Abstract

von Hippel-Lindau (VHL) disease is a dominantly inherited family cancer syndrome characterized by the development of retinal and central nervous system haemangioblastomas, renal cell carcinoma (RCC) and phaeochromocytoma. Specific germline VHL mutations may predispose to haemangioblastomas, RCC and phaeochromocytoma to a varying extent. Although dysregulation of the hypoxia-inducible transcription factor-2 and JunB have been linked to the development of RCC and phaeochromocytoma, respectively, the precise basis for genotype-phenotype correlations in VHL disease have not been defined. To gain insights into the pathogenesis of RCC in VHL disease we compared gene expression microarray profiles in a RCC cell line expressing a Type 1 or Type 2B mutant pVHL (RCC-associated) to those of a Type 2A or 2C mutant (not associated with RCC). We identified 19 differentially expressed novel VHL target genes linked to RCC development. Eight targets were studied in detail by quantitative real-time polymerase chain reaction (three downregulated and five upregulated by wild-type VHL) and for six genes the effect of VHL inactivation was mimicked by hypoxia (but hypoxic-induction of smooth muscle alpha-actin 2 was specific for a RCC cell line). The potential role of four RCC-associated VHL target genes was assessed in vitro. NB thymosin beta (TMSNB) and proteinase-activated receptor 2 (PAR2) (both downregulated by wt pVHL) increased cell growth and motility in a RCC cell line, but aldehyde dehydrogenase (ALDH)1 and ALDH7 had no effect. These findings implicate TMSNB and PAR2 candidate oncogenes in the pathogenesis of VHL-associated RCC.