Metabolism

Major finding: p53 drives metabolic reprogramming to sustain proliferation in response to serine deprivation.

Mechanism: p53/p21-induced cell-cycle arrest enables sustained GSH synthesis and limits oxidative stress.

Impact: Serine depletion may increase ROS levels and reduce viability in *TP53*-deficient cancer cells.

p53 IS REQUIRED FOR THE METABOLIC RESPONSE TO SERINE DEPLETION

To support the high rates of proliferation necessary for tumor growth, cancer cells undergo metabolic reprogramming and increase aerobic glycolysis through the Warburg effect. The tumor suppressor p53 has been implicated in the regulation of several metabolic processes, including glycolysis, oxidative phosphorylation, and the antioxidative response, and enhances cell survival following glucose deprivation. Maddocks and colleagues found that p53 also modulated the metabolic stress response to depletion of serine, which was rapidly consumed by cancer cells. Although removal of this nonessential amino acid diminished the proliferation of p53-expressing cancer cells and xenograft tumors, this defect was more pronounced with *TP53* deficiency. In cells that were wild-type for p53, serine deprivation decreased glycolysis, activated the serine synthesis pathway, and triggered an increase in tricarboxylic acid (TCA) cycle flux, which was reversed over time. Additionally, serine starvation resulted in p53 activation and induction of p21-dependent cell-cycle arrest in wild-type cells; this transient arrest promoted flux of available serine into synthesis of reduced glutathione (GSH), a cellular antioxidant, thus limiting reactive oxygen species (ROS) accumulation and increasing cell survival. In contrast, *TP53*-null cells exhibited sustained TCA flux and higher levels of oxygen consumption under conditions of serine starvation compared with wild-type cells. Furthermore, cells lacking p53 failed to initiate G_1-phase arrest and were unable to maintain GSH synthesis, resulting in loss of antioxidant capacity and elevated intracellular ROS. Addition of exogenous pyruvate and either GSH or the antioxidant N-acetyl cysteine rescued proliferation in serine-starved *TP53*-null cells, indicating that both decreased glycolysis and augmented ROS accumulation are responsible for increased sensitivity to serine deprivation in the absence of p53. These results further establish p53 as an important mediator of metabolic stress responses and suggest that serine depletion may reduce the growth of *TP53*-deficient tumors. ■

Maddocks OD, Berkers CR, Mason SM, Zheng L, Blyth K, Gottlieb E, et al. Serine starvation induces stress and p53-dependent metabolic remodelling in cancer cells. Nature 2012 Dec 16 [Epub ahead of print].

DNA Repair

Major finding: A small-molecule inhibitor of DNA ligase IV has activity in several xenograft tumor models.

Mechanism: Interference with ligase IV binding to DNA results in DSB accumulation and cytotoxicity.

Impact: Inhibition of nonhomologous end-joining may sensitize cancer cells to radio- and chemotherapy.

NONHOMOLOGOUS END-JOINING CAN BE PHARMACOLOGICALLY INHIBITED

Hyperactive double-strand break (DSB) repair pathways can allow tumors to withstand genotoxic insult, thus conferring resistance to DNA damaging agents. As one of the major DSB repair pathways, nonhomologous end-joining (NHEJ) represents an attractive target for sensitizing cancer cells to DNA damage, but specific pharmacologic inhibition of the core NHEJ machinery has not yet been possible. Srivastava and colleagues built a homology-based representative 3-dimensional model of the DNA binding domain of human ligase IV, the enzyme that mediates joining of free DNA strands during NHEJ, and used *in silico* docking to predict compounds that would compete with damaged DNA for ligase IV binding. This approach identified 5,6-bis(benzylideneamino)-2-mercapto-pyrimidin-4-ol (SCR7), which indeed bound the ligase IV DNA binding domain and blocked ligase IV activity in a cell-free extract-based system. In cancer cell lines, SCR7 suppressed NHEJ-mediated repair, resulting in the accumulation of DSBs, increased apoptotic cell death, and reduced proliferation of multiple cell lines to varying degrees at micromolar concentrations in a ligase IV–dependent manner. SCR7 was well tolerated in mice although it led to a reversible reduction in lymphocytes due to inhibition of NHEJ-mediated V(D)J recombination. SCR7 prolonged survival by either inducing tumor regression or stopping tumor growth in 3 of 4 mouse tumor models tested. Interestingly, combining SCR7 with radiation or a DSB-inducing agent blocked the growth of xenografted tumors that did not respond to SCR7 alone and further increased DSB accumulation. Although future work is needed to understand the determinants of response to ligase IV inhibition, the identification of this lead compound shows that pharmacologic inhibition of NHEJ is feasible and may block tumor progression alone or in combination with radiation or chemotherapy. ■

Srivastava M, Nambiar M, Sharma S, Karki SS, Goldsmith G, Hegde M, et al. An inhibitor of nonhomologous end-joining abrogates double-strand break repair and impedes cancer progression. Cell 2012; 151:1474–87.