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> targeting PLD4 could be a novel therapeutic strategy to reverse kidney fibrosis

CHRONIC KIDNEY DISEASE

PLD4 regulates kidney fibrosis

The transmembrane glycoprotein phospholipase D4 (PLD4) regulates fibrogenesis in the kidney, according to new findings from Vishal Vaidya, Priyanka Trivedi and colleagues. They suggest that targeting PLD4 could be a novel therapeutic strategy to reverse kidney fibrosis.

"Our group previously identified PLD4 as one of the most highly upregulated genes in mouse models of kidney fibrosis," explains Vaidya. "Given this substantial upregulation, we hypothesized that PLD4 has a pivotal role in regulating kidney fibrosis and that modulation of PLD4 might enable us to change the course of disease progression."

The researchers now confirm that PLD4 expression is upregulated in mouse models of kidney fibrosis and in biopsy samples from patients with tubulointerstitial fibrosis compared with controls. They also show that global or conditional knockdown of PLD4 in proximal tubular cells or silencing of PLD4 using short interfering RNA (siRNA) protected mice from the development of kidney fibrosis.

In the fibrosis models, global knockdown of PLD4 resulted in increased expression of anti-fibrotic cytokines and the serine protease neutrophil elastase (NE), which degrades extracellular matrix (ECM) proteins; downregulation of transforming growth factor β (TGF-β) and MAPK signalling; and a reduction in scar tissue formation. siRNA silencing of PLD4 had similar anti-fibrotic effects. "These findings provide mechanistic evidence that PLD4 mediates fibrogenesis in the kidney," says Trivedi.

The researchers conclude that PLD4 facilitates fibrogenesis by modulating innate and adaptive immune responses, promoting the TGF-β signalling pathway and inducing the downregulation of NE expression, which potentially contributes to the accumulation of ECM proteins in fibrotic kidneys. They now aim to develop modalities such as small molecules to interfere with PLD4-mediated fibrosis either by inhibiting its binding interactions with fibrogenic mediators or by inducing its degradation.

Ellen F. Carney

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