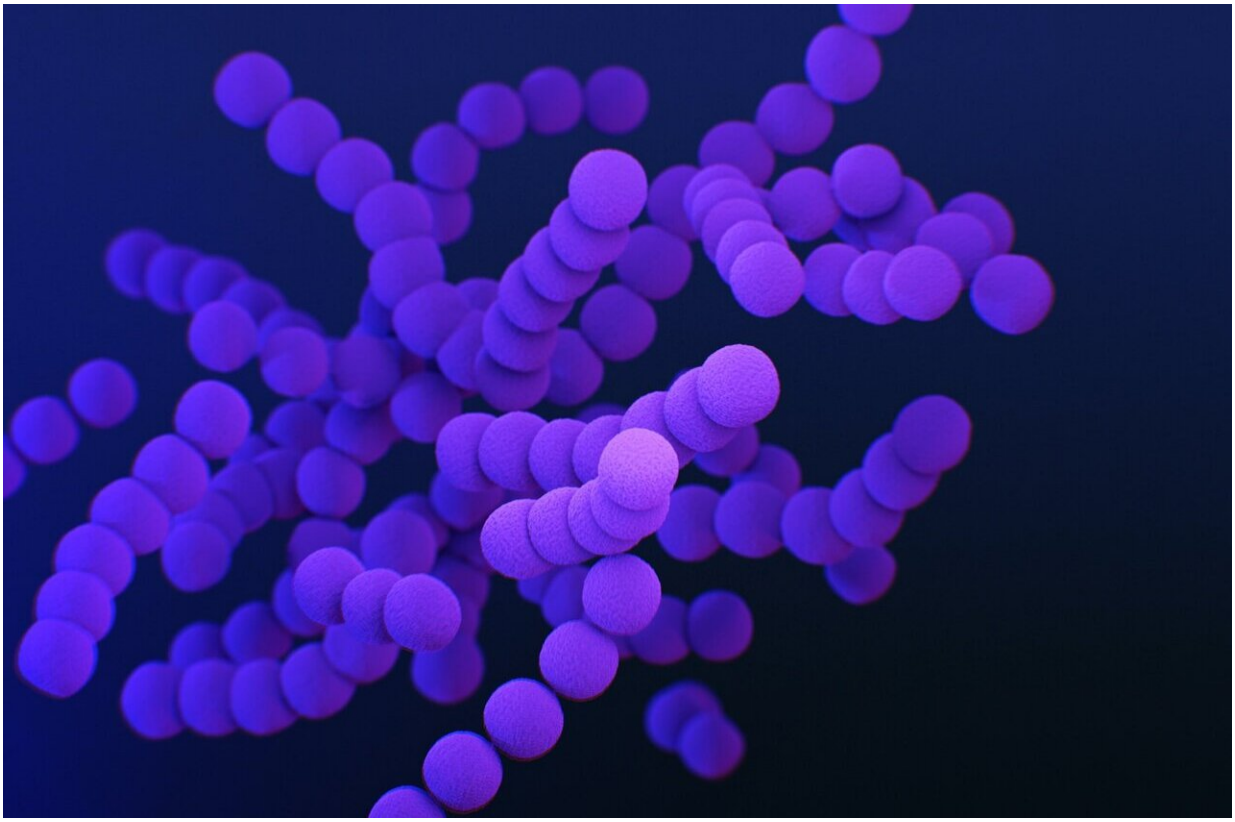
Study reveals how certain gut bacteria compromise radiotherapy

January 27 2021



Credit: Unsplash/CC0 Public Domain

A study led by Ludwig Chicago Co-director Ralph Weichselbaum and Yang-Xin Fu of the University of Texas Southwestern Medical Center has shown how bacteria in the gut can dull the efficacy of radiotherapy,

a treatment received by about half of all cancer patients. Their findings appear in the current issue of the *Journal of Experimental Medicine*.

"Our study identifies two families of gut bacteria that interfere with radiotherapy in mice and describes the mechanism by which a metabolite they produce—a short chain fatty acid called butyrate—undermines the therapy," said Weichselbaum.

A wide variety of commensal bacteria inhabit the human body, particularly the gut, where they participate in important physiological processes ranging from digestion to regulation of the immune system. Many studies have shown that gut microbes also have a profound influence on cancer therapies, most notably immunotherapies.

Since ionizing radiation is known to activate anti-tumor immune responses, Kaiting Yang, a postdoctoral researcher in Weichselbaum's lab, examined how antibiotics affect the outcomes of tumor radiotherapy.

These studies showed that vancomycin, an antibiotic against gram-positive bacteria, one of two broad classes of bacteria, enhanced responses to tumor irradiation in mice. Gentamycin, which targets gram-negative bacteria, did not have that effect. It turned out that vancomycin's decimation of two families of gram-positive gut bacteria—*Lachnospiraceae* and *Ruminococcaceae*—was most closely associated with the improved response. Further analysis revealed that a decline in levels of butyrate, a metabolite produced by these bacteria, accompanied the effect.

When *Lachnospiraceae* were introduced into mice completely devoid of bacteria, the effect of radiation on their tumors was notably diminished and the dampened response corresponded to a systemic increase in butyrate levels. The injection of butyrate directly into tumors had a

similarly dampening effect on radiotherapy.

Since butyrate did not directly protect the tumors from radiation, the researchers turned their attention to the immune response elicited by radiotherapy. Their experiments revealed that butyrate interferes with the activation of cytotoxic (or killer) T cells, immune cells that target cancer cells and are known to attack tumors following radiotherapy.

Previous studies led by Weichselbaum and Fu have shown that irradiation activates a signaling pathway in another immune cell—the dendritic cell, which can prime killer T cells to attack tumors. This biochemical pathway, controlled by a protein named STING, ramps up the dendritic cells' production of immune-stimulating factors known as type-1 interferons (IFN-I), which boosts their activation of killer T cells.

Weichselbaum, Fu, Yang and colleagues show in the current study that butyrate inhibits a step of the biochemical signaling cascade that links STING activation to the production of IFN-I. Adding an IFN-I to tumors simultaneously injected with butyrate restored the therapeutic effects of radiotherapy in the mice.

Their findings confirm and add to those of a study published by other researchers in the *Journal of Clinical Investigation* in December 2019, which also showed that butyrate compromises the activation of killer T cells by dendritic cells following tumor irradiation.

The current study also has some immediate clinical relevance. The researchers found that levels of other beneficial bacteria (*Akkermansia* and *Lactobacillus*) increase in the gut and within tumors of mice following vancomycin treatment. This suggests that butyrate depletion might not be the only mechanism behind the observed improvement in responses to radiotherapy: antibiotic treatment might also affect the microbiome in other ways to support immune responses elicited by

radiotherapy.

"Our findings offer clues to the development of new strategies to improve patient responses to radiotherapy," said Weichselbaum. "This includes the specific targeting of particular types of gut bacteria that produce butyrate—once we have a better understanding of the various ways in which these microbes interact with the immune system and cancer therapies."

More information: Kaiting Yang et al. Suppression of local type I interferon by gut microbiota–derived butyrate impairs antitumor effects of ionizing radiation, *Journal of Experimental Medicine* (2021). DOI: 10.1084/jem.20201915

Provided by Ludwig Institute for Cancer Research