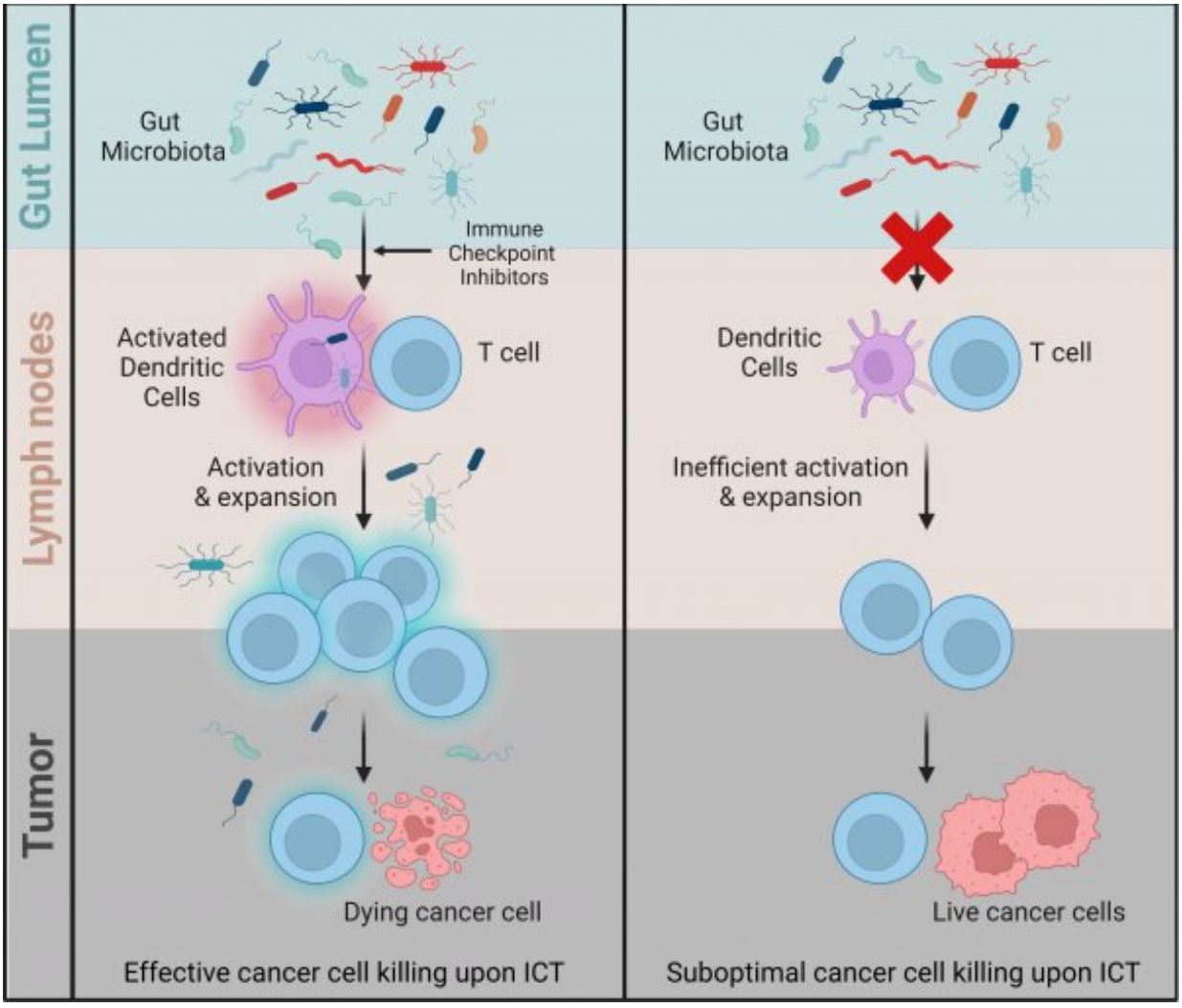
Healthy gut bacteria can help fight cancer in other parts of the body, researchers find

March 9 2023



Immune checkpoint therapy (ICT) helps gut microbiota travel from the gut to the lymph nodes where they activate immune cells (dendritic cells and T cells). Ultimately, both gut microbiota and activated immune cells then enter the tumor.

When specific bacteria cannot travel to the lymph node and tumor and activate immune cells, immune checkpoint therapy is not effective. Credit: *Science Immunology* (2023). DOI: 10.1126/sciimmunol.abo2003

Researchers at UT Southwestern Medical Center have discovered how healthy bacteria can escape the intestine, travel to lymph nodes and cancerous tumors elsewhere in the body, and boost the effectiveness of certain immunotherapy drugs. The findings, published in *Science Immunology*, shed light on why antibiotics can weaken the effect of immunotherapies and could lead to new cancer treatments.

"Scientists have been stumped as to how bacteria inside your gut can have an impact on a cancer in your lungs, breasts, or skin," said Andrew Y. Koh, M.D., Associate Professor of Pediatrics, Microbiology, and in the Harold C. Simmons Comprehensive Cancer Center at UT Southwestern. "Now we understand that mechanism much better and, in the future, hope to use this knowledge to better fight cancer."

Previous studies, including one led by Dr. Koh at UT Southwestern, have shown an association between the composition of gut microbiomes—the microorganisms found inside the digestive tract—and the effectiveness of cancer treatments that target the immune system, including pembrolizumab (Keytruda) and ipilimumab (Yervoy). However, researchers have reached conflicting conclusions about the ideal balance of microorganisms to optimize therapy, with studies pointing to different beneficial bacteria.

Dr. Koh and colleagues used mice with melanoma tumors to probe how the drugs, called immune checkpoint inhibitors, affected the movement of gut microbes through the body. They found that immune checkpoint inhibitors, which boost the activity of the immune system against

tumors, also cause inflammation in the digestive system that leads to remodeling of lymph nodes in the gut.

Due to these changes, bacteria can leave the intestines and travel to lymph nodes near the tumor and the tumor itself, the researchers found. Here, the microbes activate a set of immune cells that act to kill tumor cells.

"Immune checkpoint inhibitors work by releasing the brakes on the immune system to target cancer," said Dr. Koh, who is also Director of the Cellular and ImmunoTherapeutics Program at UTSW and Children's Health. "What we think is that these microorganisms and the immune cells they're activating are essentially pressing on the accelerator of the immune system at the same time."

The findings suggest that a course of antibiotics, which can eliminate most gut microbes, is detrimental to immune checkpoint inhibitors because the bacteria can no longer play this role of immune accelerant. It also helps explain why researchers have found many types of bacteria in patient microbiomes that seem to be beneficial for treatment.

"As long as a subset of beneficial bacteria can translocate from the gut to the lymph node or tumor, it may not matter exactly which bacteria it is," said Dr. Koh.

Dr. Koh's team is now working toward the development of bacterial-based treatments to boost the efficacy of immune checkpoint inhibitors.

More information: Yongbin Choi et al, Immune checkpoint blockade induces gut microbiota translocation that augments extraintestinal antitumor immunity, *Science Immunology* (2023). DOI: 10.1126/sciimmunol.abo2003

Provided by UT Southwestern Medical Center