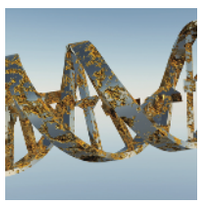
Targeted Therapy

Major finding: Pharmacologic MTH1 inhibition specifically induces cancer cell death and suppresses tumor growth.

Concept: MTH1 inhibitors induce misincorporation of oxidized nucleotides, causing lethal DNA damage.

Impact: Exploiting the altered redox state of cancer by MTH1 inhibition may be beneficial in diverse tumor types.

MTH1 IS REQUIRED FOR CANCER CELL SURVIVAL



Overexpression of MutT homolog 1 (MTH1), which hydrolyzes the oxidized forms of dATP and dGTP to prevent misincorporation of damaged nucleotides into DNA, has been shown to prevent RAS-induced DNA damage and senescence and suppress the high mutation rate of mismatch repair–defective colorectal cancer cells. Because tumor cells typically exhibit elevated levels of reactive oxygen species (ROS), Gad and colleagues hypothesized that MTH1 might be essential for sanitizing the free nucleotide pool and preventing formation of lethal DNA damage in cancer cells. Indeed, siRNA-mediated depletion of MTH1 caused the accumulation of oxidized nucleotides in cancer cell DNA, induced DNA double- strand breaks and cancer cell apoptosis, and prevented xenograft tumor growth *in vivo*, but had no effect on normal cells. Selective small-molecule MTH1 inhibitors identified in a compound library screen phenocopied MTH1 knockdown and significantly blocked growth of a patient-derived xenograft model of chemoresistant melanoma. In another study, Huber and colleagues identified MTH1 as the target of SCH51344, a small molecule with selective cytotoxicity in RAS-transformed cells, and screened a library of clinically evaluated compounds for more potent MTH1 inhibitors. Surprisingly, the *(S)*-enantiomer of the MET/ALK inhibitor crizotinib potently inhibited MTH1 activity and blocked colony formation of RAS-mutant cancer cells. *(S)*-crizotinib treatment also induced the accumulation of oxidized nucleotides in DNA and significantly impaired xenograft tumor growth *in vivo*. Notably, both studies showed that MTH1 was overexpressed across a broad range of human cancers and that the cytotoxic effects of MTH1 inhibition were independent of RAS or p53 status, suggesting that MTH1 inhibitors might be active in diverse tumor types. Taken together, these studies identify an essential role for MTH1 as an adaptive mechanism to altered redox regulation in cancer cells and raise the possibility that MTH1 inhibitors might be selectively lethal to cancer cells due to nononcogene addiction to *MTH1*. ■

Gad H, Koolmeister T, Jemth AS, Eshtad S, Jacques SA, Ström CE, et al. MTH1 inhibition eradicates cancer by preventing sanitation of the dNTP pool. Nature 2014;508:215–21.

Huber KV, Salah E, Radic B, Gridling M, Elkins JM, Stukalov A, et al. Stereospecific targeting of MTH1 by (S)-crizotinib as an anticancer strategy. Nature 2014;508:222–7.

Leukemia

Major finding: Triplication of genes on 21q22 blocks differentiation and promotes self-renewal of B cells.

Mechanism: Overexpression of a small number of 21q22 genes, including *HMGN1*, reduces H3K27 trimethylation.

Impact: H3K27 demethylase inhibitors may have activity in Down syndrome–associated B-ALL or polysomy 21 B-ALL.

CHROMOSOME 21q22 TRIPLICATION PROMOTES B-CELL TRANSFORMATION

Individuals with Down syndrome (trisomy 21) have a significantly increased risk of B-cell acute lymphoblastic leukemia (B-ALL), and polysomy 21 is the most common aneuploidy in B-ALL. To gain insight into why extra copies of chromosome 21 are associated with B-ALL, Lane and colleagues evaluated B-cell development in transgenic mice harboring a chromosomal triplication orthologous to a region of chromosome 21q22 that is recurrently amplified in B-ALL. Triplication of this region, which contains only 31 genes, led to B-cell maturation defects, conferred B cells with the ability to self-renew, and accelerated leukemogenesis induced by either *BCR–ABL* or alterations of *CRLF2* and *JAK2*. Differentially expressed genes induced by 21q22 triplication in mice were enriched among gene signatures of Down syndrome–associated B-ALLs and were highly enriched for Polycomb repressor complex 2 targets and histone H3 lysine 27 trimethylation (H3K27me3) sites. Global H3K27me3 loss was also observed in 21q22 transgenic B cells, and overexpressed genes were highly enriched for those normally bivalently marked with H3K27me3 and H3K4me3. Notably, restoration of H3K27me3 with an H3K27 demethylase inhibitor reduced self-renewal of the transgenic B cells and was toxic to Down syndrome–associated B-ALL cells, raising the possibility that inhibition of H3K27 demethylases may have therapeutic benefit in B-ALLs harboring extra copies of chromosome 21q22. Overexpression of one gene in this region, high mobility group nucleosome binding domain 1 (*Hmgn1*), led to a reduction in global H3K27me3 levels and was required for self-renewal of 21q22 transgenic B cells, and transgenic overexpression of human *HMGN1* in mice blocked B-cell differentiation, promoted B-cell self-renewal, and shortened the latency of *BCR–ABL*-induced B-ALL. Together, these findings suggest that the association between B-ALL and trisomy or polysomy 21 may be attributable to H3K27me3 loss caused by overexpression of a small number of genes on chromosome 21, including *HMGN1*. ■

Lane AA, Chapuy B, Lin CY, Tivey T, Li H, Townsend EC, et al. Triplication of a 21q22 region contributes to B cell transformation through HMGN1 overexpression and loss of histone H3 Lys27 trimethylation. Nat Genet 2014 Apr 20 [Epub ahead of print].