Driving the progression of tubulointerstitial fibrosis through the reciprocal regulation of DDR2 and CRAC channel

Chronic kidney disease (CKD) is a global health problem and a significant burden of medical expenditures. Regardless of the cause of CKD, tubulointerstitial fibrosis is an inevitable process leading to end-stage renal failure. Extensive collagen deposition and cross-linking are hallmarks of tubulointerstitial fibrosis. Reversible unilateral ureteral obstruction results indicate that collagen-induced mechanical signaling is associated with the progression of chronic kidney disease. Furthermore, blocking collagen cross-linking inhibits UUO-induced tissue stiffness and maladaptive repair. Mechanistically, activation of the interrelationship between calcium release-activated calcium (CRAC) channels and discoid domain receptor 2 (DDR2) is critical for TGF-β1-induced fibroblast activation, as evidenced by collagen and Lysyl oxidases expression and cell contractility. Through structural modeling and in vitro drug screening tests, we further identified two potential small molecules that can block both CRAC channels and DDR2 signaling. In vivo studies have shown that blocking CRAC channels and DDR2 can effectively inhibit renal fibrosis and renal function decline. Moreover, blocking CRAC channels and DDR2 can also effectively inhibit bleomycin-induced pulmonary fibrosis and increase lung compliance after injury. Together CRAC channels and DDR2 may serve as potential therapeutic targets for the prevention of fibrotic diseases.