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Impact of HNF4Â on drug response and proliferation of human kidney cells

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Hepatocyte nuclear factor 4 α (HNF4α) is a member of the family of nuclear receptors and was first described in the liver where it regulates the expression of many hepatic genes.1 In addition HNF4α is highly expressed in the proximal tubule. In the kidney HNF4α is one of the main transcriptional regulators of drug metabolizing enzymes and transporters.2 Recent studies also report that dysfunction of HNF4α may be associated with cancerous disease.3 Today we know that expression of HNF4α is downregulated in most types of tumor.4 Impaired expression of HNF4α was described in renal cell carcinoma.5 We confirmed this

observation by mRNA expression analysis for HNF4α isoforms 1/7 and 2/8. Since re-expressed HNF4α has shown an antiproliferative effect in human embryonic kidney cells HEK293 we were interested whether up-regulation of HNF4α shows an effect in other human kidney cells such as renal carcinoma cells.6 So we constructed recombinant adenoviruses carrying the coding sequences of HNF4α isoforms 1 and 2. We infected RCCEW cells with these viruses and increased HNF4α expression. Re-expressed HNF4α enhanced

mRNA expression of known HNF4α target genes HNF1α and SHP1, whereas no effect on cell cycle regulators p53, p21 and Cyclin D1 was observed. Furthermore no impact on cellular proliferation of RCC-EW cells was detected. We suppose that HNF4α re-expressed in RCCEW cells might not be active as in HEK293 cells. Maybe gene expression of enzymes regulating cell cycle was not sufficient to reach protein levels, necessary to establish a tumor suppressor effect. In addition increased HNF4α showed no notable activation of CYP3A4 and Pgp genes and had no impact on chemotherapeutic sensitivity of RCC-EW cells.

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