Published OnlineFirst January 7, 2016; DOI: 10.1158/2159-8290.CD-RW2016-001

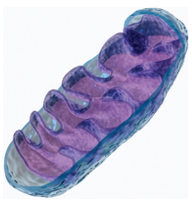
Oncogenes

Major finding: MYC indirectly inhibits YAP/TAZ activity to promote growth of mammary tumors.

Mechanism: MYC induction of PLD6 drives mitochondrial fusion-mediated activation of AMPK, which inhibits YAP.

Impact: Changes in mitochondrial dynamics are key to the MYC-activated transcriptional program of growth.

MYC INDIRECTLY REPRESSES YAP/TAZ ACTIVITY IN MAMMARY TUMORS



During development, the transcription factor MYC, which drives proliferation and regulates various cellular processes such as growth and apoptosis, promotes the expansion and differentiation of progenitor populations, resulting in depletion of the quiescent stem cell population. To elucidate the role of MYC-driven transcriptional programs in stem cell maintenance, von Eyss and colleagues transduced human mammary epithelial cells (HMLE), which exhibit the self-renewal properties of mammary stem cells and form mammospheres in culture, to inducibly express *MYC*. Expression of *MYC* ablated the sphere-forming potential of $CD44^{hi}/CD24^{lo}$ HMLEs, and RNA sequencing and MYC chromatin immunoprecipitation sequencing (ChIP-seq) revealed that the induction of *MYC* specifically repressed expression of the target genes of yes-associated protein 1 (YAP1) and tafazzin (TAZ) in the $CD44^{hi}/CD24^{lo}$ population. The authors showed that MYC inhibited YAP/TAZ activity in $CD44^{hi}/CD24^{lo}$ HMLEs *in vitro* and mammary stem cells *in vivo* by driving the expression of phospholipase D family, member 6 (*PLD6*), and not via large tumor suppressor kinase 1 (LATS) and RHO GTPase, two known upstream regulators of YAP/TAZ activity. Mechanistically, MYC-induced upregulation of *PLD6*, which facilitates mitochondrial fusion, led to activation of 5′ AMP-activated protein kinase (AMPK), which phosphorylated YAP and subsequently prevented transcription of YAP/TAZ target genes. To ascertain the role of this mechanism in tumorigenesis, a dominant-negative *MYC* allele was inducibly expressed in a transgenic *Wnt* mouse model, which resulted in differentiated tumors that exhibited decreased proliferation and AMPK activity, and increased nuclear YAP. Consistent with these findings, both MYC and PLD6 were highly expressed in tumors from patients with triple-negative breast cancer and predictive for poor patient prognosis, and elevated *PLD6* expression correlated with high MYC activity and decreased YAP/TAZ activity. Together, these results identify a negative regulatory pathway inhibiting YAP activity that is mediated by a MYC-induced transcriptional program of growth in mammary tumors. ■

Von Eyss B, Jaenicke LA, Kortlever RM, Royla N, Wiese KE, Letschert S, et al. A MYC-driven change in mitochondrial dynamics limits YAP/TAZ function in mammary epithelial cells and breast cancer. Cancer Cell 2015;28:743–57.

Ovarian Cancer

Major finding: The ReACp53 peptide reactivates p53 and reduces the growth of p53-mutant ovarian carcinomas.

Approach: ReACp53 was rationally designed from the LTIITLE amyloid adhesive segment of p53 to block aggregation.

Impact: Inhibiting p53 aggregation is a promising strategy for treating p53-mutant tumors.

BLOCKING p53 AGGREGATION RESTORES ITS ACTIVITY AND SUPPRESSES TUMORS

The essential tumor suppressor p53 is inactivated by mutations in over half of human tumors, with the highest mutation rate occurring in high-grade serous ovarian carcinomas (HGSOC). One mechanism of p53 inactivation is through mutations that partially unfold the protein, resulting in p53 aggregates. Currently, no therapies are available to restore p53 function. Soragni and colleagues developed a cell-permeable peptide inhibitor of p53 aggregation, ReACp53, to determine if blocking aggregation could restore p53 function and reduce tumor growth. The rational design was based on the X-ray structure of the LTIITLE amyloid adhesive segment of p53, which is sufficient for p53 aggregation. ReACp53 prevented p53 aggregation *in vitro* and in cells from patients with HGSOC. In HGSOC cell lines, ReACp53 induced cell death by apoptosis and necroptosis, and blocked cell-cycle progression. In a three-dimensional culture system, human primary uterine fibroblasts expressing dominant-negative $p53^{R175H}$ were responsive to ReACp53 and exhibited reduced growth and increased apoptosis. Further, in organoid cultures, ReACp53 induced cell death in HGSOC cells with aggregating mutant p53, but not in cells with normally folded wild-type p53. RNA sequencing of organoids indicated that p53 targets were upregulated by ReACp53 treatment, including the genes encoding p21, GADD45B, PUMA, THBS1, NOXA, and DRAM1, as well as genes involved in cell proliferation and cell death. *In vivo*, ReACp53 was well tolerated and stable, with approximately 20% of the peak ReACp53 still present in the circulation after 24 hours, and reduced tumor volume in HGSOC xenograft models and a physiologic intraperitoneal disseminated disease model. Altogether, these data indicate that ReACp53 blocks p53 aggregation, promotes p53 reactivation, and reduces HGSOC growth and viability. This suggests that inhibiting the aggregation of p53 may be a viable strategy to reactivate it and suppress tumor growth in patients with HGSOC and other p53-mutant tumors. ■

Soragni A, Janzen DM, Johnson LM, Lindgren AG, Nguyen AT-Q, Tiourin E, et al. A designed inhibitor of p53 aggregation rescues p53 tumor suppression in ovarian carcinomas. Cancer Cell 2016;29:90–103.

Note: *Research Watch* is written by *Cancer Discovery* editorial staff. Readers are encouraged to consult the original articles for full details. For more Research Watch, visit *Cancer Discovery* online at http://cancerdiscovery.aacrjournals.org/content/early/by/section.

AACR American Association for Cancer Research

CANCER DISCOVERY

MYC Indirectly Represses YAP/TAZ Activity in Mammary Tumors

Cancer Discov 2016;6:121. Published OnlineFirst January 7, 2016.