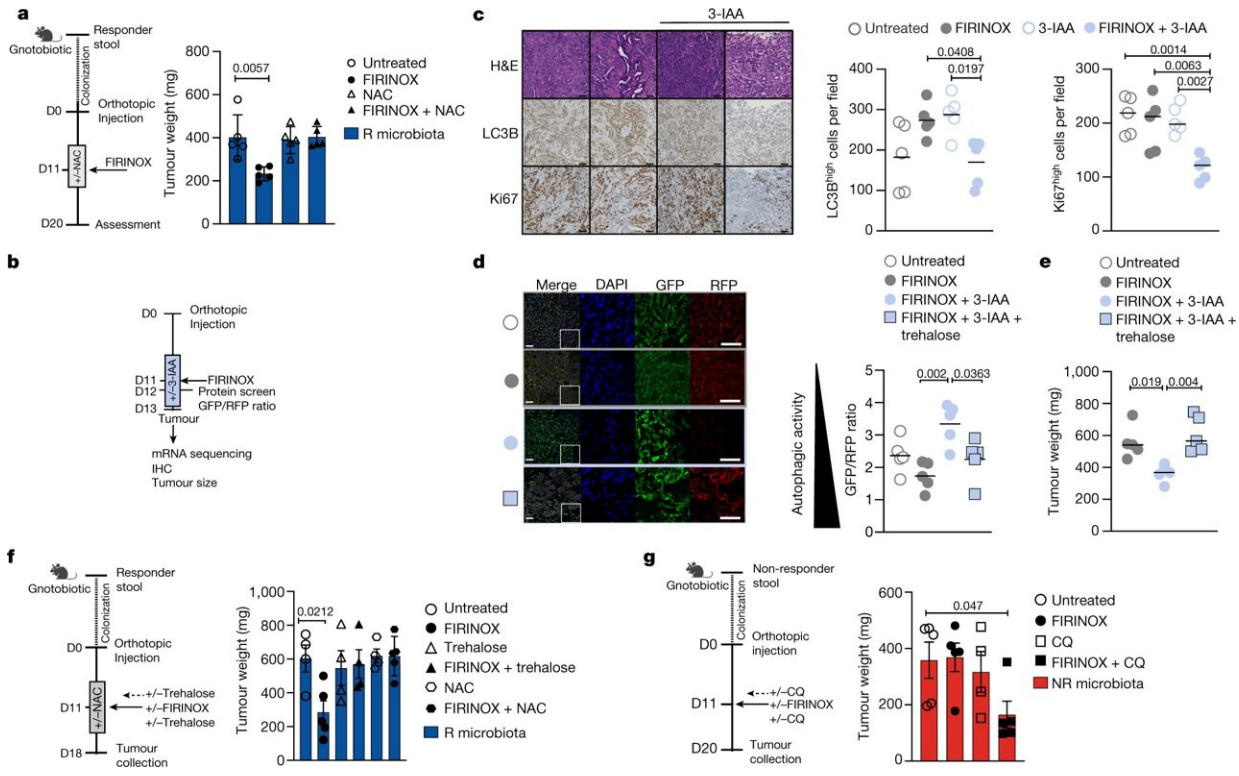
How gut bacteria can impact treatments for cancer

March 1 2023, by Bob Yirka



Treatment with 3-IAA and FIRINOX results in reduced autophagic activity. a, Gnotobiotic mice were colonized with R microbiota and KPC cells were orthotopically injected. Mice were untreated or treated with FIRINOX, NAC (day 9–13) or FIRINOX + NAC (n = 5 each). Tumor weight at day 20 of the experiment is shown. b, SPF mice bearing orthotopic KPC tumors were substituted +/− 3-IAA, treated with FIRINOX and analyzed as indicated. IHC, immunohistochemistry. c, Representative images of orthotopic tumors stained with haematoxylin and eosin (H&E), LC3B or Ki67 (left) and respective statistics for positive cells per field (n = 5 each) (right). Scale bars, 50 μm. d,e,

The GFP-LC3B-RFP reporter cell line Hy19636_GLRM was injected into SPF mice and mice were treated as indicated (n = 5 each). The graphs show the GFP/RFP ratio at day one (d) and tumor weight at day three (e) after FIRINOX treatment. Representative merged immunofluorescence images or indicated areas with a magnification of 3× are shown; scale bars, 10 μm. f, KPC cancer cells were orthotopically injected into R-microbiota-colonized mice and the indicated treatment was applied as shown in the scheme (n = 4 or 5). Tumor weight is shown at day 18 of the experiment. g, Tumor weight of orthotopic KPC tumors from gnotobiotic mice colonized with NR microbiota is shown nine days after the indicated treatment (n = 4 or 5). CQ, hydroxychloroquine. One experiment (c) or one out of two independent experiments (a,d,e–g) is shown. Each symbol represents one mouse. Error bars indicate s.e.m. Significant P values are indicated and were determined by one-way ANOVA followed by Dunnett's (a,c,f) or Tukey's (d,e) post-hoc test or Kruskal–Wallis test followed by Dunn's post-hoc test (g). Credit: *Nature* (2023). DOI: 10.1038/s41586-023-05728-y

A large team of cancer researchers affiliated with multiple institutions in Germany, working with a colleague from the U.S., has discovered some of the ways gut bacteria can positively impact treatments for cancer. In their study, published in the journal *Nature*, the group studied the impact of gut microbiota on chemotherapy given to patients with pancreatic ductal adenocarcinoma. Le Li and Florencia McAllister with the University of Texas MD Anderson Cancer Center, have published a News and Views piece in the same journal issue, outlining the work done by the team in Germany.

Prior research has shown that chemotherapy for pancreatic cancer that has metastasized sometimes works well but is sometimes ineffective, and this difference may be tied to dietary resistance, though its source is not known. In this new study, the team in Germany looked at the possibility that certain microorganisms in the gut microbiome play a role in the

process.

The team began their work by looking at samples of the gut microbiome of pancreatic cancer patients and found differences between those responding to treatment and those who were not. They also found that mice with sterilized guts who received biome samples from mice responding to chemotherapy also responded well.

To better understand how the gut microbiome might play a role in chemotherapy effectiveness, the researchers collected blood samples from patients who were responding well and from those who were not. They found higher levels of the molecule 3-IAA in better responding patients. Further investigation showed that the molecules were produced by two strains of gut bacteria. The team then tried adding 3-IAA directly to food eaten by cancerous mouse models and found that they became more responsive to chemotherapy treatment, as well.

The research team noted that 3-IAA is produced in the gut when amino acids interact with tryptophan, an acid found in many types of food. Subsequent testing with cancerous mouse models revealed that raising amounts of food with the acid might help with chemotherapy.

While exploring why higher levels of 3-IAA help chemotherapy to work better, the team found that their presence led to modulating neutrophils, which are types of immune cells. The overall takeaway was that microbes in the gut can help fight cancer by sending chemicals through the bloodstream to remote tumors where they give chemotherapy chemicals a boost by inciting the immune system into action.

More information: Joseph Tintelnot et al, Microbiota-derived 3-IAA influences chemotherapy efficacy in pancreatic cancer, *Nature* (2023). DOI: 10.1038/s41586-023-05728-y

Le Li et al, A gut reaction can tune tumour fate during chemotherapy, *Nature* (2023). DOI: 10.1038/d41586-023-00476-5

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