Microbiome provides new clues to determining development of colon cancer

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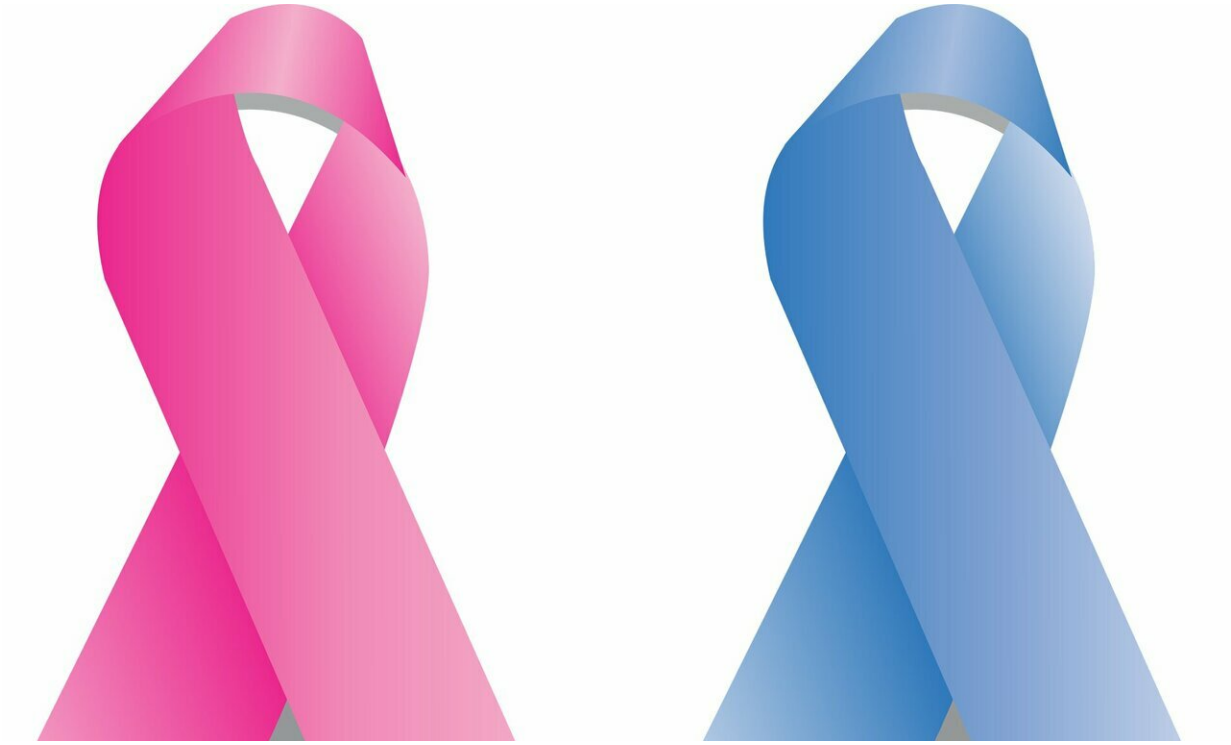

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A mutant protein found in humans with colon cancer blocks a pathway that regulates proliferation and expansion of cells, increasing amounts of bacterial species associated with the development of colon cancer. These findings, showcasing the connection between bacteria in the microbiome and colon cancer, were published by a team of researchers from the

George Washington University (GW) in the journal *Gastroenterology*.

"Colon cancer is increasing in young people. Current guidelines recommend screening those over age 50 for colon cancer, but today we are seeing that 15% of those with colon cancer are under the age of 50," said Lopa Mishra, MD, director of the Center for Translational Medicine at the GW Cancer Center and professor of surgery at the GW School of Medicine and Health Sciences. "We hypothesized that diet and its effects on the microbiome may be big players, which is where we focused our study."

Mishra and the research team looked at the interactions among proteins of the carcinoembryonic antigen related cell adhesion molecular (CAECAM) family, which interact with microbes, leading to changes in the growth factor beta (TGFB) signaling pathway. The team collected data on DNA sequences, mRNA expression levels, and patient survival times from 456 colorectal adenocarcinoma cases, and a separate set of 594 samples of colorectal adenocarcinomas, in The Cancer Genome Atlas. The team then used the GW Genomics Core to perform shotgun metagenomic sequencing analysis of feces from mice with defects in TGFB signaling to identify changes in the microbiome before colon tumors developed.

The team found that the expression of CEACAMs and genes that regulate stem cell features of cells are increased in colon cancer and inversely correlated with expression of TGFB pathway genes. They also found colon cancer to express mutant forms of CEACAM5 that inhibit TGFB signaling and increase proliferation and colony formation. This could lead to less invasive screening techniques for colon cancer, particularly for younger patients.

"We found four microbiome species profoundly altered in our mouse study," said Shuyun Rao, Ph.D., assistant research professor of surgery

at the GW School of Medicine and Health Sciences. "Our next steps are to explore this in greater detail and in a much larger population—in the future, younger patients can simply have their stool tested for these altered microbiomes and look for risk for colon cancer, preventing its development."

In addition to Mishra and Rao, the research team consisted of Shoujun Gu, Ph.D., bioinformatics scientist at the National Institutes of Health, and Sobia Zaidi, Ph.D., postdoctoral scientist at the GW School of Medicine and Health Sciences. There were also significant contributions made by Raja Mazumder, Ph.D., co-author and professor of biochemistry and molecular medicine at the GW School of Medicine and Health Sciences and Keith A. Crandall, Ph.D., director of the Computational Biology Institute at Milken Institute School of Public Health at GW, and their research teams, who just published a microbial profile in the journal *PLOS ONE.*

"Mutated CEACAMs Disrupt Transforming Growth Factor beta Signaling and Alter the Intestinal Microbiome to Promote Colorectal Carcinogenesis" was published in *Gastroenterology*.

More information: Shoujun Gu et al. Mutated CEACAMs Disrupt Transforming Growth Factor beta Signaling and Alter the Intestinal Microbiome to Promote Colorectal Carcinogenesis, *Gastroenterology* (2019). DOI: 10.1053/j.gastro.2019.09.023

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