No. 2329

Role of Mechanosensitive Ion Channel Piezo2 in the Renal Fibrosis of Salt-Sensitive Hypertension

Miki Nagase

Kyorin University School of Medicine

Summary

Mechanical overload, such as high pressure, stretch, and shear stress, is important in the pathogenesis of hypertensive target organ damage. We reported that a mechanosensor Piezo2 was expressed exclusively in the glomerular mesangial cells and renin-producing cells in normal mouse kidneys, and that Piezo2 expression was increased in the salt-induced hypertensive nephrosclerosis models, in αSMA-negative, Col1-positive perivascular fibroblasts. The purpose of this study was to investigate the role of Piezo2 in the renal fibrosis, especially in the fibrosis caused by excessive salt intake.

We created unilateral ureteral obstruction (UUO) mice and a left nephrectomy + subcutaneous aldosterone infusion + high salt diet model as renal fibrosis models. Cell-specific *Piezo2* KO mice were generated by crossing *Pdgfrb-CreER*$^{T2+/-}$ mice with *Piezo2*$^{FL/FL}$ mice to produce *Pdgfrb-CreER*^{T2}-positive *Piezo2* KO mice and *Pdgfrb-CreER*^{T2}-negative *Piezo2* WT mice, and administering tamoxifen intraperitoneally. Piezo2 expression levels were evaluated by qPCR and immunoblotting. Piezo2-expressing cells were identified by double staining with cell markers using RNAscope in situ hybridization.

In the UUO model created in wild-type mice, Piezo2 expression was significantly elevated. The increased Piezo2 was not localized in the tubular cells, but mainly in the interstitial cells. In double staining, *Piezo2* signals were colocalized with *Col1a1*, *Pdgfrb*, and *Meflin*, but not with *Acta2*. Initially, we could not obtain *Piezo2* KO mice, so we purchased different mouse strain and successfully obtained offsprings. We are currently analyzing the renal phenotype of *Piezo2* KO mice.

Meflin-positive fibroblast is a cell subpopulation that does not differentiate into myofibroblast and acts renoprotectively, suggesting that fibrosis caused by Piezo2-positive fibroblasts may also be involved in reparative fibrosis. We hope to verify this working hypothesis by analyzing *Piezo2* KO mice.