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The Role of HNF4a Isoforms in Diabetic Kidney Disease Pathogenesis

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Objectives : HNF4α is a transcription factor belonging to the nuclear receptor superfamily, playing a crucial role in gene regulation and various cellular processes. In the kidney, HNF4α is essential for the development of renal proximal tubules. This factor has multiple transcript variants and isoforms generated through alternative splicing, which are associated with various conditions such as Maturity-Onset Diabetes of the Young, Fanconi syndrome and T2DM diabetes mellitus. However, the precise relationship between HNF4α and DKD remain unclear.
Methods : To investigate the role of HNF4α isoforms in DKD, this study analyzed changes in isoform expression using semi-quantitative PCR under both healthy and kidney injury conditions. First, HNF4α isoform expression was examined in human proximal tubular cell lines exposed to high glucose and hypoxia to simulate injury conditions. Second, HNF4α isoform expression was analyzed in healthy human kidney tissues and tissues from patients with diabetic kidney disease.
Results : We observed changes in HNF4α isoform expression in human proximal tubular cells treated with high glucose and hypoxia, conditions that mimic the injury environment in diabetic kidneys. Notably, the major isoforms within each group exhibited distinct expression patterns, with some isoforms showing decreased expression in the injured groups. These trends were also observed in kidney tissue samples from patients with diabetic kidney disease.
Conclusions : These results suggest that HNF4α influences diabetic kidney disease, contributing to a better understanding of its role in DKD pathogenesis. As HNF4α plays an essential role in maintaining specific functions in the proximal tubule cells, further research is needed to determine the specific roles of each of the 12 HNF4α isoforms in DKD, and how their changes in expression contribute to disease pathogenesis. Ultimately, a deeper understanding of these isoform-specific mechanisms could pave the way for novel therapeutic strategies targeting specific HNF4α isoforms to prevent or treat DKD.