Abstract

Aims/Introduction Nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3 (NLRP3) inflammasomes produce IL-18 upon being activated by various stimuli via the P2 receptors. Previously, we showed that serum and urine IL-18 levels are positively associated with albuminuria in patients with type 2 diabetes, indicating the involvement of inflammasome activation in the pathogenesis of diabetic kidney disease (DKD). In the present study, we investigated whether the administration of suramin, a nonselective antagonist of the P2 receptors, protects diabetic KK.Cg-*A*^{y}/TaJcl (KK-Ay) mice against DKD progression.

Materials and Methods Suramin or saline was administered i.p. to KK-Ay and C57BL/6J mice once every 2 weeks for a period of 8 weeks. Mouse mesangial cells (MMCs) were stimulated with ATP in the presence or absence of suramin.

Results Suramin treatment significantly suppressed the increase in urinary albumin-to-creatinine ratio, glomerular hypertrophy, mesangial matrix expansion, and glomerular fibrosis in KK-Ay mice. Suramin also suppressed the upregulation of NLRP3 inflammasome-related genes and proteins in the renal cortex of KK-Ay

mice. P2X4 and P2X7 receptors were significantly upregulated in the isolated glomeruli of KK-Ay mice and mainly distributed in the glomerular mesangial cells of KK-Ay mice. Although neither ATP nor suramin affected NLRP3 expression in MMCs, suramin inhibited ATP-induced NLRP3 complex formation and the downstream expression of caspase-1 and IL-18 in MMCs.

Conclusions These results suggest that the NLRP3 inflammasome is activated in a diabetic kidney and that inhibition of the NLRP3 inflammasome with suramin protects against the progression of early stage DKD.