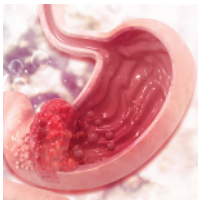
Gastrointestinal Cancer

Major Finding: Succinate dehydrogenase-deficient gastrointestinal stromal tumors have altered genome topology.

Mechanism: Hypermethylation at insulating CTCF binding sites causes aberrant superenhancer–oncogene contact.

Impact: This study identifies a previously unknown driving mechanism and demonstrates its relevance in mice.

DISRUPTED DOMAIN BOUNDARIES DRIVE SOME GASTROINTESTINAL CANCERS



Gastrointestinal stromal tumors (GIST) are usually driven by mutations in either the KIT or PDGFRA receptor tyrosine kinases (RTK), but some instead have loss of succinate dehydrogenase (SDH), which is associated with DNA hypermethylation. Flavahan, Drier, and colleagues found that DNA hypermethylation in SDH-deficient GIST leads to alterations in genome topology that trigger activation of non-mutated proto-oncogenes. Chromatin immunoprecipitation and sequencing experiments revealed that 5% of binding sites for the transcription factor CTCF were lost in SDH-deficient GIST compared with mutant TKI-driven GIST, and these sites had greatly increased DNA methylation. Mapping of topologically associating domain (TAD) boundaries along with enhancer mapping and analysis of gene-expression data showed that among these sites, 60 were CTCF loop anchors that would otherwise have prevented contact between superenhancers and specific genes. Notably, one such missing TAD boundary would normally prevent contact between a superenhancer and the oncogenes *FGF3* and *FGF4*, and *FGF3* and *FGF4* expression were increased 6-fold and 35-fold, respectively, in SDH-deficient GIST. Similar results were observed with the wild-type *KIT* proto-oncogene. Further, experiments using a GIST-derived cell line in which the two CTCF binding sites that normally insulate *FGF4* from the superenhancer were edited indicated increased contact between the superenhancer and *FGF4* as well as increased *FGF4* expression in this context. These results imply that the loss of these CTCF binding sites is directly responsible for the topological changes around *FGF4* and the associated increase in *FGF4* expression seen in SDH-deficient GISTs. In a new patient-derived xenograft mouse model of SDH-deficient GIST, treatment with a KIT inhibitor somewhat suppressed tumor growth, treatment with an FGFR inhibitor substantially reduced tumor growth, and combined treatment resulted in even greater suppression of tumor growth, implying functional significance for the observed epigenetic alterations. Collectively, these findings identify a possible driving mechanism behind SDH-deficient GIST oncogenesis and tumor maintenance and provide a proof of concept for treatment of this subset of GISTs with FGFR and KIT inhibitors. ■

Flavahan WA, Drier Y, Johnstone SE, Hemming ML, Tarjan DR, Hegazi E, et al. Altered chromosomal topology drives oncogenic programs in SDH-deficient GIST. Nature 2019;575:229–33.

Metabolism

Major Finding: A previously unknown histone modification, lysine lactylation, was found in mouse and human cells.

Concept: M1 macrophage polarization increased histone lactylation, increasing expression of M2-like genes.

Impact: Investigation of the potential consequences of histone lactylation in cancer is of interest.

HISTONE LYSINE LACTYLATION REGULATES GENE EXPRESSION

Histone modifications, such as methylation and acetylation, are key regulators of gene expression, and some dysfunctional histone-modification patterns promote cancer. In human and mouse cells, Zhang, Tang, and colleagues identified histone lysine lactylation (Kla), a previously unrecognized histone modification. Both high-performance liquid chromatography–tandem mass spectrometry experiments and immunoblotting with a pan-Kla antibody supported the existence of Kla in cells. Extracellular lactate was able to stimulate histone lactylation, and exposure of cells to glucose (from which most intracellular lactate is derived) revealed that histone Kla levels were increased by glucose in a dose-dependent fashion. In accordance with this finding, inhibitors of intracellular lactate production reduced histone Kla levels, whereas a compound that inhibits glycolysis (thus increasing intracellular lactate concentrations) increased histone Kla levels. Demonstrating the potential physiologic relevance of these results, hypoxia, which causes increased levels of intracellular lactate by enhancing glycolysis, was associated with an increase in histone Kla levels. Further, intracellular lactate and histone Kla levels were increased following M1 macrophage polarization, a process that involves a switch to aerobic glycolysis. The increase in histone Kla levels in this context had a functional consequence—an induction of M2-like genes in the M1 macrophages. Experiments in which lactate levels during M1 polarization were manipulated supported the observed role of intracellular lactate and histone Kla levels in promoting the expression of M2-like genes during M1 polarization. In summary, this study robustly demonstrates the presence and relevance of a previously unidentified histone modification, which may be important both during normal cellular processes and in cancer. ■

Zhang D, Tang Z, Huang H, Zhou G, Cui C, Weng Y, et al. Metabolic regulation of gene expression by histone lactylation. Nature 2019;574:575–80.