Leukemia

Major finding: IL1 signaling promotes degradation of wild-type MLL to enhance MLL leukemia cell proliferation.

Mechanism: IL1/IRAK4-dependent UBE2O phosphorylation enhances the MLL–UBE2O interaction to promote MLL degradation.

Impact: Stabilizing wild-type MLL may be a potential therapeutic strategy in patients with MLL leukemia.

STABILIZATION OF WILD-TYPE MLL DISPLACES ONCOGENIC MLL FUSION PROTEINS

Chromosomal translocations involving the mixed-lineage leukemia (*MLL*) gene, which encodes an enzyme that catalyzes the methylation of histone H3 lysine 4, are associated with a poor prognosis in patients with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), and more effective targeted therapies are needed. Liang and colleagues found that, despite similar mRNA expression, the wild-type MLL protein was more abundant than the chimeric MLL fusion protein in leukemia cells, suggesting the possibility that stabilizing wild-type MLL might displace chimeric MLL fusion proteins from chromatin. The E2/E3 ubiquitin ligase UBE2O was found to interact with the C-terminus of MLL, which is lacking in the MLL chimeras, thereby promoting degradation of wild-type MLL, but not the chimeric fusion proteins. Mechanistically, IL1 signaling promoted phosphorylation of UBE2O by the IRAK4 kinase, which enhanced the MLL–UBE2O interaction and promoted degradation of wild-type MLL. Thus, IRAK inhibition reduced the MLL–UBE2O interaction and increased MLL stability and occupancy at target genes, and reduced occupancy of chimeric MLL at a subset of target genes including super elongation complex genes. Further, an IRAK4 inhibitor reduced the proliferation and viability of patient-derived leukemia cell lines harboring *MLL* fusions, but not of cells without *MLL* rearrangements or of an *MLL*-rearranged cell line in which the wild-type *MLL* allele was also deleted, indicating that the wild-type MLL allele is required for enhanced sensitivity of *MLL*-rearranged cells to IRAK inhibition. Moreover, IRAK inhibition improved survival and slowed disease progression in a mouse model of MLL-AF9 leukemia, highlighting IRAK as a potential therapeutic target in MLL-rearranged leukemia. Altogether, these results suggest that stabilizing wild-type MLL may have therapeutic potential in patients with MLL-rearranged leukemia, and these findings may extend to tumors driven by other fusion proteins. ■

Liang K, Volk AG, Haug JS, Marshall SA, Woodfin AR, Bartom ET, et al. Therapeutic targeting of MLL degradation pathways in MLL-rearranged leukemia. Cell 2017;168:59–72.e13.

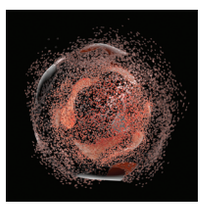
Apoptosis

Major finding: Brain, heart, and kidney tissues from young mice are highly susceptible to treatment-induced apoptosis.

Concept: Adult tissues no longer express apoptotic machinery proteins, rendering them refractory to apoptosis.

Impact: High apoptotic protein levels may increase the risk of treatment-linked toxicities in pediatric patients.

TISSUES FROM YOUNG MICE AND PATIENTS ARE PRIMED FOR APOPTOSIS



The use of chemotherapy and radiation is limited by the induction of apoptosis in healthy tissues, which is especially pronounced in very young pediatric cancer patients who experience higher levels of certain treatment-related toxicities than adults. However, it is unclear why children experience a greater risk of developing these toxicities, and although apoptosis has been extensively studied in cancer and hematopoietic tissues, less is known about apoptosis in healthy somatic tissues. Sarosiek and colleagues performed BH3 profiling to determine the propensity of various cell types to undergo apoptosis. BH3-only proteins trigger mitochondrial apoptosis by activating proapoptotic proteins (BAX or BAK). Thus, by titrating BH3 peptides, mitochondria and cells can be classified as "primed" for apoptosis if the mitochondria permeabilize readily, "unprimed" if antiapoptotic proteins render them less sensitive to apoptosis, and "apoptosis refractory" if insufficient expression of apoptotic machinery prevents apoptosis. BH3 profiling of adult mouse tissues found that hematopoietic cells were primed, cells from the intestines, lungs, and liver were unprimed, and cells from the brain, heart, and kidney were refractory. The refractory tissues were lacking both pro- and antiapoptotic proteins including BAX and BAK. In contrast, brain, heart, and kidney cells in embryonic and young mice were primed for apoptosis, and radiation and chemotherapy induced extensive apoptosis. Growth-associated MYC signaling promoted high expression levels of BAK and BAX in young mice, likely explaining their susceptibility to apoptosis, whereas BAK and BAX were downregulated in adulthood. The higher apoptotic priming in young mice contributed to cardiotoxicity in response to chemotherapy and neurotoxicity in response to radiation, which could be prevented by loss of BAX and BAK. Consistent with these findings, brain tissue from young patients was most sensitive to BH3 peptides, and BAX expression was highest prenatally and decreased throughout development. The finding that tissue from young patients and mice is primed for apoptosis may explain the increased risk of certain treatment-associated toxicities in pediatric cancer patients. ■

Sarosiek KA, Fraser C, Muthalagu N, Bhola PD, Chang W, McBrayer SK, et al. Developmental regulation of mitochondrial apoptosis by c-Myc governs age- and tissue-specific sensitivity to cancer therapeutics. Cancer Cell 2017;31:142–56.