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Molecular and cellular mechanisms underlying the heterogeneity of disease manifestations in von Hippel–Lindau disease

Oxygen is vital for aerobic organisms, which have evolved oxygen-sensing mechanisms to adapt to low-oxygen environments at the cellular level. The central effector in this pathway is hypoxia-inducible factor (HIF), whose α-subunits are regulated by the von Hippel–Lindau (VHL) tumor suppressor protein through proteasomal degradation. Functional inactivation of VHL results in stabilization of HIF-α, leading to constitutive activation of hypoxia-responsive genes and an increased risk of tumorigenesis. Germline mutations in the VHL cause von Hippel-Lindau syndrome, a disorder with a variable phenotype characterized by the development of various tumors, including renal cell carcinomas, hemangioblastomas, and pheochromocytomas. However, the molecular basis of this clinical variability remains poorly understood. Our current study in the SFB 1453 "NephGen"aims to decipher the molecular and cellular basis of this clinical heterogeneity by generating a comprehensive set of mutations by precision genome editing in an isogenic background of VHL wildtype-revertant kidney cancer cells.

This study builds on our previous project on nonstop mutations in VHL, which convert the stop into a sense codon, leading to translational readthrough until the next in-frame stop codon (Nat Cell Biol 2020, Nat Commun 2024). Nonstop mutations in VHL are enriched in renal cell carcinoma and result in proteins with short C-terminal extensions that trigger proteasomal degradation. Additionally, these mutations alter translation initiation and start site selection, favoring the expression of longer VHL isoforms (Sci Adv 2025).

Altogether, characterizing clinically relevant VHL mutations will advance our understanding of molecular and cellular mechanisms underlying the heterogeneity of VHL-associated disease manifestations.

Preferred type of presentation

Poster Presentation only

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