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GLOMERULAR DISEASE

# KLF4 promotes podocyte differentiation

The transcription factor Krueppel-like factor 4 (KLF4) promotes podocyte differentiation and protects against the development of proteinuria, say researchers. These new findings suggest that modulation of KLF4 might be a promising strategy for epigenetic control of proteinuric glomerular diseases.

Kaori Hayashi and colleagues previously showed that transient, high-dose treatment with angiotensin-receptor blockers (ARBs) resulted in a sustained decrease in albuminuria in mice with adriamycin (ADM)-induced nephropathy. "Among several candidate genes that we found were upregulated by ARB treatment in human podocytes, we were particularly interested in *KLF4* because KLF4 is reported to contribute to the induction of pluripotent stem cells by activating the expression of epithelial genes during the initial phase of reprogramming," explains Hayashi. "Therefore, we postulated that KLF4 might regulate podocyte phenotype."

Now, the researchers report that KLF4 is expressed at high levels in murine and human podocytes; its expression is decreased in mouse models of proteinuria and in biopsy samples from patients with glomerular disease. Transient induction of KLF4 in injured murine podocytes restored their phenotype and attenuated proteinuria, whereas ADM-induced proteinuria was increased in *Klf4*-knockout mice compared with controls. "These results suggest that a reduction in KLF4 expression might be a common factor that causes or exacerbates kidney disease," says Hayashi.

DNA-methylation profiling indicated that overexpression of KLF4 in podocytes results in a reduction in methylation of the promoter regions of epithelial-cell-specific genes (such as nephrin) and an increase in methylation of the promoter regions of mesenchymal-cell-specific genes (such as vimentin), suggesting that KLF4 modulates podocyte phenotypes by gene-specific epigenetic mechanisms. Hayashi concludes that 'reprogramming' injured podocytes by transient activation of KLF4 might be a novel approach to ameliorate proteinuria in patients with renal disease.

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