Colorectal Cancer

Major finding: Vitamin C inhibits GAPDH, causing selective killing of *KRAS*- and *BRAF*-mutant colorectal cancer cells.

Mechanism: GLUT1-mediated uptake of DHA leads to glutathione depletion, ROS accumulation, and GAPDH inactivation.

Impact: High-dose vitamin C is a potential treatment for *KRAS*- and *BRAF*-mutant colorectal cancer.

VITAMIN C TARGETS GAPDH TO KILL *KRAS*- AND *BRAF*-MUTANT CANCER CELLS

About half of colorectal cancers harbor activating mutations in either *KRAS* or *BRAF*. *KRAS*- and *BRAF*-mutant tumors exhibit increased glucose uptake and expression of the glucose transporter GLUT1 (also known as SLC2A1), suggesting that exploiting the reliance of these tumors on glycolysis may represent a possible therapeutic strategy. GLUT1 also transports dehydroascorbate (DHA), the oxidized form of vitamin C, into the cell, where it is reduced to vitamin C in a process that consumes the antioxidant glutathione (GSH). To test the hypothesis that increased DHA uptake would disrupt redox homeostasis and kill *KRAS*- or *BRAF*-mutant cells, Yun and colleagues treated a panel of colorectal cancer cell lines with vitamin C. Although both wild-type and mutant colorectal cancer cells preferentially took up DHA over vitamin C via the GLUT1 receptor, the increased GLUT1 expression in *KRAS*- and *BRAF*-mutant cells resulted in enhanced vitamin C uptake compared with wild-type cells. Vitamin C treatment was selectively cytotoxic in *KRAS*- and *BRAF*-mutant cells *in vitro*, and reduced tumor growth *in vivo* in xenografts and the *Apc*;*Kras*^{G12D} transgenic model of intestinal cancer. In contrast, whereas GLUT1 overexpression was sufficient to increase vitamin C uptake in wild-type cells, it did not render them sensitive to the cytotoxic effects, suggesting that oncogene-induced metabolic reprogramming is required for vitamin C–mediated toxicity. Mechanistically, DHA uptake and reduction to vitamin C depleted cellular GSH levels, resulting in increased reactive oxygen species (ROS) in *KRAS*- and *BRAF*-mutant cells. Furthermore, vitamin C induced ROS-dependent inactivation of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) via posttranslational modifications and depletion of NAD^+ substrate, leading to inhibition of glycolysis, decreased ATP levels, and cell death. Taken together, these results provide a mechanism for the selective killing of *KRAS*- and *BRAF*-mutant cancer cells by vitamin C and support continued investigation of vitamin C in human tumors. ■

Yun J, Mullarky E, Lu C, Bosch KN, Kavalier A, Rivera K, et al. Vitamin C selectively kills KRAS and BRAF mutant colorectal cancer cells by targeting GAPDH. Science 2015;350:1391–6.

Epigenetics

Major finding: Tumors with SWI/SNF subunit mutations depend on both catalytic and noncatalytic activity of EZH2.

Concept: EZH2 dependence is a shared feature of cancer cells harboring inactivating mutations in SWI/SNF subunits.

Impact: EZH2 enzymatic inhibitors may not be sufficient to disrupt the oncogenic effects of EZH2.

NONCATALYTIC EZH2 ACTIVITY IS REQUIRED IN SWI/SNF-MUTANT CANCERS

Components of the SWI/SNF chromatin remodeling complex are mutated in approximately 20% of human cancers. An antagonistic relationship has been reported between the SWI/SNF subunit SMARCB1 (also known as SNF5) and EZH2, the catalytic methyltransferase subunit of polycomb repressive complex 2 (PRC2), wherein SMARCB1-deficient tumors are genetically dependent on unrestrained EZH2 function. Kim and colleagues found that most cancer cell lines with inactivating mutations in genes encoding other SWI/SNF subunits frequently mutated in cancer, such as *ARID1A*, *SMARCA4* (*BRG1*), and *PBRM1*, were also dependent on EZH2 and selectively sensitive to EZH2 depletion. The SWI/SNF-mutant cell lines that did not require EZH2 were enriched for activating RAS pathway mutations, suggesting that RAS mutations reduce the dependence of SWI/SNF-mutant tumors on EZH2. Inhibitors targeting EZH2 histone methyltransferase activity are in clinical trials; however, it is unclear if EZH2 catalytic activity is required for the oncogenic effects of EZH2 in SWI/SNF-mutant cancers. GSK126, an enzymatic inhibitor of EZH2 histone methyltransferase activity, reduced H3K27 trimethylation in all cells, but although all SWI/SNF-mutant cells were sensitive to EZH2 knockdown *in vitro* and *in vivo*, only some were sensitive to GSK126. Surprisingly, EZH2 mutants lacking methyltransferase activity were largely able to rescue the effects of EZH2 knockdown, suggesting that the effects of EZH2 depletion on SWI/SNF-mutant cells are not entirely due to loss of EZH2 enzymatic activity. SAH-EZH2, a stapled peptide that blocks H3K27 trimethylation by destabilizing the PRC2 complex and inducing EZH2 degradation, inhibited the growth of SWI/SNF-mutant cancer cells, including those that were insensitive to GSK126. Together, these data suggest that a methyltransferase-independent function of EZH2 plays a predominant role in supporting the growth and proliferation of SWI/SNF-mutant cells. Inhibiting the methyltransferase activity of EZH2 may therefore not be sufficient to fully block its oncogenic effects. ■

Kim KH, Kim W, Howard TP, Vasquez F, Tsherniak A, Wu JN, et al. SWI/SNF-mutant cancers depend on catalytic and non-catalytic activity of EZH2. Nat Med 2015;21:1491–6.

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