The role of HIF-1 in the development of renal fibrosis in mouse UUO model with special reference to HIF-1 dependent gene expression

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Introduction: Hypoxia inducible factor (HIF) activates protective pathway to counteract hypoxia and to prevent from tissue damage in acute kidney injury. However, the role of HIF-1 in the progression of renal fibrosis is controversial. The aim of this study was to evaluate the role of HIF-1 in the development of renal fibrosis with special reference to HIF-1 dependent gene expression of profibrogenic molecules. **Methods:** HIF-1 α flox/flox mice were crossed with mice carrying Cre recombinase-ERT2 fusion gene driven by ubiquitin C promoter (ubc-cre). Ubc-cre+/- HIF-1 α flox/flox mice were given tamoxifen to induce global ablation of HIF-1 α (HIF-1 knock out group). Ubc-cre-/- HIF-1 α flox/flox mice treated with tamoxifen were served as control (wild type group). Mice in both groups were subjected to unilateral ureteral obstruction (UUO). Following 3, 7 and 14 days after UUO, renal gene expression and interstitial fibrosis were assessed. **Results:** We found ureteral obstruction stimulated mRNA expressions of prolyl hydroxylase 3 and glucose transporter-1 in HIF-1 dependent fashion at 3 days and 7 days but not at 14 days after UUO. Although the expression level of fibrosis-related molecules was up-regulated during the development of fibrosis, HIF-1 dependent gene expressions of profibrotic molecules (plasminogen activator inhibitor-1, connecting tissue growth factor, lysyl oxidase like 2, transglutaminase 2) were limited to early onset of renal fibrosis. Global HIF-1 gene depletion significantly attenuated the increase in collagen I mRNA and tended to decrease renal interstitial collagen I deposition at 3 days in UUO kidney. However, HIF-1 deletion did not affect either gene expression of extracellular matrix or renal fibrosis in the obstructed kidney either at 7 days or 14 days after UUO. **Conclusion:** HIF-1 dependent transcriptional activation appears to occur during the development of renal fibrosis. It is suggested that HIF-1 contributions to the development of fibrosis and to the gene expression of profibrotic molecules were limited to the early onset of fibrosis and then declined with the progression of renal fibrosis in mouse UUO model.