Oncogenes

Major finding: YAP1-mediated transcription overcomes oncogenic KRAS addiction and promotes tumor-cell survival.

Mechanism: YAP1 cooperates with TEAD2 and FOS to regulate cell-cycle and EMT genes, respectively.

Impact: Targeted inhibition of YAP1 may limit tumor relapse in pancreatic cancer and other RAS-driven tumors.

THE TRANSCRIPTIONAL COACTIVATOR YAP1 SUBSTITUTES FOR ONCOGENIC KRAS

Many human cancers, including pancreatic ductal adenocarcinoma (PDAC), harbor activating mutations in *KRAS* and exhibit a dependence on sustained expression of oncogenic KRAS for tumor survival. However, despite initial tumor regression following KRAS suppression, acquired resistance enables KRAS-independent tumor recurrence in some cases. To identify the mechanisms underlying this escape from oncogenic KRAS addiction, Kapoor, Yao, Ying, and colleagues analyzed spontaneous relapse tumors in a genetically engineered mouse model of PDAC driven by inducible $Kras^{G12D}$ expression. Relapse tumors that did not reactivate $Kras^{G12D}$ expression were characterized by amplification of the gene encoding the transcriptional coactivator YAP1, which was required for tumor growth in the absence of $Kras^{G12D}$ and substituted for oncogenic KRAS to promote tumor maintenance. The ability of YAP1 to induce tumor recurrence was dependent on its interaction with the TEA domain family member 2 (TEAD2) transcription factor and activation of cell-cycle and DNA replication genes in cooperation with E2F1. Intriguingly, *YAP1* expression was also elevated in KRAS-independent human PDAC cells. Consistent with these findings, Shao, Xue, and colleagues identified *YAP1* in a genome-scale screen for genes that rescued the viability of *KRAS*-mutant human cancer cell lines following KRAS suppression and found that YAP1 was necessary for KRAS-induced transformation *in vitro*. YAP1 recapitulated oncogenic KRAS signaling and promoted tumor-cell survival via regulation of AP-1 transcription factors, in particular FOS, and coordinate stimulation of an epithelial–mesenchymal transition (EMT) transcriptional program by YAP1 and FOS. In addition, increased nuclear localization of YAP1, upregulation of YAP1 transcriptional activity, and enrichment of an EMT gene signature were associated with bypass of KRAS suppression and tumor relapse in a mouse model of KRAS-driven lung cancer. Taken together, these results establish YAP1 activation as a mechanism by which tumors may overcome KRAS dependence and suggest that inhibition of YAP1 may be therapeutically beneficial in RAS-driven cancers. ■

Kapoor A, Yao W, Ying H, Hua S, Liewen A, Wang Q, et al. Yap1 activation enables bypass of oncogenic Kras addiction in pancreatic cancer. Cell 2014;158:185–97.

Shao DD, Xue W, Krall EB, Bhutkar A, Piccioni F, Wang X, et al. KRAS and YAP1 converge to regulate EMT and tumor survival. Cell 2014;158:171–84.

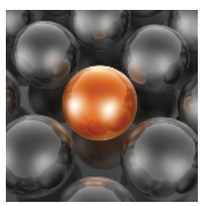
Medulloblastoma

Major finding: Rare, quiescent SOX2$^+$ cells drive SHH group medulloblastoma propagation and are chemoresistant.

Mechanism: SOX2$^+$ cells express a neuronal stem cell transcriptional program that promotes self-renewal *in vivo*.

Impact: Targeting the SOX2$^+$ cell population may clinically benefit patients with SHH medulloblastoma.

QUIESCENT SOX2$^+$ CELLS UNDERLIE SHH MEDULLOBLASTOMA GROWTH AND RELAPSE



The finding that approximately 30% of medulloblastomas display deregulated sonic hedgehog (SHH) pathway signaling has led to the clinical development of Hedgehog pathway inhibitors in SHH medulloblastomas, but reports of resistance suggest that a certain cell population may be inherently refractive to SHH pathway inhibition. A subset of medulloblastoma cells expressing neuronal stem markers have been shown to circumvent irradiation by entering into quiescence, prompting Vanner and colleagues to examine whether specific subpopulations of cells can drive tumor cell expansion in SHH medulloblastoma. Characterization of tumors formed in the $Ptch1^{+/-}$ mouse model of SHH medulloblastoma revealed phenotypic heterogeneity, with the bulk of the tumor expressing markers of neural progenitor cells or nascent neurons and fewer than 5% of cells expressing the neural stem cell marker SOX2. Assessment of proliferative capacity revealed slow, continuous cycling of SOX2$^+$ cells that was indicative of quiescence, and SOX2$^+$ cells were shown to possess self-renewal and differentiation capacity *in vitro* and *in vivo*. Lineage tracing experiments further confirmed that the rare SOX2$^+$ cell population is self-renewing and capable of differentiating into the rapidly cycling cells that make up the bulk of tumors, implicating SOX2$^+$ cells as tumor-propagating cells in SHH medulloblastoma. Importantly, treatment of tumors with an antimitotic agent or the Smoothened inhibitor vismodegib led to an enrichment of SOX2$^+$ cells, suggesting that these tumor-propagating cells are spared by traditional or targeted therapies and may comprise a reservoir for tumor relapse. Consistent with this concept, high SOX2 expression and a SOX2$^+$ cell signature correlated with poor patient prognosis. A screen for compounds that target primary SOX2-expressing SHH medulloblastoma cells identified mithramycin, which limited self-renewal and tumor growth in the $Ptch1^{+/-}$ model. These findings implicate the SOX2$^+$ quiescent cell population in SHH medulloblastoma propagation and provide a rationale for therapeutic strategies that target this population as well as the tumor bulk. ■

Vanner RJ, Remke M, Gallo M, Selvadurai HJ, Coutinho F, Lee L, et al. Quiescent Sox2$^+$ cells drive hierarchical growth and relapse in Sonic Hedgehog subgroup medulloblastoma. Cancer Cell 2014;26:33–47.