# A HIF-regulated VHL-PTP1B-Src signaling axis identifies a therapeutic target in renal cell carcinoma



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Metastatic renal cell carcinoma (RCC) is a molecularly heterogeneous disease that is intrinsically resistant to chemotherapy and radiotherapy. Although therapies targeted to the molecules vascular endothelial growth factor and mammalian target of rapamycin have shown clinical effectiveness, their effects are variable and short-lived, underscoring the need for improved treatment strategies for RCC. Here, we used quantitative phosphoproteomics and immunohistochemical profiling of 346 RCC specimens and determined that Src kinase signaling is elevated in RCC cells that retain wild-type von Hippel-Lindau (VHL) protein expression. RCC cell lines and xenografts with wild-type VHL exhibited sensitivity to the Src inhibitor dasatinib, in contrast to cell lines that lacked the VHL protein, which were resistant. Forced expression of hypoxia-inducible factor (HIF) in RCC cells with wild-type VHL diminished Src signaling output by repressing transcription of the Src activator protein tyrosine phosphatase 1B (PTP1B), conferring resistance to dasatinib. Our results suggest that a HIF-regulated VHL-PTP1B-Src signaling pathway determines the sensitivity of RCC to Src inhibitors and that stratification of RCC patients with antibody-based profiling may identify patients likely to respond to Src inhibitors in RCC clinical trials.
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