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Beta Catenin: A New Kidney Cancer Oncogene

Peruzzi B, Athauda G, and Bottaro DP. The von Hippel-Lindau tumor suppressor gene product represses oncogenic beta-catenin signaling in renal carcinoma cells. *Proc Natl Acad Sci U S A* 103: 14531–6, 2006.

Loss of von Hippel-Lindau (*VHL*) tumor suppressor gene function occurs in familial and most sporadic renal cell carcinoma (RCC) cases, resulting in the aberrant expression of genes that control cell proliferation, invasion, and angiogenesis. The molecular mechanisms by which *VHL* loss leads to tumorigenesis are not yet fully defined. The *VHL* gene product, pVHL, is part of an E3 ubiquitin ligase complex that targets hypoxia inducible factors for polyubiquitination and proteosomal degradation, implicating hypoxia response genes in RCC oncogenesis. *VHL* loss also allows robust RCC cell invasiveness and morphogenesis in response to hepatocyte growth factor (HGF), an important regulator of kidney development and renal homeostasis. Our recent analysis of the mechanism by which pVHL represses HGF-driven invasiveness has revealed another oncogenically relevant pVHL target: β -catenin (Figure 1).

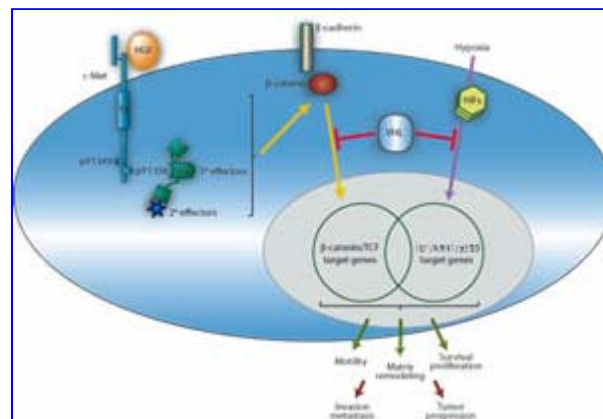


Figure 1. Activation of the hepatocyte growth factor (HGF)/c-Met signaling pathway results in β -catenin tyrosyl phosphorylation, through interactions with the c-Met tyrosine kinase (TK) or with primary and/or secondary effectors. This results in the dissociation of β -catenin from E-cadherin in adherens junctions and its accumulation in the cytosol. If not rapidly ubiquitinated and degraded, cytosolic β -catenin translocates to the nucleus, where it regulates the transcription of genes that mediate processes that are known to contribute to tumorigenesis, malignancy, and metastasis. The

product of the von Hippel-Lindau (*VHL*) tumor suppressor gene has been known to suppress RCC tumorigenesis through the ubiquitination and subsequent proteosomal destruction of hypoxia inducible factors (HIFs). As we recently reported, VHL protein is also critical for targeting cytoplasmic β -catenin for proteosomal destruction in renal epithelial cells; *VHL* gene loss in RCC thus promotes oncogenic signaling through both β -catenin and HIF pathways. ARNT, aryl hydrocarbon receptor nuclear translocator; TCF, T-cell factor; SH2, Src homology 2 domain.

HGF signaling between mesenchymal and adjacent epithelial cell compartments is a major driving force in embryonic kidney morphogenesis and differentiation, and inappropriate HGF pathway activation in cancer can resemble these epithelial-to-mesenchymal transitions (Birchmeier C et al. *Nat Rev Mol Cell Biol* 4: 915–25, 2003). Expression of HGF and its receptor, c-Met, persists in the adult kidney, but striking changes occur in the quality of the response of renal epithelial cells to HGF stimulation upon completion of development. Morphogenic and proliferative responses are minimized, but HGF continues to protect kidney tissue from toxicity and stress, and it counteracts renal fibrosis. Many intracellular c-Met signaling pathways persist through development into adulthood, but how some signals are silenced to provide a homeostatic, as opposed to developmental or pathological, response remains unclear.

Under hypoxic conditions or when the *VHL* gene is mutated or lost, the hypoxia inducible factors that pVHL targets for degradation accumulate, leading to increased expression of hypoxia response genes that shift energy metabolism toward glycolysis and initiate angiogenesis through the increased production of proteins such as vascular endothelial growth factor, platelet-derived growth factor, and c-Met. Hypoxia also enhances HGF signaling through undefined mechanisms and, in turn, promotes invasive growth in cultured cells and mouse tumor models. Cultured *VHL*-negative RCC cells accumulate hypoxia inducible factors aberrantly and respond to HGF with increased motility, extracellular matrix invasion, and branching morphogenesis—responses typical of embryonic renal cells that are repressed in adulthood (Koochekpour S et al. *Mol Cell Biol* 19: 5902–12, 1999). These HGF-driven activities are abolished when wild-type *VHL* gene expression is reconstituted in RCC cells, directly linking loss of *VHL* function to an invasive tumor phenotype.

We recently elucidated the molecular mechanism by which pVHL represses HGF-driven RCC cell invasiveness, hypothesizing that pVHL negatively regulates β -catenin signaling downstream of c-Met in mature renal tubule epithelial cells and that *VHL* loss in RCC permits β -catenin to signal an aberrantly motile and invasive phenotype (Peruzzi B et al. *Proc Natl Acad Sci U S A* 103: 14531–6, 2006). Distinct roles for β -catenin have been established in the maintenance of intercellular adhesion and in the transcriptional activation of genes involved in normal growth and development; intracellular localization of β -catenin away from regions of cell-cell contact is correlated with the latter. Consistent with a shift in the balance of function from adhesion to signaling, we found that HGF stimulated the redistribution of β -catenin from peripheral to cytoplasmic and nuclear pools in *VHL*-

negative RCC cells. In non-tumor, pVHL-positive, renal epithelial cells, *VHL* gene silencing was required to elicit a similar HGF-driven redistribution of β -catenin, matrix invasion, and cellular morphogenesis. Conversely, restoration of pVHL expression in RCC cells led to the repression of HGF-stimulated adherens junction disruption, cytoplasmic β -catenin stabilization, nuclear translocation, and target gene activation. Finally, ectopic expression of an ubiquitination-resistant β -catenin mutant bypassed wild-type *VHL* function, enabling HGF-driven invasion and morphogenesis in cells otherwise incapable of these responses. These findings identify β -catenin as a critical substrate of pVHL and as a novel target for biomarker and drug development in the effort to successfully treat metastatic RCC.

Oncogenic β -catenin signaling has been demonstrated in colon, breast, prostate, and lung carcinomas as well as melanoma (Polakis P. *Cell* 105: 563–6, 2001). In all of these cancers, failure to degrade cytoplasmic β -catenin protein is the common link to oncogenic signaling. In colorectal cancer, mutations in genes involved in β -catenin ubiquitination occur in more than 90% of all tumors. In contrast, mutations in these genes are rare in non-colon cancers. Nonetheless, a wide variety of tumor samples show cytoplasmic and/or nuclear accumulation of β -catenin protein. RCC now joins the list of cancers in which β -catenin contributes to oncogenesis, but through an unexpected relationship with an E3 ligase component specifically lost in most renal cancers: pVHL.

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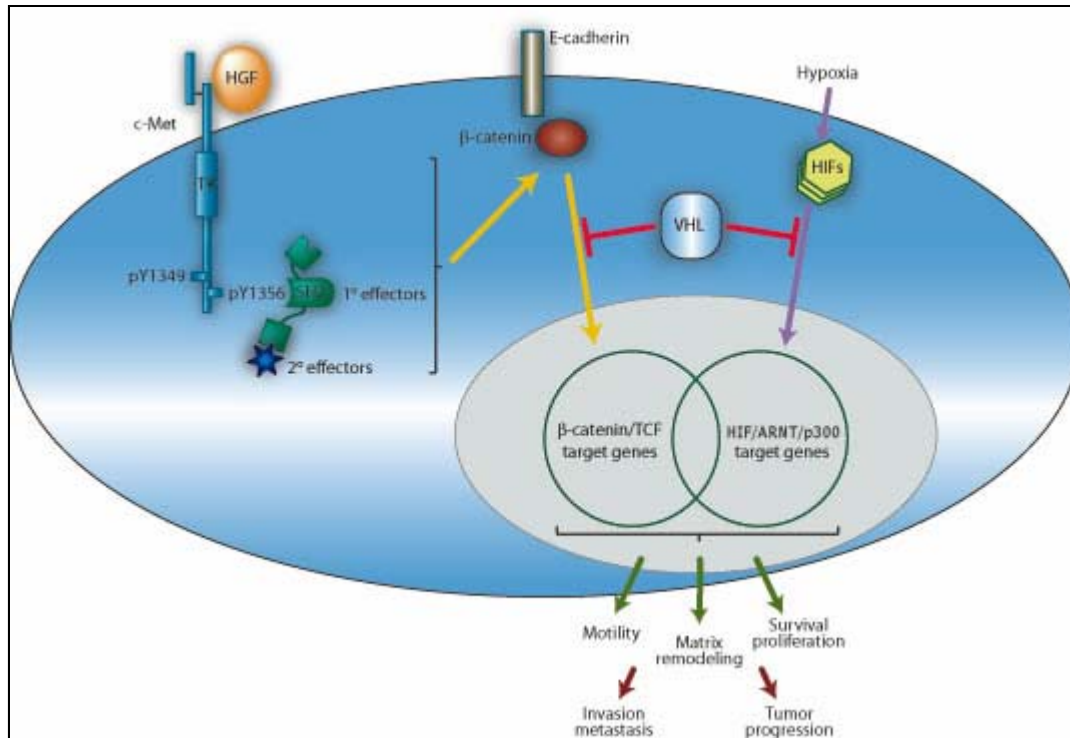


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