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Podocyte and proximal tubular cell participate in the ST2 related renal fibrosis

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Objectives : Soluble ST2 (sST2) which is the receptor of IL-33 is involved in renal inflammation and it is also correlated with disease severity in chronic kidney disease (CKD). Here, we report the ameliorating effect of the ST2 blockade as well as the role of sST2 in the progression renal fibrosis.

Methods : Serum and urine levels of sST2 were measured by ELISA in 296 CKD patients. And ST2 mRNA levels were quantified in blood and urine cells. Immunohistochemistry (IHC) stain of ST2 was performed in human kidney biopsy samples of CKD patients. Further, urine cells were co-stained with podocalyxin and ST2 to characterize the cell type. And fibrosis induced by TGF-beta in primary cultured podocytes and proximal tubular epithelial cells (PTECs) were evaluated with fibronectin, IL-33 and ST2 mRNA expressions. Anti-ST2 monoclonal antibody (mAb) was treated to evaluate the neutralizing effect of ST2 on renal fibrosis.

Results : Serum ($P = 0.002$) and urine ($P < 0.001$) sST2 levels significantly increased as renal function deteriorates. Urine sST2 level adjusted by urine creatinine showed the same pattern. ($P < 0.001$) Serum ($P = 0.023$) and urine ($P = 0.03$) ST2 mRNA expressions were elevated in CKD stage 5 patients compared with other CKD stages. ST2 IHC stain in CKD stage 5 showed 3-fold increase than CKD stage 1. A large portion of urine cells were ST2-rich podocytes/PTECs and the proportion of podocytes/PTECs increased as renal function decreases, when we performed flow-cytometry using ST2, podocalyxin and aquaporin-1 antibody. When the patients were subdivided by 0.5 g/g proteinuria, patients with more proteinuria had a high concentration of urine ST2. ($P = 0.02$) After fibrosis induction in primary cultured podocytes, mRNA and protein expressions of fibronectin, IL-33 and ST2 showed positive correlation with the fibrosis severity. And anti-ST2 dose-dependently reduced

the fibrosis.

Conclusions : Elevated serum and urine sST2 levels are associated with the progression of CKD and podocytes/PTECs involved in this process. ST2-mediated IL-33 signaling may have a considerable role in the progression renal dysfunction. And ST2 blockade is a potential therapeutic target for renal preservation.

Keywords : ST2, podocyte, proximal tubular epithelial cell, chronic kidney disease, renal fibrosis.