FIBROSIS

A NEW TARGET FOR RENAL FIBROSIS?

Dysregulation of microRNA (miRNA) miR-324-3p and its target prolyl endopeptidase (Prep) contributes to the progression of experimental nephropathy and may be a therapeutic target for halting renal fibrosis, say researchers. “Our findings are consistent with previous studies showing the involvement of different miRNAs in TGF- β –Smad-driven fibrosis”, explains researcher Daniela Macconi.

To investigate the role of miRNAs in promoting renal fibrosis, Macconi and colleagues studied miRNA expression in microdissected glomeruli from Munich Wistar Fromter (MWF) rats. These rats develop spontaneous progressive nephropathy that is sensitive to treatment with angiotensin-converting-enzyme inhibitors (ACEIs).

Of 365 miRNAs examined, the researchers found miR-324-3p to be the most highly expressed. *In situ* hybridization demonstrated that miR-324-3p localized to glomerular podocytes, parietal cells of the Bowman capsule and, most abundantly, to cortical tubules. Macconi *et al.* then used an *in silico* approach to identify Prep—a serine peptidase involved in angiotensin metabolism and in the synthesis of the antifibrotic peptide Ac-SDKP—as a downstream target of miR-324-3p.

To validate Prep as a target of miR-324-3p, the researchers first transfected cultured tubular cells with a miR-324-3p mimic. “By using different strategies ... we found a functional link between overexpression of miR-324-3p and reduced Prep protein and activity”, says Macconi. Investigation of MWF rats revealed reduced levels of Prep in regions of glomeruli and cortical tubules corresponding to areas of fibrosis.

Administration of an ACEI to MWF rats resulted in reduced glomerular and tubular levels of miR-324-3p and increased levels of Prep. This treatment also increased urinary Ac-SDKP levels and partially normalized renal expression of Ac-SDKP in association with reduced interstitial fibrosis. “An important finding is that the renoprotective effects of ACEIs may result, in part, from modulation of the miR-324-3p–Prep–Ac-SDKP pathway, suggesting that further investigation of this pathway may reveal other antifibrotic targets”, explains Macconi.

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