectives : Podocytopathies, which easily progress to end-stage kidney disease, are increasing worldwide. Podocyte injury plays a vital role in the pathogenesis and progression of proteinuria, as well as decline of renal function; however, the underlying mechanisms of podocyte injury remain unclear.

Methods : Bioinformatic analysis of public datasets was used to identify key genes related to focal segmental glomerulosclerosis (FSGS). Additionally, we examined the expression of podocyte protective proteins (Nephrin and TMEM30A) and pyroptosis protein (NLRP3) in adriamycin (ADR)-induced podocyte injury mouse model and renal tissue collected from patients with FSGS and normal kidney tissues, using multiplexed immunofluorescence staining. Podocyte-specific Tmem30a^{loxP/loxP};NPHS2-Cre mice were constructed and the expression of Nephrin and NLRP3 in renal podocytes was investigated. ADR-induced mouse podocytes and Tmem30a knockdown (Tmem30a^{-/-}) mouse podocytes were treated with the NLRP3 inhibitor to examine the changes in podocyte-related proteins and pyroptosis-related proteins.

Results : TMEM30A and Nephrin expression was significantly downregulated in the kidney tissues of patients with FSGS, ADR-induced mice, and Tmem30a^{loxP/loxP};NPHS2-Cre mice, whereas NLRP3 expression was significantly upregulated, with notable colocalization of the three proteins. Treatment with the pyroptosis inhibitor MCC950 effectively inhibited the expression of NLRP3, prevented the conversion of pro-caspase-1, GSDMD, and pro-IL-1 β into their active forms, and increased the expression of TMEM30A and podocyte-related proteins (WT1 and Nephrin) in ADR-induced mouse podocytes and Tmem30a^{-/-} mouse podocytes.

Conclusions : This study indicates the protective role of TMEM30A in pyroptosis against podocyte injury, making it a potential therapeutic target for podocyte injury.

Figure 1.jpg

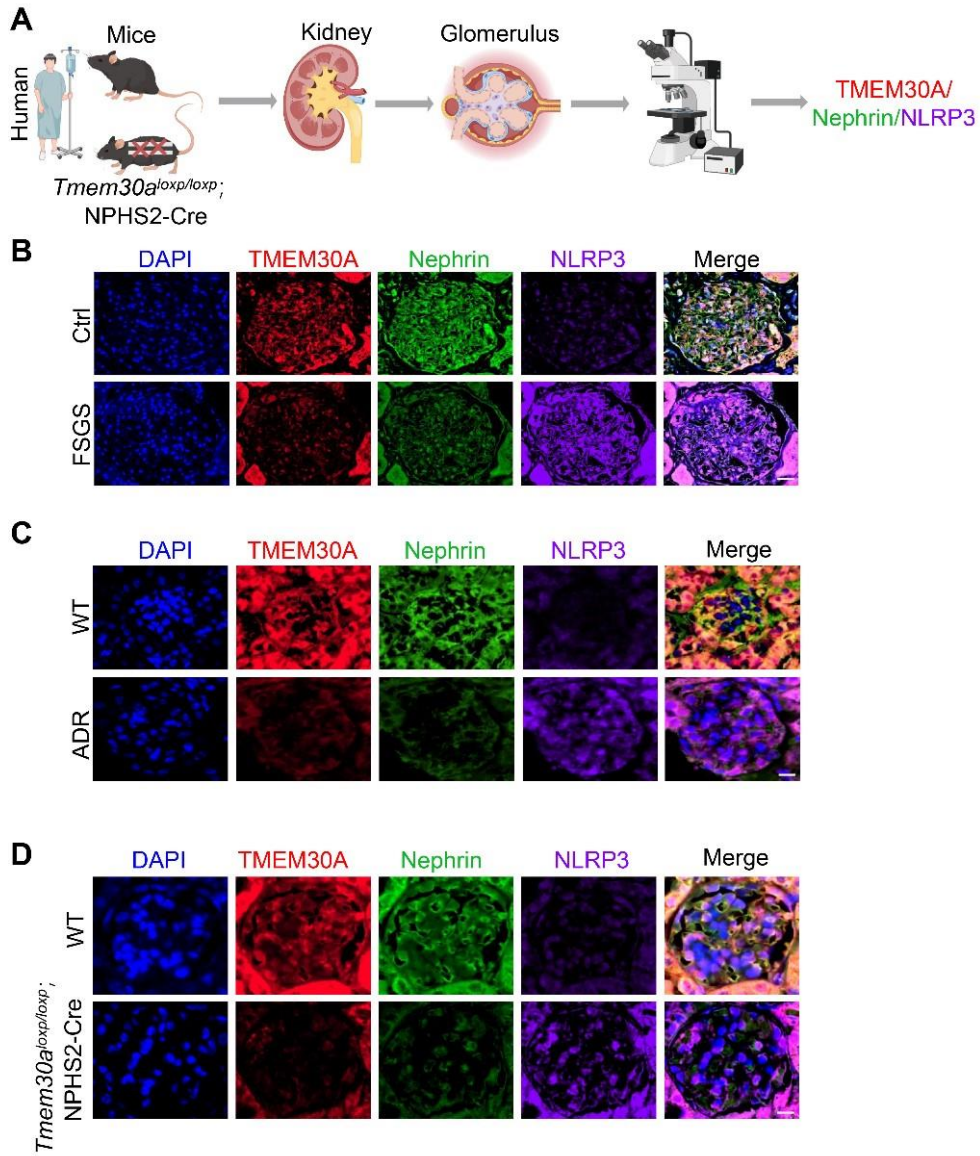
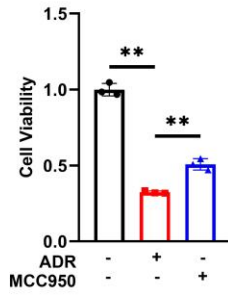
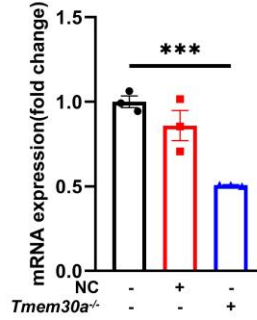


Figure 1.jpg

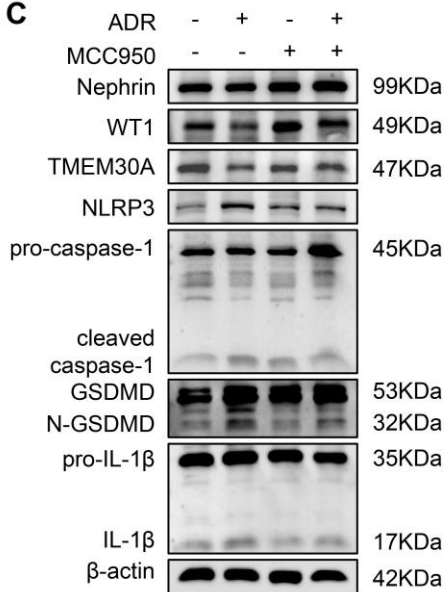
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