SPOP acts as the key regulatory hub in hypoxia induced kidney cancer

Supported by the National Natural Science Foundation of China, the groups of Dr. Liu Jiang at Beijing Institute of Genomics, CAS and Dr. Kevin White from the University of Chicago, reported that the E3 ligase adaptor SPOP acts as the key regulatory hub in hypoxia induced tumorigenesis in kidney cancer. The work has been published in *Cancer Cell* (2014, 25(4): 455—468).

Hypoxic stress and hypoxia-inducible factors (HIFs) play important roles in a wide range of tumors. But limited is known about the mechanism of hypoxia stress on the tumorigenesis. The clear cell Renal Cell Carcinoma (ccRCC), the most common type of kidney cancer, is a good model to explore the adaption of cancer to a hypoxia microenvironment. Although recent targeted therapies that use inhibitors against VEGF, PDGF and mTOR signaling pathways have been developed, the clinical outcome is very limited, suggesting that more important targets are required to be identified.

Here their studies demonstrate that SPOP is a direct transcriptional target of HIFs in ccRCC. Furthermore, hypoxia stress can result in cytoplasmic accumulation of SPOP which is sufficient to induce tumorigenesis. This tumorigenic activity occurs through the ubiquitination and degradation of multiple regulators of cellular proliferation and apoptosis, including the tumor suppressor PTEN, ERK phosphatases, the pro-apoptotic molecule Daxx and the Hedgehog pathway transcription factor Gli2. These targets are down-regulated in all primary ccRCC examined, further supporting that SPOP orchestrates cancer phenotypes through the modulation of several critical cellular pathways. These results have elucidated a major mechanism that contributes to the tumorigenesis in ccRCC, connecting hypoxia response and ubiquitin-mediated degradation of tumor suppressors. The oncogenic role of cytoplasmic SPOP makes it a promising candidate for therapeutic intervention.

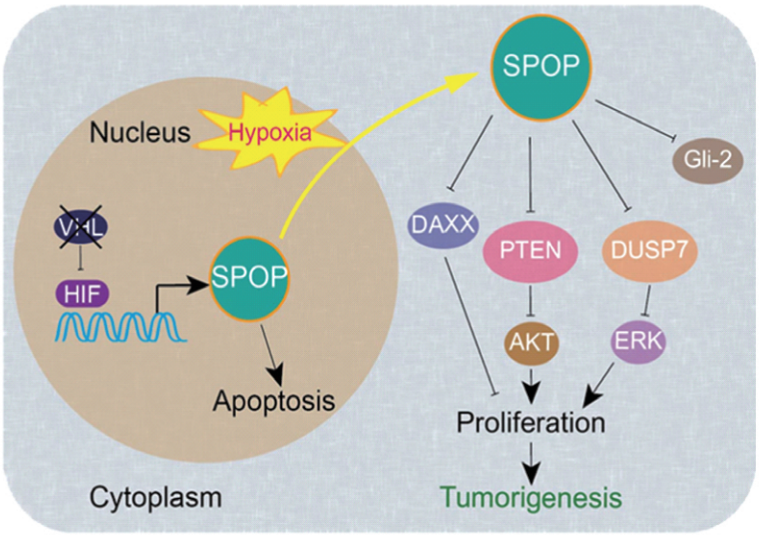

Figure Graphic abstract shows the role of SPOP in promoting kidney cancer. HIF regulates the expression of SPOP in ccRCC. Hypoxia drives SPOP accumulation in cell cytoplasm, which promotes the tumorigenesis. SPOP mediates the ubiquitination and degradation of PTEN and DUSP7, which result in promoting cancer cells proliferation and kidney tumorigenesis.