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 tumors, and 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 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, deletion 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.


Epigenetics

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.
