DNA Repair

Major finding: DNA polymerase θ (POLθ) inhibits homologous recombination (HR) and promotes alternative NHEJ.

Clinical relevance: HR-deficient cancer cells depend on POLθ-mediated alternative NHEJ repair for survival.

Impact: DNA POLθ may serve as a potential biomarker and therapeutic target in HR-deficient cancers.

DNA POLθ SUPPRESSES HR AND IS REQUIRED FOR HR-DEFICIENT CELL SURVIVAL

Defects in homologous recombination (HR) repair lead to genomic instability in specific types of tumors such as breast and epithelial ovarian cancers, and result in dependence on alternative PARP-driven and error-prone DNA repair pathways. Ceccaldi and colleagues found that DNA polymerase theta (POLθ, encoded by *POLQ*) expression increased with epithelial ovarian cancer grade and suppressed HR by binding the RAD51 recombinase and inhibiting its assembly at single-stranded DNA. POLθ ATPase activity and RAD51 binding were stimulated by replicative stress, and suppression of POLθ sensitized cells to genotoxic stress and DNA damage, resulting in reduced DNA replication fork dynamics and impaired cell-cycle progression and suggesting a role for POLθ at stalled replication forks. Importantly, POLθ expression was increased in HR-deficient ovarian cancer cells, predicted patient response to platinum chemotherapy, and conferred hypersensitivity to HR deficiency, indicative of synthetic lethality. Consistent with these findings, Mateos-Gomez and colleagues identified POLθ as a key modulator of HR and alternative nonhomologous end-joining (alt-NHEJ) DNA repair using genetically engineered mouse models that allow for differentiation between classical and alt-NHEJ. Suppression of POLθ inhibited the generation of telomere fusions and chromosomal translocations formed by alt-NHEJ, but not classical NHEJ. POLθ was recruited to DNA double-strand breaks in a PARP1-dependent manner, and suppression of POLθ led to decreased alt-NHEJ and a concomitant increase in HR via enhanced RAD51 accumulation. Moreover, suppression of POLθ in HR-deficient *BRCA*-mutant cells led to increased chromosomal aberrations and reduced cell survival, further supporting the notion that HR-deficient tumors are dependent on POLθ to maintain genomic stability. Together, these studies highlight a previously unrecognized role for POLθ in regulating the balance between HR and alt-NHEJ repair and provide a rationale for the therapeutic targeting of POLθ in HR-deficient cancers. ■

Ceccaldi R, Liu JC, Amunugama R, Hajdu I, Primack B, Petalcorin MI, et al. Homologous-recombination-deficient tumours are dependent on Polθ-mediated repair. Nature 2015;518:258–62.

Mateos-Gomez PA, Gong F, Nair N, Miller KM, Lazzerini-Denchi E, Sfeir A. Mammalian polymerase θ promotes alternative NHEJ and suppresses recombination. Nature 2015;518:254–7.

MicroRNA

Major finding: mTORC1 inhibits miRNA biogenesis in response to nutrient deprivation by decreasing DROSHA stability.

Mechanism: mTOR upregulates MDM2, which ubiquitylates DROSHA, targeting it for proteasomal degradation.

Impact: DROSHA-mediated miRNA biogenesis promotes cellular resistance to glucose deprivation.

mTOR SIGNALING REGULATES DROSHA STABILITY AND miRNA BIOGENESIS

Development of cancer frequently coincides with loss of miRNA expression, but increased activity of the nutrient sensor mTOR, suggesting a functional link between mTOR signaling and miRNA biogenesis. Ye and colleagues found that deletion of tuberous sclerosis 1 (*TSC1*), a negative regulator of mTOR activity, resulted in downregulation of miRNA expression and a decrease in precursor miRNA processing, which was reversed with rapamycin treatment, suggesting that mTOR activation inhibits miRNA biogenesis. Consistent with this notion, deletion of the regulatory associated protein of mTOR (Raptor), a component of mTOR complex 1 (mTORC1), resulted in a global increase in miRNAs. In addition, protein levels of DROSHA, which is required for primary miRNA processing, were significantly reduced in *Tsc1*$^{-/-}$ mouse embryonic fibroblasts, suggesting that mTOR activity modulates miRNA processing via post-transcriptional regulation of DROSHA. In support of this idea, expression of the E3 ubiquitin ligase MDM2 was induced by mTOR activity in both *Trp53*$^{+/+}$ and *Trp53* $^{-/-}$ cells and resulted in decreased DROSHA protein levels due to proteasomal degradation. Recombinant MDM2 was sufficient to ubiquitylate DROSHA *in vitro*, and depletion of MDM2 in human cells decreased DROSHA ubiquitylation, supporting the hypothesis that mTOR-mediated upregulation of MDM2 directly regulates DROSHA stability. Nutrient availability also affected this signaling pathway, as deprivation of either amino acids or glucose, which reduces mTOR activity, resulted in decreased MDM2 expression and a reciprocal stabilization of DROSHA protein levels and protected glucose-deprived cells from apoptosis. Furthermore, expression of four miRNA mimics identified in a high-throughput screen rescued DROSHA-depleted cells from glucose deprivation, whereas inhibition of these miRNAs sensitized cells to glucose starvation. Together, these data provide evidence for mTOR-mediated regulation of miRNA processing, and suggest that miRNA biogenesis may promote resistance to nutrient deprivation. ■

Ye P, Liu Y, Chen C, Tang F, Wu Q, Wang X, et al. An mTORC1-Mdm2-Drosha axis for miRNA biogenesis in response to glucose- and amino acid-deprivation. Mol Cell 2015 Jan 29 [Epub ahead of print].