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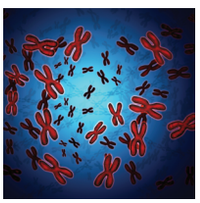
Genomic Instability

Major finding: BCL9L depletion reduces *CASP2* levels to promote aneuploidy tolerance in colon tumors.

Mechanism: Reduced BCL9L inhibits TCF4-mediated *CASP2* transcription to decrease cleavage of MDM2 and BID.

Impact: Therapeutic targeting of aneuploidy tolerance mechanisms may inhibit tumor evolution and heterogeneity.

BCL9L DYSFUNCTION PROMOTES ANEUPLOIDY TOLERANCE IN COLON TUMORS



Genomic instability due to the missegregation of chromosomes, termed chromosomal instability (CIN), results in aneuploidy, frequently occurs in cancer, and drives intratumoral heterogeneity. Cancer cells exhibit aneuploidy tolerance, and potential mechanisms underlying aneuploidy tolerance include *TP53* mutations and maintenance of protein stoichiometry. Microsatellite-stable (MSS) colorectal tumors exhibit a wide range of aneuploidy and CIN, and aneuploid MSS tumors frequently harbor *TP53* mutations. To identify the genetic determinants of CIN in MSS colorectal tumors, López-García and colleagues performed whole-exome sequencing (WES) of 17 MSS colorectal adenocarcinomas, 10 of which were aneuploid, and 8 aneuploid MSS cell lines. WES showed that six aneuploid MSS tumors harbored inactivating mutations or LOH of the β-catenin transcriptional co-factor B-cell CLL/lymphoma 9-like (*BCL9L*). Aneuploid MSS tumors were also enriched for *TP53* mutations as expected. Analysis of The Cancer Genome Atlas (TCGA) MSS colorectal cancer cohort demonstrated the frequent co-occurrence of deleterious *BCL9L* alterations and *TP53* mutations in MSS colon tumors. Truncating *BCL9L* mutations generated by CRISPR/Cas9 induced aneuploidy tolerance in wild-type *TP53* and *TP53*-null cells *in vitro*, and ablation of *BCL9L* promoted intratumoral heterogeneity in mouse xenograft models. Depletion of *BCL9L* in aneuploid-induced wild-type TP53 cells prevented TP53 accumulation, decreased levels of caspase-2 (*CASP2*), which cleaves MDM2 to produce MDM2-p60, and reduced the levels of MDM2-p60, which stabilizes TP53. Further, depletion of *BCL9L* in aneuploid-induced *TP53*-null cells reduced the formation of the cleavage product of the *CASP2* substrate BH3 interacting domain death agonist (tBID), which is required for death receptor–induced apoptosis. Chromatin immunoprecipitation assays demonstrated the interaction of TCF4 with the *CASP2* promoter, and inhibition of the β-catenin–TCF4 interaction reduced CASP2 mRNA and protein expression. Together, these results elucidate the mechanism by which loss-of-function *BCL9L* alterations promote aneuploidy tolerance in colon tumors and suggest that mechanisms driving aneuploidy tolerance may be potential therapeutic targets. ■

López-García C, Sansregret L, Domingo E, McGranahan N, Hobor S, Birkbak NJ, et al. BCL9L dysfunction impairs caspase-2 expression permitting aneuploidy tolerance in colorectal cancer. Cancer Cell 2017;31:79–93.

Epigenetics

Major finding: Oxidative stress targets TET2 and DNMT1 to chromatin to increase both DNA methylation and 5hmC.

Mechanism: p300-mediated acetylation of TET2 at K110 enhances TET2 activity, stability, and binding to DNMT1.

Impact: HDAC inhibitors may enhance TET2 activity to suppress abnormal DNA methylation in patients with cancer.

A TET2–DNMT1 COMPLEX PREVENTS ABNORMAL DNA METHYLATION

The TET proteins promote DNA demethylation by converting 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC). TET2 is frequently mutated or inactivated in cancer, and it has been suggested that the TET proteins may protect against abnormal DNA methylation at promoters. Zhang and colleagues found that the enzymatic activity of TET2 was enhanced by acetylation at K110 by p300, and, conversely, that TET2 activity was reduced by HDAC1/2-mediated deacetylation. Acetylation stabilized TET2 by preventing its ubiquitination and subsequent proteasomal degradation, thereby increasing TET2 activity. Mechanistically, TET2 acetylation enhanced the interaction between TET2 and the DNA methyltransferase DNMT1, which increased the stability of both proteins. Oxidative stress has been previously associated with abnormal methylation and recruitment of DNMT complexes to promoter CpG islands, and, consistent with these findings, acetylation of TET2 promoted its DNMT1-dependent association with chromatin under conditions of oxidative stress. TET2 bound to thymine-DNA glycosylase (TDG), which is required for TET2-mediated demethylation. The TET2–TDG interaction was independent of TET2 acetylation, but oxidative stress recruited acetylated TET2–TDG to chromatin in a DNMT-dependent manner. Enhanced TET2 activity and chromatin binding was associated with increased global levels of 5hmC and a global decrease in DNA methylation. Depletion of TET2 induced DNA hypermethylation especially at promoter CpG islands, resulting in downregulation of genes including those with bivalent chromatin in embryonic stem cells, many of which are involved in development, differentiation, or transcriptional regulation. Taken together, these results indicate that TET2 may oppose the function of DNMT1 in TET2–DNMT1 complexes, and suggest that TET2 activity may protect against abnormal DNA methylation under conditions of oxidative stress. Further, these findings raise the possibility that HDAC inhibitors may potentially be used to maintain TET2 activity and prevent aberrant DNA methylation in patients with cancer. ■

Zhang YW, Wang Z, Xie W, Cai Y, Xia L, Easwaran H, et al. Acetylation enhances TET2 function in protecting against abnormal DNA methylation during oxidative stress. Mol Cell 2017;65:323–35.

AACR American Association for Cancer Research

CANCER DISCOVERY

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