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Effect of long-term tubular overexpression of hypoxia-inducible factor-2 alpha on the progressive renal fibrosis in chronic kidney disease model

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Objectives:

Although hypoxia-inducible factor (HIF) is a key transcriptional factor in the response to hypoxia, and the effect of selective tubular activation of HIF-2α on renal fibrosis was demonstrated recently, there is no study for the effect of long-term tubular activation of HIF-2α on the progressive renal fibrosis.

Methods: We are mainly performed using PAX8-rtTA/tetO-Cre/HIF2dPA-HA transgenic mice(Tg). For the induction of renal fibrosis and CKD, the mice were fed a 0.2% adenine-containing diet for 2, 4, and 6 weeks with doxycycline (DOX, 2mg/ml) administration at day 0. Moreover, isolated primary renal tubular epithelial cells (TECs) from Tg mice were divided into one of four groups: the control, DOX (5ug/ml), TGF-β1(10ng/ml), and DOX+TGF-β1 groups (for 24, 48 and 72 h), *in vitro*. For renal function, Cr and BUN were measured, and real-time PCR, western blotting and immunohistochemical staining were performed.

Results: Serum Cr and BUN levels were significantly higher in WT and Tg CKD mice compared with the control mice at 2, 4 and 6 weeks. However, those levels of only 6-week HIF-2α activated CKD mice were significantly decreased compared to those in 6-week WT CKD model. The WB (fibronectin, E-cad/α-SMA, type I collagen) and IHC also showed the increased renal fibrosis in WT CKD mice at 2, 4 and 6 weeks compared with control mice. However, in only 6-week Tg CKD mice, the increased fibrosis was significantly attenuated compared to that in the same week WT CKD mice.In vitro, the increased fibronectin and type I collagen protein expressions after TGF-β1 stimulation were significantly decreased in the 72 h HIF-2α continuous activation except for 24 and 48 h groups.

Conclusions: These findings showed that long-term HIF-2α activation in CKD might inhibit the progression of renal fibrosis and improve renal function, which suggests that long-term renal HIF-2α activation could represent a new therapeutic way in CKD.