DNA Repair

Major finding: ATR and DNA-PK cooperate to activate CHK1 and prevent replication catastrophe during cell division.

Mechanism: ATR and DNA-PK/CHK1 protect cells from ssDNA accumulation by limiting CDK activity and origin firing.

Impact: ATRi-induced ssDNA reflects intrinsic replicative stress and predicts cancer cell sensitivity to ATRi.

ATR AND DNA-PK/CHK1 ELICIT DISTINCT RESPONSES IN CANCER CELLS

Under high levels of DNA replication stress, the ataxia telangiectasia and Rad3-related (ATR) kinase is thought to activate the downstream effector kinase CHK1 in order to inhibit origin firing and prevent massive replication fork collapse. However, recent work shows that replicating cells are more dependent on CHK1 and that inhibitors targeting ATR (ATRi) or CHK1 (CHK1i) induce differential levels of DNA damage, suggesting that ATR and CHK1 may function in a nonlinear pathway in response to intrinsic DNA replication stress. Buisson and colleagues showed that, in the absence of exogenous replication stress, ATR inhibition led to a rapid increase in single-stranded DNA (ssDNA) in a subset of early S-phase cells due to impaired accumulation of the ribonucleotide reductase subunit RRM2. Decreased RRM2 expression in the presence of ATRi was attributed to destabilization of the transcriptional activator E2F1 and was reversed upon inhibition of cyclin-dependent kinase 2, indicating that ATR limits CDK2 activity to induce RRM2 accumulation. In addition, ATR-mediated inhibition of CDK2 also restricted origin firing in early S-phase cells. Compared with ATRi, inhibition of CHK1 led to accumulation of higher levels of ssDNA and DNA damage, suggesting that CHK1 may protect ATRi-treated cells with lower levels of ssDNA. Indeed, DNA-PK–dependent CHK1 activation inhibited further CDK2-driven origin firing and prevented further ssDNA accumulation by destabilizing cell division cycle 25A (CDC25A) in cells treated with ATRi for longer time points. Consistent with a CHK1-mediated threshold effect, cells exposed to high levels of replicative stress were more dependent on ATR, whereas CHK1i-treated cells were sensitive to more moderate levels of replicative stress. Moreover, ATRi-induced ssDNA levels predicted ATRi sensitivity across a panel of cancer cell lines. Together, these data suggest that the ATR–CHK1 pathway protects cells from high DNA replication stress in unperturbed S phase, and that the DNA-PK–CHK1 axis protects cells from lower levels of replicative stress in the absence of ATR. Buisson R, Boissert JL, Benes CH, Zou L. Distinct but concerted roles of ATR, DNA-PK, and Chk1 in countering replication stress during S phase. Mol Cell 2015;59:1011–24.

Leukemia

Major finding: Glutaminase inhibition enhances the sensitivity of Pten-positive T-ALL to anti-NOTCH1 therapy.

Concept: Glutaminolysis provides an energy source for tumor cell survival downstream of NOTCH1 signaling.

Impact: Strategies that target cell metabolism may improve the efficacy of anti-NOTCH1 therapy in T-ALL.

GLUTAMINASE INHIBITION SYNERGIZES WITH NOTCH1 INHIBITION IN T-ALL

Aberrant NOTCH1 signaling is implicated in the majority of cases of T-cell acute lymphoblastic leukemia (T-ALL), but inhibition of NOTCH1 using small-molecule γ-secretase inhibitors (GSI) has met with limited clinical success. GSI resistance has been attributed to mutational loss of the PTEN tumor suppressor, leading Herranz and colleagues to explore the specific mechanisms by which PTEN inactivation drives GSI resistance. In a mouse model of NOTCH1-induced T-ALL, Pten loss and consequent constitutive activation of PI3K–AKT signaling, which is known to induce glycolysis, abrogated the antitumor effect of GSI therapy. Gene expression profiling revealed that anti-NOTCH1 therapy suppressed anabolism and increased catabolism, apoptosis, and autophagy in Pten-positive, but not Pten-deleted, leukemias, indicating that NOTCH1 inhibition creates a metabolic crisis in Pten-positive T-ALL cells that confers reliance on the autophagy salvage pathway. Consistent with this finding, suppression of autophagy enhanced the antileukemic effect of NOTCH1 inhibition. Metabolic tracing studies revealed that NOTCH1-induced leukemia cells used glutamine as a primary source of carbon, that NOTCH1 inhibition impaired both glutaminolysis and glycolysis, and that Pten deletion attenuated the decrease in glycolytic efficiency mediated by NOTCH1 blockade, suggesting that Pten loss induces glycolysis to overcome NOTCH1 inhibition. In mice with Pten-positive NOTCH1-induced leukemia, GSI therapy eventually led to drug resistance and disease progression, which was accompanied by lower Pten expression and higher expression of glutaminase. Overexpression of glutaminase was sufficient to confer resistance to NOTCH1 inhibition, whereas combined treatment with GSI and the glutaminase inhibitor BPTES showed strong and synergistic antitumor effects in Pten-positive, but not Pten-deleted, T-ALL cell lines, human leukemia xenografts, and mouse models. These results indicate that glutaminolysis provides a primary energy source for Pten-positive leukemia cell survival downstream of NOTCH1 signaling and suggest that glutaminase inhibition may be a viable therapeutic strategy to improve the efficacy of GSIs in the treatment of T-ALL.


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ATR and DNA-PK/CHK1 Elicit Distinct Responses in Cancer Cells

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