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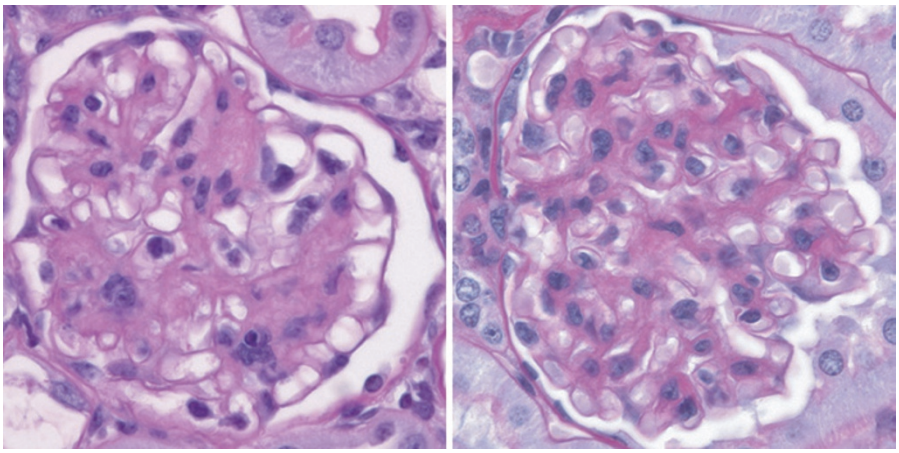
BASIC RESEARCH

An oral cyclic peptide drug to reverse kidney fibrosis?

A peptide agonist that targets the bone morphogenic protein (BMP) 7 receptor, Alk3, reverses fibrosis and facilitates kidney regeneration in several experimental models of renal injury, according to new research. "The most significant findings were the identification of Alk3 as a renoprotective receptor in the kidney and the discovery of a new class of drugs that can target this receptor to repair, regenerate, and reverse fibrosis", explains lead researcher Raghu Kalluri.

BMP7 has been shown to have renoprotective and antifibrotic effects in models of kidney disease. Kalluri and colleagues found that levels of Alk3 were increased early after kidney injury. In addition, deletion of Alk3 from the tubular epithelium resulted in enhanced fibrosis and reduced renal function after exposure to nephrotoxic serum, demonstrating a protective role for Alk3-mediated signaling in the kidney.

The researchers then designed a library of small peptide agonists of BMP signaling that function through Alk3. They investigated one peptide, THR-123, in five different models of kidney disease—ischemic–reperfusion injury, unilateral ureteral obstruction, Alport syndrome, nephrotoxic serum-induced kidney fibrosis and diabetic nephropathy. The peptide attenuated structural kidney damage and suppressed fibrosis in all five models. In diabetic, streptozotocin-treated mice, administration of THR-123 from month 5 to month 6 after the induction of diabetes reversed mesangial matrix expansion compared with that seen prior to THR-123 administration. THR-123 also inhibited tubular atrophy and interstitial volume expansion, reversed renal dysfunction as assessed by levels of blood urea nitrogen, inhibited epithelial-to-mesenchymal transition and reduced macrophage infiltration.



Mice received either vehicle (left) or THR-123 (right) after induction of diabetic nephropathy. Permission obtained from Nature Publishing Group Ltd © Sugimoto, H. *et al. Nat. Med.* doi:10.1038/nm.2629.

Kalluri and colleagues also administered THR-123 in combination with captopril to mice with established renal fibrosis induced by diabetes. Combination treatment had additive beneficial effects, with greater reductions in mesangial matrix expansion, tubular atrophy, interstitial volume expansion, macrophage infiltration and apoptosis compared with captopril alone.

Kalluri says that these results support the development of oral BMP signal agonists for use in humans. "One member in this new class of drugs has completed phase I safety studies ... the results will be reported soon."

Susan J. Allison

Original article Sugimoto, H. *et al*. Activin-like kinase 3 is important for kidney regeneration and reversal of fibrosis. *Nat. Med*. doi:10.1038/nm.2629