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The protective role of proximal tubule specific P21-activated kinase4 (PAK4) in UUO-induced renal fibrosis

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Objectives : Renal fibrosis, a hallmark of chronic kidney disease (CKD), is characterized by excessive extracellular matrix (ECM) accumulation, leading to kidney failure. Tubular injury, particularly in the proximal tubule, is crucial in fibrosis progression. However, the role of P21-activated kinase 4 (PAK4) in renal fibrosis remains underexplored.
Methods : This study investigated the role of PAK4 in proximal tubule injury and fibrosis using a unilateral ureteral obstruction (UUO) mouse model.
Results : Proximal tubule-specific PAK4 knockout ($PAK4^{flox/flox}$; $Ggt1\text{-}Cre^{+}$) mice showed reduced markers of tubular injury, inflammation, and ECM deposition following UUO, indicating a protective role of PAK4 deletion against renal fibrosis. In vitro studies using HK-2 cells further demonstrated that PAK4 inhibition with ND201651 mitigated TGF-β1-induced ECM accumulation by modulating the mTORC1 pathway. Specifically, a direct interaction between PAK4 and S6K1, a key mTORC1 component, was confirmed.
Conclusions : These findings suggest that PAK4 contributes to regulating fibrotic processes in the proximal tubule.

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