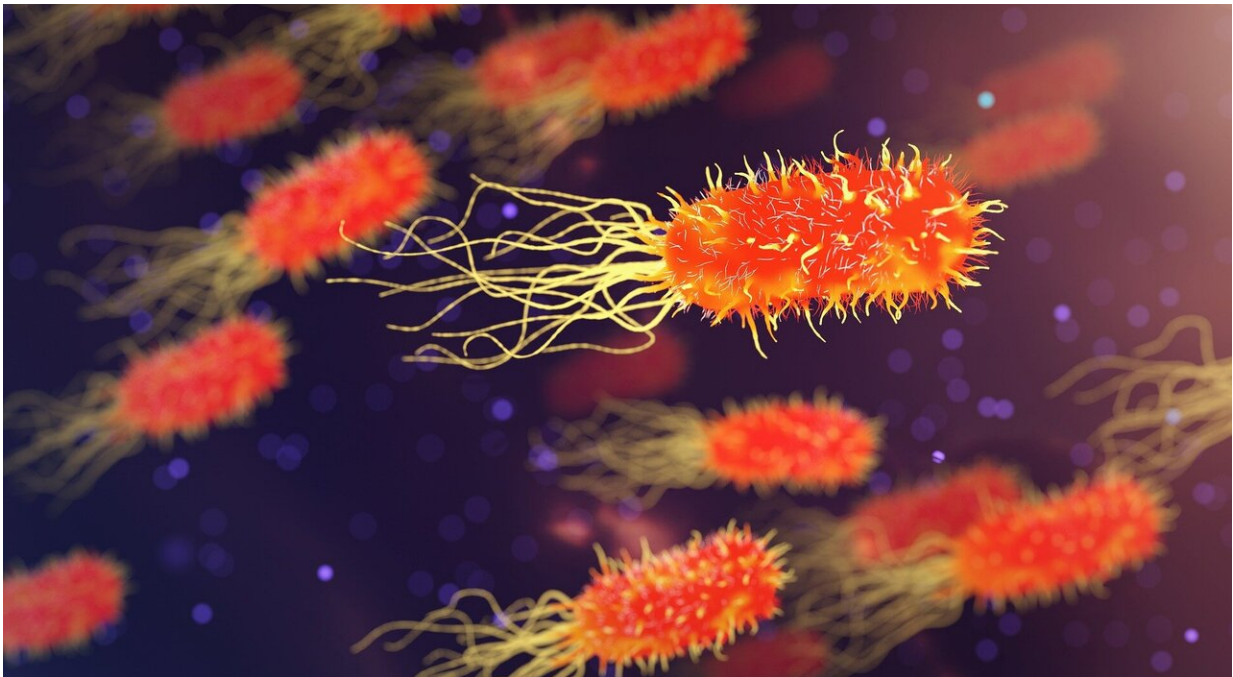


Two new studies show how bacteria could help tumors progress and resist treatment

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Two new studies from researchers at Fred Hutchinson Cancer Center in Seattle reveal how bacteria infiltrate tumors and could be helping tumors progress and spread. The research team also showed that the different microbial players in a tumor's microbiome could influence how a cancer responds to treatment.

The findings also suggest a link between oral health and [cancer](#), as microbes in the mouth are associated with cancers elsewhere in the body.

The two papers—one published Nov. 15 in [Cell Reports](#) and the other published Nov. 16 in [Nature](#)—focus on an oral bacterium called *Fusobacterium nucleatum*, which has been linked to [colorectal cancer](#).

Tumors often have help in their efforts to survive and grow. Non-cancerous [cells](#) around a tumor can help it avoid attacks by the [immune system](#), resist therapies that target them and allow it to spread to other parts of the body. Researchers are now finding that some of these helpful neighbors aren't even [human cells](#)—they're [bacteria](#).

"What we're showing is that there are regions of the tumor that are heavily colonized by bacteria—micro-niche regions—and they differ functionally from regions that do not harbor bacteria," said Fred Hutch cancer microbiome researcher and study co-lead Susan Bullman, Ph.D., referring to the work outlined in the Nature study. "And these bacteria-rich regions have increased metastatic potential."

Bullman and her collaborator, Fred Hutch molecular microbiologist Christopher D. Johnston, Ph.D., combined observations from tumors with lab-based experiments and small-molecule drug screens to show that *F. nucleatum* may shape conditions in tumors to keep them safe from immune attack and help them spread through the body. They discovered that some cancer therapeutics may work because they not only target tumor cells, but also the bacteria that are helping them.

The research team, which includes first author Jorge Galeano Niño a postdoctoral researcher at Fred Hutch, also found that other microbes—including the intestinal bug *Escherichia coli*, or E. coli—may render an anti-microbicidal and chemotherapeutic drug ineffective,

which could shield both the tumor and *F. nucleatum* from treatment. These findings could help researchers develop new strategies to treat or target cancer by tackling its microbiome.

"This work is at the intersection of cancer and microbiome research," Bullman said. "There's compelling emerging data to suggest that nearly all major cancer types harbor an intra-tumoral microbiota."

An association with bacteria may seem logical in colorectal cancer, but breast, pancreatic and lung tumors are among other cancers shown to harbor microbial communities, and studies are showing that tumor microbiomes may shape development, progression and response to treatment.

Adapting a leading-edge technology that allows researchers to detect where genes are turned on and off in slices of tumor tissue—spatial transcriptomics—the team found that a range of bacterial species were living within oral and [colorectal cancers](#), but they weren't spread evenly.

"We observed bacterial hotspots, or micro-niches, which opened up a number of questions as to how these formed and might be impacting cancer biology," Johnston said.

Regions colonized by bacteria were highly immune suppressive and had fewer cancer-killing T cells than other areas. Areas that had T cells near bacteria also had an upregulation of immune checkpoint proteins, which restrain the cancer-killing effects of T cells. Several checkpoint inhibitors are approved for use in colorectal cancer, and this study may help explain how a patient's microbiota could influence whether their cancer responds to a checkpoint inhibitor.

Specific findings from the studies:

- Regions with bacteria were more likely to be necrotic—dying—with fewer dividing cells. Ironically, according to other research, this can be associated with metastasis because cells break off and travel to distant sites in the body.
- In the lab, the researchers grew colorectal cancer spheroids, which are tumor cells grown in 3D clusters, with immune cells called neutrophils, which reduce T-cell migration and invasion. The neutrophils spread through spheroids without bacteria. But in those with bacteria, neutrophils migrated to the center of the spheroid and became trapped—a finding that could explain why there are few T cells in regions colonized by bacteria.
- Tumor cells in the spheroids moved differently when bacteria were present. Instead of moving in masses as a group, cancer epithelial cells migrated as single cells, bringing bacteria with them. This is consistent with Bullman's previous work showing that *F. nucleatum* often hitches rides with colorectal cancer metastases.
- Tumor cells infected with bacteria ramped up genes associated with cancer progression and metastasis. In oral tumor samples, the researchers saw that bacteria preferentially infected cancer epithelial cells and specific immune cells within patients' tumors. Infected tumor cells had increased DNA damage signaling, a hallmark of cancer. These findings support bacteria having a direct role in shaping these micro-niche regions, the researchers said.
- Some anti-cancer drugs may be effective because they are also antimicrobials that target bacteria supporting [tumor](#) development. The cancer-promoting bacterium *F. nucleatum* is highly sensitive to a common chemo drug called 5-fluorouracil, or 5-FU, but the researchers found that *E. coli* bacteria protected colorectal cancer cells from 5-FU. *E. coli* apparently has a way to metabolize the drug and minimize its exposure to cancer cells or other bacteria. "The findings show that intra-tumoral microbes are not innocent

bystanders during [disease progression](#), and suggest that the microbiota should be taken into consideration when thinking about optimal cancer treatments," Johnston said.

Related to these studies, the researchers are studying possible links between [oral health](#) and cancer risk.

"There is a trend emerging of microbes that are traditionally associated with oral inflammatory disease being found in association with extra-oral and gastrointestinal cancers—which highlights the oral cavity as a breeding ground for pathogenic onco-microbes," Johnston said.

In addition to allowing pathogens to spread to new areas of the body, it is possible that inflammation in the mouth, in the form of periodontal or endodontic disease, could be selecting for and encouraging the outgrowth of bacteria that are more specialized for growth in adverse conditions and capable of evading immune attack, he said.

The research team will continue to explore the possibility of making tumors more responsive to immunotherapy or chemotherapy by manipulating the microbiome, and they are seeking to design microbiome-modulating therapeutics that will prevent and treat cancer and stop its spread. Showing that microbes cluster in hard-to-reach areas of tumors, they have already clarified some of the hurdles they will have to overcome to develop these new approaches.

"This holistic approach to assessing the [tumor](#) microenvironment, which is a multi-species ecosystem, will advance our understanding of [cancer biology](#), and I believe will reveal new therapeutic vulnerabilities in cancer," Bullman said.

More information: Susan Bullman, Effect of the intratumoral microbiota on spatial and cellular heterogeneity in cancer, *Nature*

(2022). [DOI: 10.1038/s41586-022-05435-0](https://doi.org/10.1038/s41586-022-05435-0).
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