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Signaling

Major finding: EGLN1-mediated prolyl-hydroxylation suppresses activity of AKT by promoting its recognition by VHL.

Clinical relevance: Some cancer-associated *AKT1* and *AKT2* mutations reduce AKT hydroxylation to hyperactivate AKT.

Impact: AKT targeting may be effective in VHL-deficient or hypoxic tumors.

HYPOXIA PREVENTS AKT HYDROXYLATION AND PROMOTES AKT HYPERACTIVATION

VHL is a tumor suppressor commonly inactivated in von Hippel-Lindau (VHL) disease and sporadic clear-cell renal cell carcinomas (ccRCC). Loss of *VHL* increases sensitivity to mTOR inhibitors, and *VHL*-defective renal carcinomas are associated with AKT hyperactivation. Thus, Guo and colleagues hypothesized that VHL might directly regulate AKT, and consistent with this hypothesis, deletion of *Vhl* in mouse embryonic fibroblasts or mutation of *VHL* in patients with ccRCC increased AKT activity as indicated by increased phosphorylation of threonine 308 (pT308-AKT). Additionally, exposing cells to hypoxic conditions or an inhibitor of the oxygen-dependent hydroxylase EGLN1 reduced AKT phosphorylation in VHL-proficient, but not VHL-deficient, ccRCC cells, indicating that AKT inhibition by VHL is oxygen dependent. AKT bound to EGLN1, and binding of VHL to AKT and subsequent suppression of AKT activity required EGLN1, whereas depletion of EGLN1 increased AKT activity. Mechanistically, EGLN1 hydroxylated AKT at proline residues 125 and 313, and VHL bound to hydroxylated AKT to suppress its activation in an E3 ubiquitin ligase-independent manner through PP2A-mediated dephosphorylation of pT308-AKT. Hydroxylation-deficient AKT mutants induced enhanced anchorage-independent growth *in vitro* and tumor formation *in vivo* compared with wild-type AKT, demonstrating that hydroxylation of AKT modulates oncogenic signaling. Moreover, two cancer-associated mutations, $AKT1^{G311D}$ and $AKT2^{P127N}$, were identified that reduce AKT hydroxylation, disrupt the VHL–AKT interaction, and enhance AKT activation. Taken together, these results indicate that hypoxia and defects in the VHL–EGLN pathway lead to hydroxylation-dependent hyperactivation of AKT, and suggest that targeting the AKT pathway may be effective in patients with VHL-deficient tumors as well as more generally in hypoxic tumors. ■

Guo J, Chakraborty AA, Liu P, Gan W, Zheng X, Inuzuka H, et al. pVHL suppresses kinase activity of Akt in a proline-hydroxylation–dependent manner. Science 2016;353:929–32.

Hepatocellular Carcinoma

Major finding: GOLM1 promotes hepatocellular carcinoma (HCC) metastasis by enhancing EGFR/RTK signaling.

Mechanism: GOLM1 promotes EGFR/RTK anchoring to the trans-Golgi network and recycling to the plasma membrane.

Impact: GOLM1 is linked to poor survival in patients with HCC and GOLM1 targeting may block metastasis.

GOLM1 PROMOTES HCC METASTASIS BY REGULATING EGFR/RTK RECYCLING

Receptor tyrosine kinase (RTK) signaling can promote transformation and metastasis via multiple mechanisms, including defects in RTK endocytosis and recycling that increase RTK availability at the plasma membrane to enhance growth factor signaling. After RTKs are activated by ligand binding, they are internalized and undergo Golgi-mediated sorting leading to degradation or recycling, but it is unclear how the Golgi-related proteins that regulate these processes contribute to cancer and metastasis. Ye and colleagues found that the Golgi-related golgi membrane protein 1 (*GOLM1*) was upregulated in hepatocellular carcinoma (HCC) metastases compared to metastasis-free HCC and normal liver tissue. Further, in patients with HCC, high expression of GOLM1 was associated with early tumor recurrence and reduced overall survival. Consistent with these findings, GOLM1 depletion in HCC cell lines expressing high levels of GOLM1 reduced proliferation, migration, and invasion *in vitro*, and reduced tumor growth and lung metastases in tumor xenografts *in vivo*, indicating that GOLM1 promotes HCC growth and metastasis. GOLM1 regulates EGFR/RTK signaling by binding to activated and internalized EGFR, promoting EGFR recycling and return to the plasma membrane, and preventing EGFR degradation. The physical interaction between GOLM1 and EGFR was required for the GOLM1-mediated enhancement of cell migration, and GOLM1 mediated the polarized delivery of EGFR from the Golgi complex to the leading edge of HCC cells to promote migration and metastasis. The endosomal recycling compartment GTPase RAB11 is known to be involved in recycling RTKs from the trans-Golgi network to the plasma membrane, and GOLM1-mediated EGFR/RTK recycling was shown to require RAB11 with the GOLM1/RAB11/EGFR complex facilitating EGFR recycling to the plasma membrane. Collectively, these findings indicate that GOLM1 may promote metastasis in patients with HCC by regulation of EGFR/RTK recycling, and suggest that therapeutic targeting of GOLM1 may be a potential strategy for preventing metastasis in patients with HCC. ■

Ye QH, Zhu WW, Zhang JB, Qin Y, Lu M, Lin GL, et al. GOLM1 Modulates EGFR/RTK cell-surface recycling to drive hepatocellular carcinoma metastasis. Cancer Cell 2016;30:444–58.

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AACR American Association for Cancer Research

CANCER DISCOVERY

Hypoxia Prevents AKT Hydroxylation and Promotes AKT Hyperactivation

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