Metabolism

Major finding: Repression of glutamine metabolism by SIRT4 in response to DNA damage inhibits tumorigenesis.

Mechanism: SIRT4 loss enhances glutamine-driven cancer cell proliferation and genomic instability.

Impact: *SIRT4* expression is decreased in many human tumors and correlates with poor prognosis.

SIRT4 CONTROLS THE CELLULAR METABOLIC RESPONSE TO DNA DAMAGE

Dysregulation of the DNA damage response, which protects against genomic instability by triggering cell-cycle arrest and DNA repair, is commonly associated with tumorigenesis. Recent studies have shown that DNA damage also induces changes in cellular metabolism, including increased synthesis of nucleotide precursors to enable DNA repair, but the metabolic pathways that limit proliferation under these conditions are unknown. Jeong and colleagues found that genotoxic stress repressed glutamine consumption without affecting glucose uptake, resulting in reduced production of tricarboxylic acid (TCA) cycle intermediates in both primary and tumor cell lines. This repression of glutamine metabolism was mediated by the mitochondrial protein sirtuin 4 (SIRT4), which was upregulated in response to DNA-damaging agents in cell lines and normal lung tissue and impaired glutamine utilization by the TCA cycle. In contrast, SIRT4 deficiency enhanced glutamine incorporation into TCA cycle intermediates and prevented the suppression of mitochondrial glutamine uptake after DNA damage. Additionally, loss of SIRT4 impaired DNA damage–induced cell-cycle arrest and resulted in accumulation of DNA damage and increased aneuploidy, suggesting that SIRT4-dependent regulation of glutamine metabolism limits growth and protects cells from genomic instability under genotoxic stress. Consistent with this idea, SIRT4-deficient cells exhibited transformed phenotypes, including augmented proliferation and colony formation, which were suppressed by inhibition of glutamine metabolic enzymes. Furthermore, SIRT4 loss augmented allograft tumor growth and resulted in an age-dependent increase in spontaneous lung tumor formation, whereas SIRT4 reconstitution reduced glutamine uptake and repressed the proliferation and genomic instability of lung tumor cells. Decreased *SIRT4* expression was also detected in several human cancers, particularly lung cancer, and was correlated with reduced survival. These findings identify SIRT4 as a tumor suppressor linking glutamine metabolism and genomic integrity and suggest that targeting of this metabolic pathway may be clinically beneficial. ■

Jeong SM, Xiao C, Finley LW, Lahusen T, Souza AL, Pierce K, et al. SIRT4 has tumor-suppressive activity and regulates the cellular metabolic response to DNA damage by inhibiting mitochondrial glutamine metabolism. Cancer Cell 2013;23:450–63.

Targeted Therapy

Major finding: Recruitment of client kinases to HSP90 by CDC37 is blocked by ATP-competitive kinase inhibitors.

Concept: CDC37 recruits client kinases to HSP90 and inhibits their activity by antagonizing ATP binding.

Impact: ATP-competitive kinase inhibitors may also induce kinase degradation by blocking chaperone access.

KINASE INHIBITORS CAN INDUCE CHAPERONE DEPRIVATION

The molecular chaperone HSP90 stabilizes client proteins and protects them from proteasomal degradation. The cochaperone CDC37 specifically recruits kinases to HSP90, but the basis for this specificity is unknown. Because CDC37 interacts with a wide range of kinases, Polier and colleagues hypothesized that CDC37 would interact with a universal feature of client kinases. The authors formed a complex of HSP90, CDC37, and BRAF, an HSP90 client kinase, by mixing the individually purified proteins and showed not only that CDC37 was essential for the interaction between BRAF and HSP90 but also that binding of a fluorescently labeled ADP analogue to the BRAF ATP-binding site and BRAF-dependent phosphorylation were reduced in the presence of CDC37. These findings show that CDC37 inhibits the activity of client kinases stabilized by HSP90 by interacting with their ATP-binding clefts and suggest that ATP-competitive kinase inhibitors might disrupt this interaction. Indeed, treatment of cancer cells with ATP-competitive kinase inhibitors such as vemurafenib, lapatinib, and erlotinib led to a time- and concentration-dependent loss of association between CDC37 and its cognate kinases as well as decreased phosphorylation of downstream targets. Interestingly, at higher inhibitor concentrations where the kinase no longer bound CDC37 or HSP90, total kinase amounts decreased, consistent with increased proteasomal degradation due to chaperone deprivation. These findings raise the possibility that the activity of ATP-competitive inhibitors is not only attributable to inhibition of kinase activity but is also related to promotion of kinase degradation through antagonism of CDC37-mediated recruitment to HSP90. Consistent with this possibility, a significantly higher concentration of vemurafenib was required to inhibit the growth of CDC37-overexpressing cells than cells in which CDC37 was knocked down. This additional role in chaperone deprivation may factor into clinical responses to ATP-competitive inhibitors that target HSP90 client kinases. ■

Polier S, Samant RS, Clarke PA, Workman P, Prodromou C, Pearl LH. ATP-competitive inhibitors block protein kinase recruitment to the Hsp90-Cdc37 system. Nat Chem Biol 2013 Mar 17 [Epub ahead of print].