Lymphoma

Major finding: *MEF2B* mutations enhance MEF2B transcriptional activity and stimulate *BCL6* expression in DLBCL.

Mechanism: Mutations impair binding to the corepressor CABIN1 or prevent inhibitory C-terminal modifications.

Impact: MEF2B-driven induction of BCL6 and other germinal center B-cell genes may promote lymphomagenesis.

MEF2B MUTATIONS ARE FUNCTIONALLY SIGNIFICANT IN DLBCL

Expression of B-cell lymphoma 6 (*BCL6*), an oncogene that encodes a transcriptional repressor and critical regulator of the germinal center (GC) B-cell lineage, is frequently deregulated in the GC B-cell–derived non-Hodgkin lymphomas diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma. The gene encoding the transcriptional coactivator myocyte enhancer factor 2B (*MEF2B*) is also recurrently mutated in these tumors, but the functional significance of these mutations is unknown. Ying and colleagues identified 11 somatic, heterozygous *MEF2B* mutations in a large panel of DLBCL and follicular lymphoma samples and cell lines; the majority of these were missense mutations within the N-terminus of MEF2B, which controls its transcriptional activity, but frameshift and nonsense mutations in the C-terminal region of MEF2B were also detected and predicted to yield truncated proteins or isoform switching. MEF2B was expressed in activated GC B cells and directly activated *BCL6* transcription in both normal GC B cells and DLBCL cell lines, suggesting that MEF2B functions upstream of BCL6 to define GC B cells and that *MEF2B* mutations may contribute to lymphomagenesis. Consistent with this idea, depletion of MEF2B impaired the proliferation of DLBCL cells, in part due to diminished BCL6 expression. N-terminal mutations prevented the interaction of MEF2B with its corepressor, calcineurin binding protein 1 (CABIN1), and reduced recruitment of CABIN1 to the *BCL6* promoter, resulting in augmented MEF2B transcriptional activity and increased BCL6-dependent gene repression in DLBCL cells. In contrast, C-terminal substitutions prevented protein kinase A-dependent phosphorylation and monosumoylation of MEF2B, thereby disrupting the inhibitory effects of these modifications on MEF2B transcriptional activity. These findings establish *MEF2B* mutation as an alternative mechanism to activate BCL6 in DLBCL and suggest that inhibition of MEF2B may suppress induction of *BCL6* and other GC B-cell–specific genes important for lymphomagenesis. ■

Ying CY, Dominguez-Sola D, Fabi M, Lorenz IC, Hussein S, Bansal M, et al. MEF2B *mutations lead to deregulated expression of the oncogene* BCL6 *in diffuse large B cell lymphoma. Nat Immunol 2013;14:1084–92.*

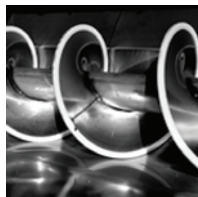
Drug Development

Major finding: A peptide that prevents EZH2 from binding EED inhibits growth of EZH2-dependent cancer cells.

Concept: Stabilized alpha helix of EZH2 (SAH-EZH2) is a stapled peptide that mimics the EED-binding domain.

Impact: Preventing PRC2 complex assembly is an alternative strategy for H3K27 methyltransferase inhibition.

TARGETING THE EZH2–EED INTERACTION INHIBITS EZH2 ACTIVITY



The histone methyltransferase enhancer of zeste homolog 2 (EZH2), which catalyzes histone H3 lysine 27 (H3K27) trimethylation as part of Polycomb repressive complex 2 (PRC2), is an attractive therapeutic target because its upregulation or mutational activation promotes the development and maintenance of several cancer types. Most efforts to develop EZH2 inhibitors have focused on small molecules that bind the EZH2 active site, an approach that fails to inhibit alternative PRC2 complexes containing the EZH2 homolog EZH1. Kim and colleagues developed a strategy to inhibit PRC2 enzymatic activity by blocking the interaction between EZH2 and another PRC2 subunit, embryonic ectoderm development (EED). Hydrocarbon "stapling" was used to create a stabilized alpha helix (SAH) that mimicked the alpha-helical EED-binding domain of EZH2, which shares 86% amino acid identity with EZH1. This stapled peptide, SAH-EZH2, was cell permeable, disrupted interactions between EED and both EZH2 and EZH1, and selectively inhibited H3K27 methylation in a dose-dependent manner. Importantly, SAH-EZH2 treatment inhibited proliferation and induced differentiation in *MLL–AF9*-expressing murine leukemia cells, which are dependent on EZH2 and PRC2 activity for growth, while sparing nontumorigenic cells. SAH-EZH2 also impaired proliferation in EZH2-overexpressing human breast and prostate cancer cell lines and *EZH2*-mutant B-cell lymphoma cells. Although a small-molecule catalytic site EZH2 inhibitor more potently inhibited H3K27 methylation *in vitro*, SAH-EZH2 had stronger and more specific effects on cancer cell viability and reduced EZH2 stability in addition to inhibiting its activity. Combined use of the two agents led to synergistic inhibition of EZH2-dependent cancer cell growth, providing further evidence for distinct and complementary mechanisms of action. These findings thus establish the feasibility of targeting EZH2 through disruption of PRC2 complex formation and provide a framework for targeting other epigenetic modifiers that are deregulated in human cancers. ■

Kim W, Bird GH, Neff T, Guo G, Kerenyi MA, Walensky LD, et al. Targeted disruption of the EZH2–EED complex inhibits EZH2-dependent cancer. Nat Chem Biol 2013;9:643–50.

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