How mouth microbes may worsen colorectal cancer

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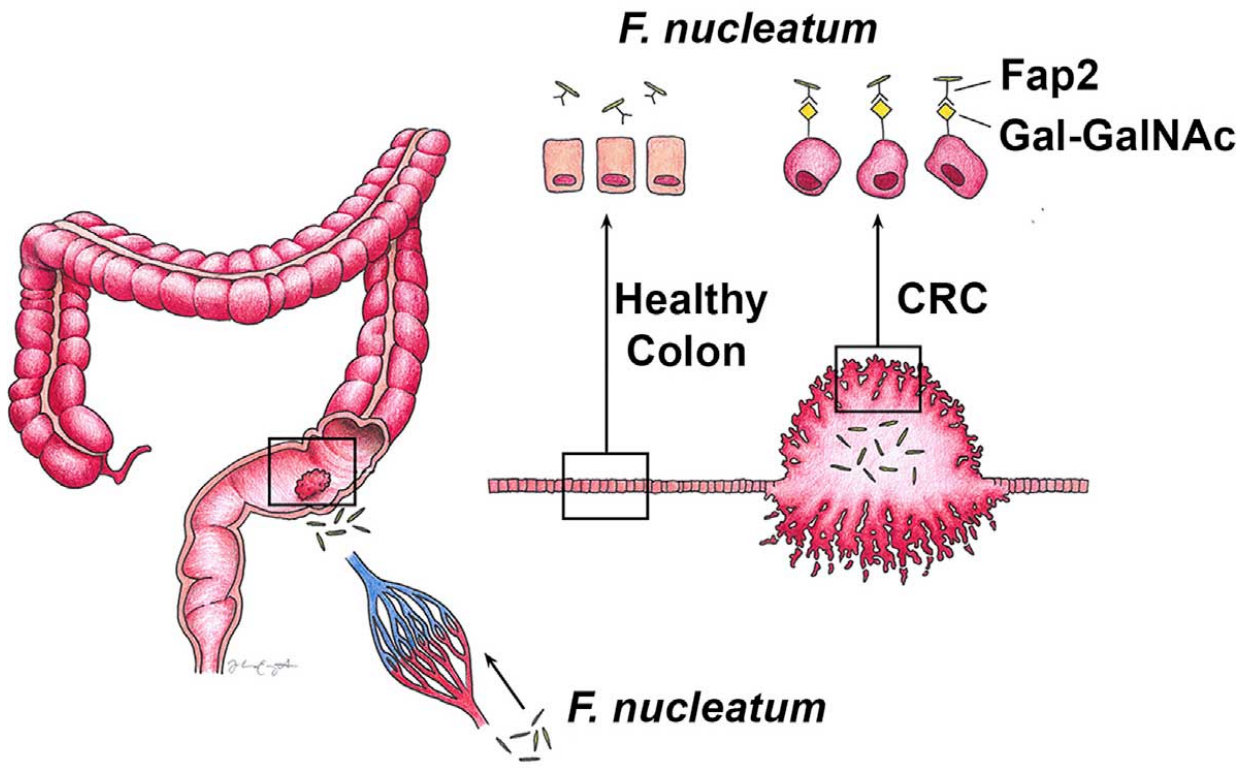

This visual abstract depicts the findings of Abed and Emgard et al., who identify a host polysaccharide, Gal-GalNAc, and fusobacterial lectin (Fap2) that explicates fusobacteria abundance in CRC. Targeting Fap2 or host Gal-GalNAc may provide a means to reduce F. nucleatum potentiation of CRC. Credit: Abed and Emgard et al./*Cell Host & Microbe* 2016

Bacteria commonly found in the mouth have been recently shown to worsen colorectal cancer in animals, but it has not been clear how these microbes make their way to the gut in the first place. A study published August 10 in *Cell Host & Microbe* sheds light on this question, revealing that oral microbes called fusobacteria may use the bloodstream to reach colorectal tumors. The findings also show exactly how these bacteria home in on colorectal tumors, where they proliferate and subsequently accelerate colorectal cancer.

"As fusobacteria contribute to colon tumor development, revealing the mechanism that guides them to the tumor and why fusobacteria become abundant there might inform ways of blocking this," says co-senior study author Wendy Garrett of the Harvard T.H. Chan School of Public Health and the Dana-Farber Cancer Center. "Alternatively, and perhaps more importantly, if we know how fusobacteria localize and become enriched in colon tumors, hopefully we can utilize the same or similar mechanisms to guide and deliver cancer therapeutics to colon tumors."

Colorectal cancer is the third leading cause of cancer-related deaths in the United States, and microbes have emerged as key factors that influence the development and progression of the disease. Recent studies have shown that fusobacteria promote the formation of colon tumors in animals and are enriched in human colorectal tumors compared to adjacent normal tissue. But these studies left it unclear how bacteria from the mouth localize to, and become abundant in, colorectal tumors.

Garrett and co-senior study author Gilad Bachrach of the Hebrew University-Hadassah School of Dental Medicine suspected that oral microbes might reach colorectal tumors through the bloodstream. To test this idea, they injected fusobacteria into the tail veins of two mouse models with either precancerous or malignant colorectal tumors. In both types of mice, the fusobacteria became enriched in colorectal tumors compared to adjacent normal tissue. The researchers also detected

fusobacteria in the majority of human colorectal cancer metastases tested, but not in most samples taken from tumor-free liver biopsies.

Using human samples and mouse models, the researchers went on to discover that the Fap2 protein located on the surface of fusobacteria recognizes a sugar called Gal-GalNac, which is abundant on the surface of colorectal tumor cells. Additional experiments showed that Fap2 mediates fusobacterial colonization of colorectal cancer tumors and metastases. Recent studies have shown that this protein also impairs the ability of the host immune system to kill tumor cells. Taken together, the findings suggest that fusobacteria travel through the bloodstream to reach colorectal tumors, and then use their Fap2 protein to bind to host cells and proliferate in tumors, thereby accelerating colorectal cancer.

"The strengths are that the study involved both human samples and mouse models. The weakness is that the available mouse models for colorectal adenocarcinoma do not completely reflect the slowly developing disease in humans," Bachrach says. "Based on our findings, it's too early to say whether we can prevent mouth bacteria from traveling through blood to the colon and promoting tumor formation or if some people are more at risk than others."

In future studies, the researchers will further examine how fusobacteria contribute to the development, growth, and spread of colorectal cancer. "Although it may not be possible to prevent oral microbes from entering the bloodstream and reaching colorectal tumors, our findings suggest that drugs targeting either Fap2 or Gal-GalNac could potentially prevent these bacteria from exacerbating colorectal cancer," Garrett says.

More information: Abed and Emgard et al.: "Fap2 Mediates Fusobacterium nucleatum Colorectal Adenocarcinoma Enrichment by Binding to Tumor-Expressed Gal-GalNAc," *Cell Host & Microbe*. www.cell.com/cell-host-microbe … 1931-3128(16)30305-5. DOI:

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