Transcription factor found to play pivotal role in development of right-sided colon cancers

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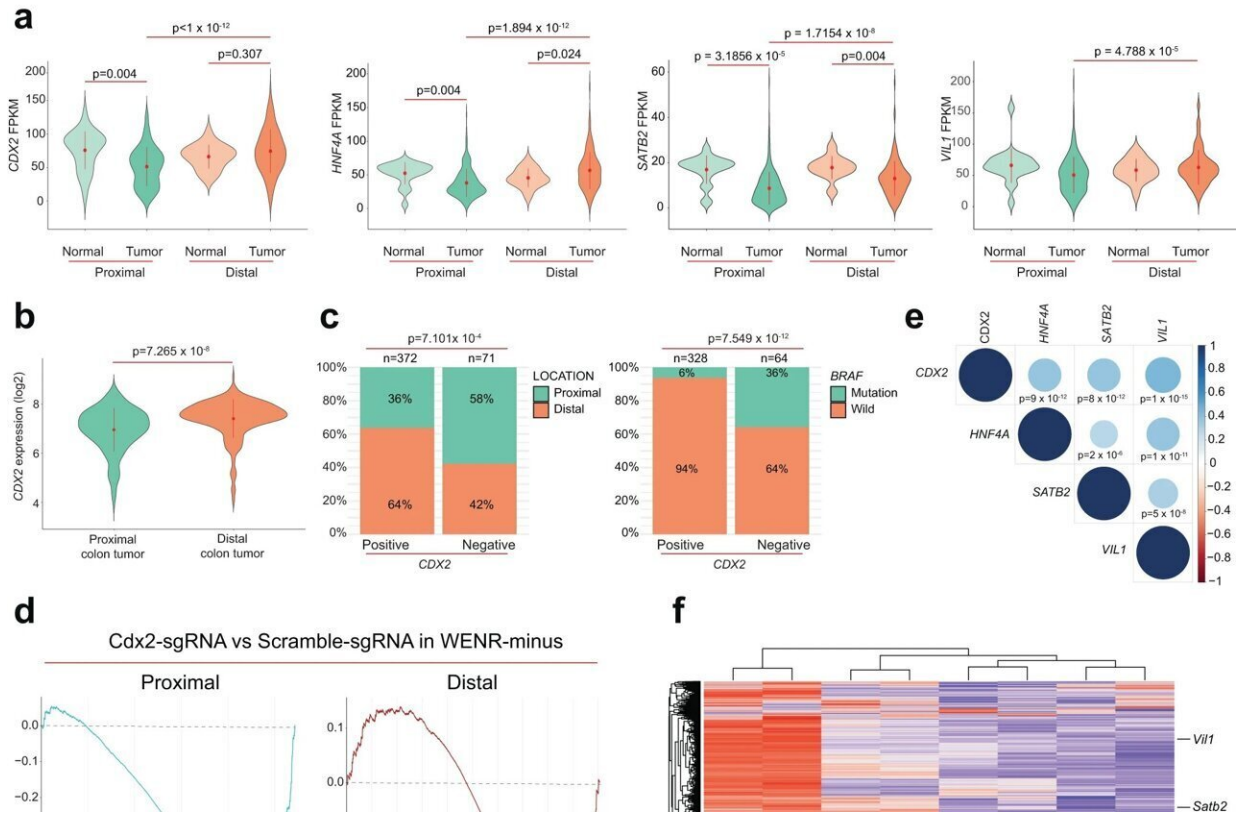

Cdx2 loss in mouse proximal colon organoid recapitulates gene expression patterns of human colon cancers with low *CDX2* expression. Credit: *Nature Communications* (2024). DOI: 10.1038/s41467-024-45605-4

The colon is often thought of as one organ, but the right and left parts of the colon have different molecular features in cancers. New research in mice from investigators at the Johns Hopkins Kimmel Cancer Center demonstrates that these regions also have distinct transcriptional programs, or cellular processes, that regulate the development of normal and cancerous cells.

The transcription factor CDX2—which plays an important role in the development and function of the digestive system—is a key mediator of these differences in proximal (right) colon stem cells, according to the research, which was published in *Nature Communications*.

CDX2 has distinct roles in regulating stem cell differentiation in the proximal and distal (left) colon regions, the study finds. This distinction in stem cell regulation could help explain various features of colon cancers housed in these two areas of the colon.

In cancers, the proximal and distal regions of the colon have a tendency to house different gene mutations, explains senior study author Hariharan Easwaran, Ph.D., an associate professor of oncology at the Johns Hopkins University School of Medicine. For example, mutations in the BRAF gene contribute to cancers mainly in the proximal region, while mutations in the KRAS gene more commonly contribute to cancers in the distal colon and rectal regions.

There also are a lot of epigenetic differences—modifications to DNA that regulate whether genes are turned on or off—between the two regions. The BRAF-driven proximal colon cancers are associated with a very high frequency of DNA methylation, a chemical modification of DNA, in gene regulatory elements such as the CpG islands.

BRAF mutations are associated with a poor prognosis in colon cancers. However, drugs that target mutations in BRAF haven't performed as well

in colon cancers compared to other types of cancer, such as melanoma, Easwaran says.

"Dissecting this biology is important to understanding the basis for key differences in the molecular genetics and clinical features of these cancers, and in general for understanding why cancers arising within highly similar tissues in the colon may exhibit distinct features," he says.

During the study, investigators derived proximal and distal colon organoids from 2-month-old mice and introduced the BRAF cancer-causing gene. Organoids are lab-grown clusters of cells that resemble specific organs, such as the colon, and can grow indefinitely. They mimic the stem cell and differentiation patterns of the original tissue source, in this case, the colon.

The investigators identified small differences in gene expression in the proximal and distal colon-derived organoids. However, the loss of CDX2 produced distinct differences in the regulation of genes controlling stem cells and differentiation.

The investigators observed that CDX2 specifically promotes changes to stem cells in the proximal colon that allow typical cell differentiation into various cell types of the colon. But the loss of CDX2 function instead causes them to become more primitive and stem-cell-like. Because BRAF-mutant colon cancers are associated with loss of CDX2 expression, the investigators suppressed CDX2 in cells containing the BRAF mutation to see what would happen.

In proximal colon stem cells, silencing CDX2 allowed BRAF mutations to drive tumor initiation in the stem cells, whereas in the distal colon, silencing CDX2 did not yield much change. The work found that CDX2 serves important roles in regulating stem and differentiated cell states, specifically in epithelial cells lining the proximal colon.

"What this means is when CDX2 function is lost, it immediately alters the state of cells to promote tumor initiation in the proximal colon, whereas, in the distal colon, this doesn't happen," says lead author Lijing Yang, M.D., an oncologist at Zhongnan Hospital of Wuhan University in China. Yang was at Johns Hopkins at the time the study was conducted.

"There is something very different in how stem cells are regulated in these two regions, and it underscores the potential for epigenetic factors in modulating tumor initiation differently in the proximal and distal colon," Yang says.

The work has implications for new combinations of existing therapies for colon cancers, such as drugs designed to inhibit the BRAF and KRAS genes, Easwaran says.

"Colon cancers are very notorious in that they develop resistance to these inhibitors," he says. "There's a lot of interest in trying to figure out how else we can actually improve the efficiency of these drugs."

The next steps are to try to determine what central mechanisms are occurring in the distal colon that reduce the incidence of BRAF-driven tumors and create a higher likelihood for KRAS-driven cancers. "Our study shows that the transcriptional states regulating stem cell and differentiation states are important for the cancer driver mutations to drive cancers," Easwaran says.

"It also helps explain why tumors arising in different anatomical locations may rely on different cancer-driving mutations. Therefore, determining the mechanisms will help identify novel ways of targeting critical dependencies for these oncogenic mutations."

More information: Lijing Yang et al, Tissue-location-specific transcription programs drive tumor dependencies in colon cancer, *Nature*

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