Abstract

Diabetic nephropathy (DN) remains the most common cause of end stage renal failure. Nearly 10% of patients with diabetes develop nephropathy. Hyperglycaemia in the kidneys leads to the activation of alternative metabolic pathways of glucose (glycation, activation of protein kinase C, and polyol pathway). These biochemical alterations lead to hypoxia and oxidative stress due to the increased formation of reactive oxygen species (ROS). Cellular response to hypoxia is controlled by hypoxia-induced factor 1 (HIF1), which is involved in the regulation of more than 800 genes. Target molecules of the HIF1 pathway participate in a wide range of physiological and pathological processes, e.g. angiogenesis, energy metabolism, apoptosis, migration, and proliferation. DN is associated with the pathological tissue remodelling process, epithelial-mesenchymal transition (EMT), and inflammation. HIF1 regulates key molecules of these pathological processes. EMT is regulated by TGFβ1, CTGF, and SOX9. The progression of inflammation is regulated by VEGFA and AngII. The exact role of HIF1 signalling in the development of DN is not yet fully understood. This thesis evaluates the functional role of the HIF1 signalling pathway in the development of DN using a global heterozygous mutant with the deletion of the Hif1α gene. Under diabetic conditions, the partial deletion of Hif1α stimulated profibrotic and inflammatory processes in the kidneys. Expression of molecular activators of EMT (Tgfβ1, Ctgf, Sox9) was significantly affected by the combination of diabetic environment and mutation. Partial deletion of Hif1α caused a high variability in the expression of Vegfa. Several Hif1α+/− mutants had 10-fold higher or lower expression when compared to controls. VEGFA levels in glomeruli was significantly affected by the interaction of diabetes and mutation. VEGFA expression in diabetic wt was increased compared to wt control, but also compared to diabetic Hif1α+/−. WT1 is required for a normal podocyte function. Due to the mutation was WT1 expression reduced in wt controls compare to Hif1α+/− controls. Additionally, the level of WT1 was decreased by diabetic environment. Diabetes reduced expression of a negative regulator of apoptosis, Ntn1, in the kidney cortex, which can be associated with an increased number of apoptotic cells in the kidneys. Our results suggest that HIF1α has a protective role in the development of early stage of DN and that impairment of HIF1α pathways may play a functionally causative role in DN and more rapid disease progression.

Key words: Tgfβ1, Ctgf, Sox9, AngII, Vegfa, Wt1, Ntn1, Hif1α+/−

(in Czech)