Microbes in the gut help determine risk of tumors

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Transferring the gut microbes from a mouse with colon tumors to germ-free mice makes those mice prone to getting tumors as well, according to the results of a study published in *mBio*, the online open-access journal of the American Society for Microbiology. The work has implications for human health because it indicates the risk of colorectal cancer may well have a microbial component.

"We know that humans have a number of different community structures in the gut. When you think about it, maybe different people - independent of their genetics - might be predisposed," says Joseph Zackular of the University of Michigan, an author on the study.

Scientists have known for years that inflammation plays a role in the development of colorectal cancer, but this new information indicates that interactions between inflammation and subsequent changes in the gut microbiota create the conditions that result in colon tumors.

Co-author Patrick Schloss, also of the University of Michigan, was somewhat surprised by the clarity of the results.

"We saw more than two times the number of tumors in mice that received the cancerous community [than in mice that received a healthy gut community]," says Schloss. "That convinced us that it is the community that is driving tumorigenesis. It's not just the microbiome, it's not just the inflammation, it's both."

Known risk factors for developing colorectal cancer include consuming a diet rich in red meat, alcohol consumption, and chronic inflammation in the gastrointestinal tract (patients with inflammatory bowel diseases, such as ulcerative colitis, are at a greater risk of developing colorectal cancer, for instance). Cancer patients also exhibit shifts in the composition of their gut microbiota - a phenomenon called dysbiosis - but it's unclear whether changes in the microbiome drive the development of cancer or the cancer drives changes in the microbiome.

It's a question of the chicken and the egg, says Zackular. "Is this the microbiome of someone with cancer or is the microbiome driving tumorigenesis?"

Schloss, Zackular, and their colleagues reasoned that the composition, structure, and functional capacity of the gut microbiome all directly affect tumor development in the colon, so they set out to address this chicken-and-egg conundrum with mice. Using a tumor-inducing regimen, they induced the formation of colorectal tumors in a set of mice, then collected feces and bedding from those tumor-bearing mice and gave them over to germ-free mice. (Mice are coprophagic, so inoculating germ-free mice with a new gut microbiome is as easy as that.) They then administered the regimen to these new mice.

The results were stark: mice given the microbiota of the tumor-bearing mice had more than two times as many colon tumors as the mice given a healthy microbiota. What's more, normal mice that were given antibiotics before and after inoculation had significantly fewer tumors than the mice that got no antibiotics, and tumors that were present in these antibiotic-treated mice were significantly smaller than tumors in untreated mice. This suggests that specific populations of microorganisms were essential for the formation of tumors, so the researchers then drilled down into which groups of bacteria were present in the test animals and controls.

Looking at the microorganisms, they found that tumor-bearing mice harbored greater numbers of bacteria within the *Bacteroides*, *Odoribacter*, and *Akkermansia* genera, and decreased numbers of bacteria affiliated with members of the Prevotellaceae and Porphyromonadaceae families. Three weeks after they were inoculated with the communities from the tumor-bearing mice, the germ-free mice had a gut microbiome that was very similar to the tumor-bearing mice, and they had a greater abundance of the same bacterial groups associated with tumor-formation.

"In all these [mouse] models the inflammation is critical, but so is the change in the communities," says Schloss. "We liken it to a feed-forward type mechanism where the inflammation is changing the community and the community is inducing inflammation. They make each other worse to the point that you have higher rates of tumor formation."

To follow up on the work, Schloss and Zackular are now studying the functions of the groups that are and are not associated with tumor formation.

"If you can better understand what functions in the microbial community are important for protecting against tumor formation or making it worse, we can hopefully translate those results to humans to understand why people do or do not get colorectal cancer, to help develop therapeutics or dietary manipulations to reduce people's risk," says Schloss.

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