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CKD & associated complications

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Selective Tubular Activation of Hypoxia-inducible Factor-2α Has Dual Effects on Renal Fibrosis

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Background: Hypoxia-inducible factor (HIF) is a key transcriptional factor in the response to hypoxia. Although the effect of HIF activation in chronic kidney disease (CKD) has been widely evaluated, the results have been inconsistent until now. This study aimed to investigate the effects of HIF-1α or HIF-2α activation on renal fibrosis according to activation timing in inducible tubule-specific transgenic mice with non-diabetic CKD.
Methods: Mice with tubular selective HIF-2α activation, which have HIF2dPA, PAX8-rtTA, and TetO-Cre, were generated by multiple breeding strategies. For the induction of renal fibrosis and CKD, the mice were fed a custom-made diet containing 0.2% (w/w) adenine for 2 or 4 weeks. Transgenic and wild-type mice were divided into 5 experimental groups: (i) wild-type mice fed a standard diet (control), (ii) wild-type mice fed adenine-containing diet for 2 weeks, (iii) transgenic mice fed adenine-containing diet for 2 weeks with DOX administration at day 0, (iv) transgenic mice fed adenine-containing diet for 4 weeks with DOX administration at day 0, and (v) transgenic mice fed adenine-containing diet for 4 weeks with DOX administration at day 14. Mice were sacrificed at 2 or 4 weeks, and the kidneys were removed for histological evaluation and molecular analysis. We also performed in vitro experiments with cultured renal tubular epithelial cells.
Results: In transgenic mice with CKD, activation of HIF-2α at the beginning of CKD significantly aggravated renal fibrosis, whereas activation at a late-stage of CKD abrogated renal fibrosis, which was associated with restoration of renal vasculature and amelioration of hypoxia. Similarly, renal function assessed by serum creatinine in mice with HIF-2α activation at the beginning of CKD was comparable to that of wild-type CKD mice, but serum creatinine in CKD mice with activation at a late-stage was significantly lower than in wild-type CKD mice. HIF-2α activation in renal tubular cells upregulated mRNA expression of VEGF, PAI-1, lysyl oxidase, Bnip3, type I collagen, fibronectin, and PGK1, suggesting that it induced both profibrotic and antihypoxic pathways. However, tubule-specific HIF-1α activation had no significant effect on increased serum creatinine level or on histologic change in CKD mice. In human IgA nephropathy, expression of HIF-2α and VEGF expression was downregulated at the stage T2 according to the Oxford classification.

Conclusion: Renal tubular HIF-2α activation has dual effects on renal fibrosis, and it could represent a therapeutic target in late-stage CKD when HIF-2α expression is not sufficient to maintain renal vascular integrity.

Keywords: chronic kidney disease, hypoxia-inducible factor, renal fibrosis