Medical Xpress

Gene pair plays crucial role in colon cancer, research shows

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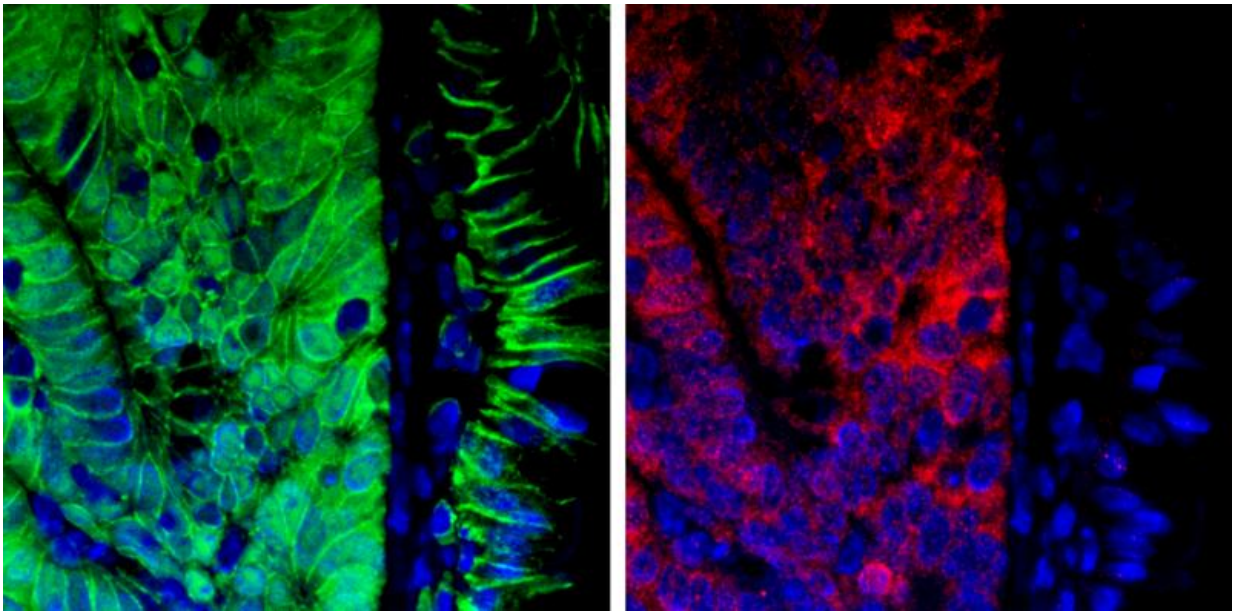

β-catenin (green) and MSI1 (red) are differently expressed in tumors (left portion of each panel) compared to normal tissue.

Colon cancer is one of the leading causes of cancer-related deaths worldwide, and researchers are hard at work to understand the disease's complex molecular underpinnings. In a new study out this month in the journal *Cell Reports*, researchers from the University of Pennsylvania describe two related genes in the Musashi family that are required for colon cancer to develop, and that may be useful targets for effective

treatment.

The work, led by Christopher Lengner, an assistant professor in the Department of Biomedical Sciences in Penn's School of Veterinary Medicine, challenges a paradigm in the field whereby activation of a molecular signaling cascade known as the Wnt pathway is held responsible for the majority of colon cancer cases in humans. The new findings suggest that the Musashi genes, MSI1 and MSI2, act in a path parallel to the Wnt pathway and may be equally important for driving colon cancer.

The work also indicates that the two genes, which encode RNA-binding proteins, are functionally redundant.

"The data suggest that either MSI protein is sufficient to support cancer," Lengner said. "If you want to use these proteins as a drug target, you'd have to design a drug that will inhibit both of them."

While researchers have known for some time that MSI1 was expressed in colon cancer, the mechanism by which it acted and its functional requirement for the disease were not well understood. The related protein MSI2 had not been rigorously examined in the context of colon cancer until earlier this year, when a paper in Nature Communications by Lengner and colleagues found that it could trigger activation of cellular metabolic processes that fuel cancerous cells in the intestines.

"Considering the expression patterns of these two proteins during homeostasis, or normal conditions, you would expect their function when they were hijacked by cancer could be similar in supporting tumor growth," said Ning Li, first author on the study and a postdoctoral fellow in Lengner's lab.

The current work took both proteins into account. Whereas the prior

paper found that MSI2 was consistently overexpressed in intestinal cancer tissue, Lengner and colleagues found that MSI1 was more variable, overexpressed in some samples and underexpressed in others, compared to normal tissue. When they bred mice in which they could induce overexpression of MSI1 in the intestine, the cells of the intestine began to divide rapidly and lost their ability to differentiate, just as mice with inducible overexpression of MSI2 had.

They found that inducing MSI1 turned on a similar set of genes as MSI2 overexpression did, including genes related to RNA processing and translation, necessary processes for manufacturing the required components for cancer's rapid cell growth. The analysis also revealed that activating MSI1 caused a set of genes to be expressed that match the effect of losing the function of APC, a tumor suppressor gene that is inactivated in more than 80 percent of cases of human colon cancer.

As they had done with MSI2, the researchers also conducted an experiment that reveals the RNA transcripts to which MSI1 binds, and they found high levels of similarity to the set of transcripts bound by MSI2. Notably, both proteins bind tumor suppressors, such as Pten, which activates cellular metabolism through a protein complex called mTORC1. Further experiments confirmed MSI1 promoted mTORC1 activity.

"We concluded that these proteins are functioning in the same pathways and acting redundantly not only because they are binding similar proteins but also because when you overexpress them, the phenotype is identical," Lengner said. "They appear to have identical oncogenic properties."

To confirm whether both MSI1 and MSI2 are necessary for tumor formation, the researchers inhibited one or the other or both in several human colorectal cancer cell lines. Whereas inhibiting only MSI1 blocked growth of some cell lines but not others, inhibiting both MSI1

and MSI2 together effectively blocked cell growth in all of them. Adding an inhibitor of β-catenin, the downstream mediator of the Wnt pathway, synergized with MSI inhibition to completely block tumor cell growth.

The research team performed a similar experiment in vivo, developing mice that had only one copy of APC, and were thus at a heightened risk of developing colorectal tumors, and could be induced to either lack MSI1, MSI2 or both in their intestinal tissue. While knocking out one or the other MSI proteins didn't affect tumor formation, knocking out both genes markedly reduced the tumors in these mice. Performing the same experiments in mice that develop an inflammation-induced form of colorectal cancer that more closely resembles the human disease, the team again found Msi loss was completely protective against tumor formation.

"By deleting both MSIs we find that it completely blocks the tumors from forming, but other than that the tissue seems to be perfectly normal," Lengner said. "This is interesting because it's what one would look for in an ideal cancer target, something that, when you inhibit it, it can block cancer progression without adversely effecting the normal tissue."

Lengner also noted that blocking the mTORC1 pathway might be another viable strategy for targeting the downstream activity of the MSI proteins, perhaps in combination with an inhibition of Wnt/β-catenin, a pathway the researchers believe may act distinctly but parallel to MSI activity.

"There are already mTORC1 inhibitors in existence, so one could imagine a combined approach could be an effective strategy," Lengner said.

Moving forward with this work, Lengner and colleagues plan to investigate which specific cell types the MSI proteins act upon and to delve deeper to understand how APC inactivation triggers colon cancer through β-catenin and other avenues.

Provided by University of Pennsylvania