Stem Cells

Major finding: Hypoxia inactivates DYRK1, preventing ID2 phosphorylation and promoting CSCs and HIF2α stabilization.

Mechanism: DYRK1-driven phosphorylation of ID2 at Thr27 prevents ID2 from disrupting the VCB–CUL2 complex.

Impact: Loss of DYRK1-mediated regulation of ID2 and HIF2α may facilitate cancer progression.

HYPOXIA PROMOTES CANCER STEM CELLS VIA ID2-DEPENDENT VHL INACTIVATION

The hypoxia-inducible transcription factor α (HIFα) proteins mediate cellular responses to hypoxia, and HIFα signaling is disrupted in cancer by mutations in von-Hippel Lindau (*VHL*). Both HIF2α and inhibitor of DNA binding 2 (ID2) have been implicated as critical regulators of cancer stem cells (CSC). However, the pathways by which these proteins maintain CSC stemness are not well understood. To investigate potential cross-talk between HIF2α and ID2 in CSCs, Lee and colleagues used mass spectrometry to identify Ser14 and Thr27 as sites of phosphorylation on ID2. Mutation of ID2 Thr27 to an unphosphorylatable Ala residue increased the ability of neural stem cells to form neurospheres. A conserved putative binding motif for the dual specificity tyrosine-(Y)-phosphorylation regulated kinase 1A (DYRK1A) and DYRK1B was found surrounding the Thr27 residue. Consistent with this result, ID2 co-precipitated with DYRK1A/B, and DYRK1 knockdown reduced ID2 phosphorylation at Thr27, indicating that ID2 is phosphorylated by DYRK1. Under normoxia, the activity of DYRK1 kinases was potentiated by prolyl hydroxylase 1, whereas hypoxia reduced Thr27 phosphorylation by preventing DYRK1 autophosphorylation and activity. DYRK1-mediated phosphorylation of ID2 regulated glioma stem cells by reducing the accumulation of HIF2α. ID2 interacted with Elongin C, a component of the VCB–cullin 2 (CUL2) ubiquitin ligase complex, as well as VHL, and DYRK1-mediated phosphorylation of ID2 blocked these interactions. In glioma cells, hypoxia promoted the interaction between VHL and ID2 and disrupted the association with CUL2, allowing for HIF2α stabilization by dissociation from the ubiquitin ligase and preventing ubiquitin-mediated proteasomal degradation. In human glioblastomas, high ID2 activity was associated with increased HIF2α transcriptional activity. Further, deletion of *Id1* and *Id2* in a mouse model of glioma reduced HIF2α protein expression, and DYRK1B expression in glioma xenografts reduced tumor growth and prolonged survival. Together, these data provide a mechanism by which DYRK1-driven phosphorylation of ID2 leads to HIF2α destabilization, loss of stem cell traits, and tumor reduction. ■

Lee SB, Frattini V, Bansal M, Castano AM, Sherman D, Hutchinson K, et al. An ID2-dependent mechanism for VHL inactivation in cancer. Nature 2016;529:172–7.

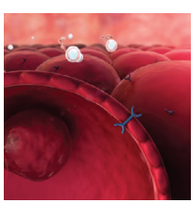
Hematologic Cancers

Major finding: Mice lacking AIRAPL develop myeloproliferative neoplasms caused by disrupted IGF1 signaling.

Mechanism: AIRAPL binds to pro-IGF1R and promotes its ubiquitination and proteasomal degradation.

Impact: IGF1R inhibitors may have promise as potential therapeutics to treat myeloproliferative neoplasms.

DEREGULATION OF IGF1R PROTEOSTASIS PROMOTES MYELOID TRANSFORMATION



Arsenite-inducible RNA-associated protein-like (AIRAPL; encoded by *ZFAND2B*) is an evolutionarily conserved endoplasmic reticulum protein known to regulate cellular proteostasis in *Caenorhabditis elegans*, but its function in mammals is unknown. Osorio and colleagues generated a *Zfand2b*$^{-/-}$ mouse, which has a number of defects including a shortened lifespan, progressive weight loss, splenomegaly due to extramedullary hematopoiesis and myeloid lineage expansion, elevated peripheral blood leukocytes, and increased myeloid cells that collectively recapitulate myeloproliferative neoplasms (MPN). *Zfand2b*$^{-/-}$ mice had increased expression and phosphorylation of IGF1R, and *in vitro* overexpression of AIRAPL led to a reduction in IGF1R levels that was reversible by proteasome inhibition, suggesting a mechanism of AIRAPL-mediated IGF1R regulation involving ubiquitination and degradation by the proteasome. Consistent with these findings, AIRAPL expression increased IGF1R monoubiquitination, and AIRAPL immunoprecipitated with proteasome and ER-associated degradation subunits. AIRAPL associated only with pro-IGF1R, and reduced the levels of mature IGF1R translocated out of the ER, indicating that AIRAPL modulates IGF1R levels by regulating the translocation and degradation of IGF1R. *Igf1r* haploinsufficiency or inhibition in *Zfand2b*$^{-/-}$ mice resulted in a reduction in the MPN phenotypes, supporting a role for IGF1R as a driver of MPN in *Zfand2b*$^{-/-}$ mice. The mouse data were validated in human MPNs, which did not express AIRAPL and exhibited increased IGF1R expression. Increased IGF1R expression associated with AIRAPL loss was similarly observed in a MPN mouse model (*Jak2*^{V617F}), and in acute myeloid leukemia cell lines with the *JAK2*^{V617} mutation, IGF1R inhibition induced growth arrest, whereas overexpression increased proliferation. Mechanistically, *ZFAND2B* expression was found to be regulated in MPNs by the miRNA miR-125a-3p, and the reduction of this miRNA resulted in a reversion of the myeloproliferative phenotype. Altogether, these findings indicate that AIRAPL acts as a tumor suppressor in myeloid cells by negatively regulating IGF1R and provide a rationale for evaluation of IGF1R inhibitors in patients with MPNs. ■

Osorio FG, Soria-Valles C, Santiago-Fernández O, Bernal T, Mittelbrunn M, Colado E, et al. Loss of the proteostasis factor AIRAPL causes myeloid transformation by deregulating IGF-1 signaling. Nat Med 2016;22:91–6.