Transcriptional regulation of urate transportosome member SLC2A9 by nuclear receptor HNF4α

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Renal tubular handling of urate is realized by a network of uptake and efflux transporters, including members of drug transporter families such as solute carrier proteins and ATP-binding cassette transporters. Solute carrier family 2, member 9 (SLC2A9), is one key factor of this so called ”urate transportosome.” The aim of the present study was to understand the transcriptional regulation of SLC2A9 and to test whether identified factors might contribute to a coordinated transcriptional regulation of the transporters involved in urate handling. In silico analysis and cell-based reporter gene assays identified a hepatocyte nuclear factor (HNF)4α-binding site in the promoter of SLC2A9 isoform 1, whose activity was enhanced by transient HNF4α overexpression, whereas mutation of the binding site diminished activation. HNF4α overexpression induced endogenous SLC2A9 expression in vitro. The in vivo role of HNF4α in the modulation of renal SLC2A9 gene expression was supported by findings of quantitative real-time RT-PCR analyses and chromatin immunoprecipitation assays. Indeed, mRNA expression of SLC2A9 and HNF4α in human kidney samples was significantly correlated. We also showed that in renal clear cell carcinoma, downregulation of HNF4α mRNA and protein expression was associated with a significant decline in expression of the transporter. Taken together, our data suggest that nuclear receptor family member HNF4α contributes to the transcriptional regulation of SLC2A9 isoform 1. Since HNF4α has previously been assumed to be a modulator of several urate transporters, our findings support the notion that there could be a transcriptional network providing synchronized regulation of the functional network of the urate transportosome.

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