

Leukemia

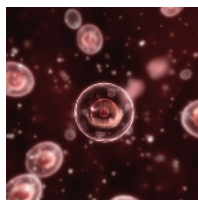
Major finding: *IDH1/2* mutations confer sensitivity to BCL2 inhibition in AML.

Mechanism: (R)-2-HG inhibits cytochrome *c* oxidase and increases BCL2 dependence in *IDH1/2*-mutant cells.

Impact: *IDH1/2* mutation status may determine sensitivity to the BCL2 inhibitor ABT-199 in patients with AML.

BCL2 IS SYNTHETIC LETHAL TO IDH1/2 MUTATIONS IN AML

Approximately 15% of patients with acute myeloid leukemia (AML) harbor mutations in the citric acid cycle enzymes isocitrate dehydrogenase 1 (*IDH1*) or *IDH2*, resulting in accumulation of the oncometabolite (R)-2-hydroxyglutarate (2-HG) and an altered epigenetic landscape. To identify non-oncogenes that are synthetic lethal to mutant *IDH* and that may represent potential therapeutic targets, Chan and colleagues performed an RNA interference screen in AML cells. Intriguingly, *IDH1*^{R132H}-mutant AML cells exhibited increased dependence on the anti-apoptotic gene *BCL2* for survival compared with AML cells expressing wild-type *IDH1*. Intracellular accumulation of 2-HG was sufficient to render wild-type AML cells sensitive to BCL2 depletion, indicating that the activity of mutant *IDH* induces synthetic lethality to BCL2. Consistent with this finding, *IDH1/2* mutation enhanced the sensitivity of AML cell lines and primary human AML blasts to pharmacologic BCL2 inhibition with ABT-199, a specific BCL2 inhibitor currently in clinical trials. Treatment with ABT-199 reduced the engraftment of *IDH1*-mutant, but not wild-type *IDH1/2*, human AML cells in mice and targeted *IDH1*-mutant AML blasts as well as leukemic



stem cells *in vivo*. Mechanistically, 2-HG accumulation inhibited the enzymatic activity of cytochrome *c* oxidase (COX), which comprises complex IV of the mitochondrial electron transport chain (ETC), mimicking a state of oxygen deprivation and resulting in a decreased mitochondrial threshold for the induction of apoptosis. COX inhibition was both necessary and sufficient to confer increased dependence on BCL2 for cell viability and sensitized AML cells to ABT-199, which triggered cytochrome *c* release and mitochondrial outer membrane permeabilization to induce apoptosis in *IDH1/2*-mutant AML cells. These results suggest that mutant *IDH*-mediated dysregulation of mitochondrial function may promote leukemogenesis and that *IDH1/2* mutations may identify patients most likely to respond to treatment with ABT-199. In addition, combined treatment with drugs that disrupt ETC function may enhance the efficacy of ABT-199. ■

Chan SM, Thomas D, Corces-Zimmerman MR, Xavy S, Rastogi S, Hong WJ, et al. Isocitrate dehydrogenase 1 and 2 mutations induce BCL-2 dependence in acute myeloid leukemia. *Nat Med* 2015; 21:178–84.

Tumor Suppressors

Major finding: Cancer-associated PKC mutations result in loss of function and enhance tumor growth.

Concept: PKC mutations disrupt second-messenger binding, processing phosphorylation, or kinase activity.

Impact: These data explain the failure of PKC inhibitors and support restoration of PKC activity in cancer cells.

PROTEIN KINASE C ISOZYMES ARE TUMOR SUPPRESSORS

The protein kinase C (PKC) family functions as receptors for the tumor-promoting phorbol esters, supporting the idea that activation of these isozymes promotes cancer progression. However, PKC isozymes have been shown to act as tumor suppressors in certain contexts, and PKC inhibitors have proven unsuccessful in clinical trials, calling into question the role of PKC in tumorigenesis. To address this issue, Antal and colleagues analyzed 46 PKC mutations identified in human cancers to determine how they affect PKC activity. Intriguingly, none of the mutations were activating; rather, the majority (61%) of mutations analyzed resulted in loss of PKC function by various mechanisms. Although there were no mutational hotspots, PKC inactivating mutations frequently localized to highly conserved residues and were enriched in certain cancers. Cancer-associated mutations in the regulatory C1 and C2 domains, which are required for translocation of PKC to membranes, resulted in ablation of agonist-stimulated PKC activity and membrane translocation due to impaired second-messenger binding. In addition, 16 of 21 kinase domain mutations analyzed were

loss-of-function mutations, primarily as a result of defective processing by phosphorylation. Of note, a majority of PKC mutations were heterozygous, suggesting that PKC may be a co-driver of tumorigenesis, and several mutations functioned as dominant negatives to inhibit global PKC activity. Consistent with a tumor-suppressive function of PKC, reversion of a loss-of-function PKC β mutation to wild-type in colon cancer cells using CRISPR/Cas9-mediated genome editing resulted in increased PKC activity, reduced anchorage-independent growth, and decreased tumor growth *in vivo*. Furthermore, hemizygous deletion of PKC β enhanced anchorage-independent growth, suggesting that PKC β is a haploinsufficient tumor suppressor. These data identify PKC isozymes as tumor suppressors and support the development of therapeutic strategies to restore, rather than inhibit, PKC activity in cancer cells. ■

Antal CE, Hudson AM, Kang E, Zanca C, Wirth C, Stephenson NL, et al. Cancer-associated protein kinase C mutations reveal kinase's role as tumor suppressor. *Cell* 2015;160:489–502.