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Glutamyl-Prolyl-tRNA Synthetase 1 (EPRS1) as a Novel Therapeutic Target for Kidney Fibrosis

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Objectives : Kidney fibrosis, characterized by excessive accumulation of extracellular matrix (ECM), is a common final pathway of chronic kidney disease (CKD). Glutamyl-prolyl-tRNA synthetase 1 (EPRS1), an aminoacyl-tRNA synthetase, is hypothesized to play a role in kidney fibrosis due to its key function in synthesizing proline-rich proteins such as collagen. However, its involvement in kidney fibrosis remains largely unexplored. In this study, we investigated the role of EPRS1 in kidney fibrosis and evaluated the therapeutic potential of its inhibition.
Methods : EPRS1 expression was analyzed in kidney tissues from CKD patients and folic acid (FA)-induced CKD mice using immunostaining and single-cell analysis. The effects of EPRS1 inhibition were assessed in Eprs1 heterozygous knockout mice ($Eprs1^{+/-}$) and through pharmacological inhibition with EPRS1 inhibitor. In vitro studies were performed using TGF-β-stimulated NRK-49F and HK-2 cells to examine how EPRS1 influences fibroblast activation and kidney mitochondrial dysfunction.
Results : EPRS1 expression was significantly upregulated in fibrotic kidneys, particularly in fibroblasts and proximal tubular cells. Both genetic and pharmacological inhibition of EPRS1 suppressed fibroblast activation, reduced hydroxyproline levels, alleviated fibrosis, and improved kidney function. In vitro, EPRS1 enhanced SMAD3 phosphorylation, promoting fibroblast activation and collagen production in response to TGF-β stimulation. Additionally, EPRS1 activated STAT3 phosphorylation, contributing to tubular damage. Furthermore, EPRS1 played a role in mitochondrial dysfunction in proximal tubular cells, a process that was reversed upon its inhibition.
Conclusions : This study provides novel insights into the role of EPRS1 in kidney fibrosis, identifying it as a critical mediator of fibroblast activation and mitochondrial dysfunction. By modulating both SMAD3 and STAT3 signaling pathways, EPRS1 promotes fibrosis and kidney dysfunction. Importantly, targeting EPRS1 through pharmacological inhibition or genetic suppression holds promising therapeutic potential for mitigating kidney fibrosis.