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GENETICS

Epigenetic reversal attenuates renal fibrosis

Inhibition of kidney fibrosis in mice by administration of bone morphogenetic protein-7 (BMP-7)—a leading candidate for antifibrotic therapy—is associated with reversal of pathologic epigenetic modifications, according to findings from researchers at Göttingen University Medical Center, Germany, and MD Anderson Cancer Center, Houston, USA.

"Chronic kidney disease in humans and mice is invariably associated with aberrant DNA methylation—a process by which genes are turned off—and this strong correlative evidence supports a role for epigenetics in progressive kidney disease," explains lead investigator Michael Zeisberg. Building on previous work that demonstrated promoter hypermethylation of *Rasal1*, which encodes RasGAP-activating-like protein 1, and subsequent silencing of *Rasal1* in kidney fibrosis, the researchers investigated whether antifibrotic therapy with BMP-7 could reverse pathologic hypermethylation of *Rasal1*.

In four mouse models of kidney fibrosis—unilateral ureteral obstruction, streptozotocin-induced diabetic nephropathy, *Col4a3* knockout, and 5/6 nephrectomy—treatment with BMP-7, a potent antagonist of profibrotic TGF-β (a known inducer of aberrant *Rasal1* methylation), inhibited kidney fibrosis and was associated with normalization of *Rasal1* promoter hypermethylation. To investigate the underlying mechanism responsible for this epigenetic correction, the researchers focused on the 10–11 translocation enzymes (Tet1, Tet2, and Tet3)—known regulators of physiological demethylation. In all four fibrosis models, expression levels of Tet3, but not Tet1 or Tet2, were markedly decreased. Furthermore, this reduction could be reversed by effective BMP-7 treatment, confirming the involvement of Tet3 in BMP-7-mediated normalization of *Rasal1* hypermethylation.

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"The kidney has an endogenous mechanism involving Tet3 to correct its aberrant epigenome in disease settings and effective antifibrotic BMP-7 therapy in mice is indeed associated with repair of the epigenome," states Zeisberg. "Epigenetics are a promising therapeutic target and induction of Tet3 might be a potential therapeutic approach to treat renal fibrosis," he concludes.

David Holmes

Original article Tampe, B. *et al.* Tet3-mediated hydroxymethylation of epigenetically silenced genes contributes to bone morphogenic protein 7-induced reversal of kidney fibrosis. *J. Am. Soc. Nephrol.* doi:10.1681/ASN.2013070723