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Chemotherapy

Major Finding: PRIMPOL shields replication forks after multiple rounds of cisplatin in BRCA-deficient cancer cells.

Mechanism: The protective effect relies on PRIMPOL's primase activity and is dependent on the ATR pathway.

Impact: This study elucidates the role of PRIMPOL in the DNA-damage response in cells treated with cisplatin.

THE PRIMPOL PROTEIN SHIELDS REPLICATION FORKS IN BRCA-DEFICIENT CELLS

BRCA proteins shield reversed replication forks, protecting them from damage that could otherwise be incurred during DNA-replication stress, such as that caused by some chemotherapeutic agents. However, cells of many cancer types (particularly breast and ovarian cancers) commonly have inactivating mutations in BRCA proteins. Quinet and colleagues studied the ways DNA replication is altered in BRCA1-deficient cancer cells repeatedly treated with cisplatin, a DNA–cross-linking chemotherapy drug often used to treat ovarian cancers. They found that in a *BRCA1*-null human ovarian cancer cell line and a human osteosarcoma cell line depleted for *BRCA1* using siRNA, repeated dosing with cisplatin prevented the degradation of nascent DNA strands typically seen with replication stress in BRCA-deficient cells, indicating a compensatory mechanism must have been activated. Further experiments revealed that this compensatory mechanism was based on PRIMPOL, a DNA polymerase and primase involved in translesion DNA synthesis; specifically, the mechanism was dependent on PRIMPOL's primase activity, not its polymerase activity. The PRIMPOL-mediated adaptive response to multiple rounds of cisplatin treatment required the activity of the ATR pathway, named for the serine/threonine kinase ATR, which is involved in the DNA-damage response. Overexpression of PRIMPOL alone appeared to be sufficient to prevent deleterious levels of replication-fork reversal following cisplatin dosing in BRCA1-deficient cells, and suppressing fork reversal in both BRCA1-deficient and BRCA1-proficient cells caused a shift toward PRIMPOL-mediated DNA repriming after cisplatin treatment. Hinting at the potential clinical relevance of these findings, PRIMPOL overexpression in BRCA1-deficient cells reduced their sensitivity to treatment with the combination of an ATR inhibitor and cisplatin, which is currently being tested in clinical trials. Further, PRIMPOL appeared to be indispensable for cell survival in the absence of BRCA1, implying that targeting PRIMPOL may be a useful strategy. Collectively, these findings establish a new role for PRIMPOL in the response to replication stress and provide mechanistic insight into how cells cope with multiple doses of DNA-damaging drugs such as cisplatin. ■

Quinet A, Tirman S, Jackson J, Šviković S, Lemaçon D, Carvajal-Maldonado D, et al. PRIMPOL-mediated adaptive response suppresses replication fork reversal in BRCA-deficient cells. Mol Cell 2019 Oct 29 [Epub ahead of print].

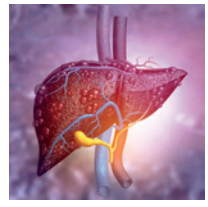
Signaling

Major Finding: Peritumoral expression of Hippo-pathway members YAP and TAZ restricts liver-tumor growth in mice.

Mechanism: Peritumoral YAP and TAZ activation triggered nonapoptotic programmed cell death in the tumor cells.

Impact: If present in humans, this may hinder the effectiveness of future YAP- or TAZ-targeting drugs.

PERITUMORAL YAP AND TAZ EXPRESSION SUPPRESSES TUMOR GROWTH IN MICE



Hyperactivation of the Hippo signaling pathway via upregulation of its two downstream effectors, the transcriptional coactivators YAP and TAZ, has been shown to promote tumorigenesis. In a mouse model of intrahepatic cholangiocarcinoma, Moya, Castaldo, Van den Mooter, Soheily, and colleagues detected large amounts of YAP and TAZ in tumor cells, as expected. However, there was also YAP accumulation in peritumoral hepatocytes and an increase in expression of classic YAP targets along with an increase in a proliferation marker in these cells. Deletion of *Yap* and the homologous *Taz* in normal hepatocytes but not tumor cells increased tumor-cell proliferation, resulting in increased tumor burden, implying that YAP and TAZ in peritumoral hepatocytes normally function to restrict tumor growth. Consistent with this notion, condtional deletion of the genes encoding the YAP and TAZ inhibitors LATS1 and LATS2 in peritumoral hepatocytes substantially diminished tumor growth, and conditional overexpression of a constitutively active form of human YAP in the normal liver cells caused tumor regression in the mice. Further investigation revealed that activation of YAP or TAZ in peritumoral hepatocytes exerted its antitumor effects by inducing nonapoptotic programmed cell death in the tumor cells. Notably, the tumor cells required YAP and TAZ for survival only when the surrounding cells possessed wild-type YAP and TAZ. The tumor-suppressive effects of peritumoral YAP and TAZ extended to a mouse model of hepatocellular carcinoma as well as a mouse model of aggressive, *NRAS*-mutant melanoma that had metastasized to the liver. Together, these results suggest that cell competition akin to that originally detailed in *Drosophila* may be at work; specifically, the dependence of tumor cells on YAP and TAZ was specified by the levels of YAP and TAZ in the surrounding normal tissue. Given the interest in developing YAP- and TAZ-targeting drugs, further work to determine whether this effect is present in humans is needed, as it implies that systemic inhibition of YAP and TAZ may actually have protumorigenic effects. ■

Moya IM, Castaldo SA, Van den Mooter L, Soheily S, Sansores-Garcia L, Jacobs J, et al. Peritumoral activation of the Hippo pathway effectors YAP and TAZ suppresses liver cancer in mice. Science;366:1029–34.

AACR American Association for Cancer Research

CANCER DISCOVERY

Peritumoral YAP and TAZ Expression Suppresses Tumor Growth in Mice

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