

WHERE DOES THE TUMOR MICROBIOME COME FROM?

Among the many questions that remain about the cancer microbiome is where tumor-bound bacteria come from. One likely source is the abundant microbiome of the gastrointestinal tract. When MD Anderson physician-scientist Florencia McAllister and colleagues sequenced samples of patient tumors, they found that “surprisingly, around twenty percent of microbes in tumors was coming from the gut,” McAllister says (*Cell*, 178:795–806.E12, 2019). And the fact that they were absent in adjacent tissues suggested that “they were uniquely translocated to the tumors,” she adds. Indeed, when the team treated mice orally with fecal microbes from pancreatic cancer patients and then implanted mouse pancreatic cancer cells, some of those bacteria showed up in the animals’ subsequent tumors. McAllister and her colleagues also found plenty of microbes in the mice’s tumors that were in neither the gut nor the healthy tissue, however. McAllister says she suspects these are coming from the oral microbiome.

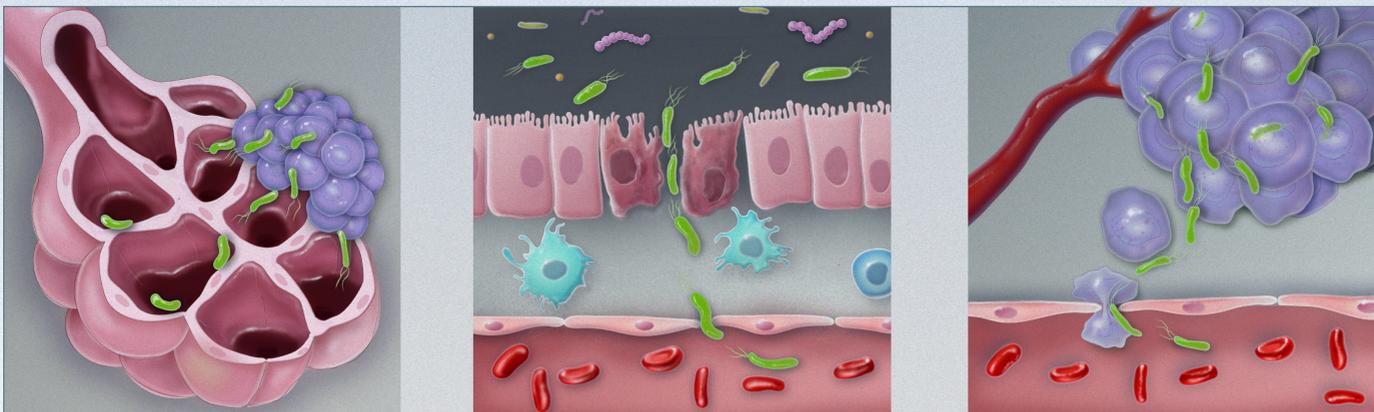
Karolinska Institutet clinical immunologist Margaret Sällberg Chen and colleagues have found evidence of just that in precancerous pancreatic cysts. “We were just surprised” to initially see bacteria known to be members of the oral microbiome, Sällberg Chen says, but the results held up in a larger cohort (*Gut*, 68:2186–94, 2019). Suspecting they had traveled through the blood to get there, the

team looked in plasma from patients who had developed pancreatic cancer and found increased antibody levels against some of the oral microbes, including *Fusobacterium*, which had previously been associated with other types of cancer. “So that was seemed like confirmation that oral microbes might have some role,” she says.

One type of cancer *Fusobacterium* has been strongly linked to is colorectal, which is perhaps not surprising as the bacteria are common members of the gut microbiome in addition to the oral microbiome. But the *Fusobacterium* in colorectal tumors may not come from the nearby gut but rather from the bloodstream, having entered the circulation from the oral cavity (*Front Cell Infect Microbiol*, 10:400, 2020). “Even though it’s close to the lumen of the colon, many of the bacteria may end up in the tumor from the bloodstream and not from the colon,” says Ravid Straussman of the Weizmann Institute of Science in Israel who was not involved in the study.

Regardless of where they originate, the bacteria found in tumors may then travel to distant sites in the body during metastasis. In December 2017, researchers published evidence that *Fusobacterium* and a suite of bacteria that it often co-occurs with are found in primary colorectal tumors and in metastases in the liver and other organs (*Science*, 358:1443–48, 2017). “[W]e hypothesize that *Fusobacterium* travels with the primary tumor cells to distant sites, as part of metastatic tissue colonization,” the authors write.

MICROBES ALL AROUND: Bacteria that reside in tumors likely come from multiple sources, including from surrounding healthy tissues and from the gut and other organs, potentially transported via the bloodstream. As cancer metastasizes, cells travelling to other parts of the body may be accompanied by bacteria originating in the primary tumor.



Local spread of commensal bacteria in healthy tissue

Translocation of bacteria across the gut epithelium into circulation, often due to cancer treatment

Metastatic spread of bacteria alongside tumor cells