Cancer-death button gets jammed by gut bacterium

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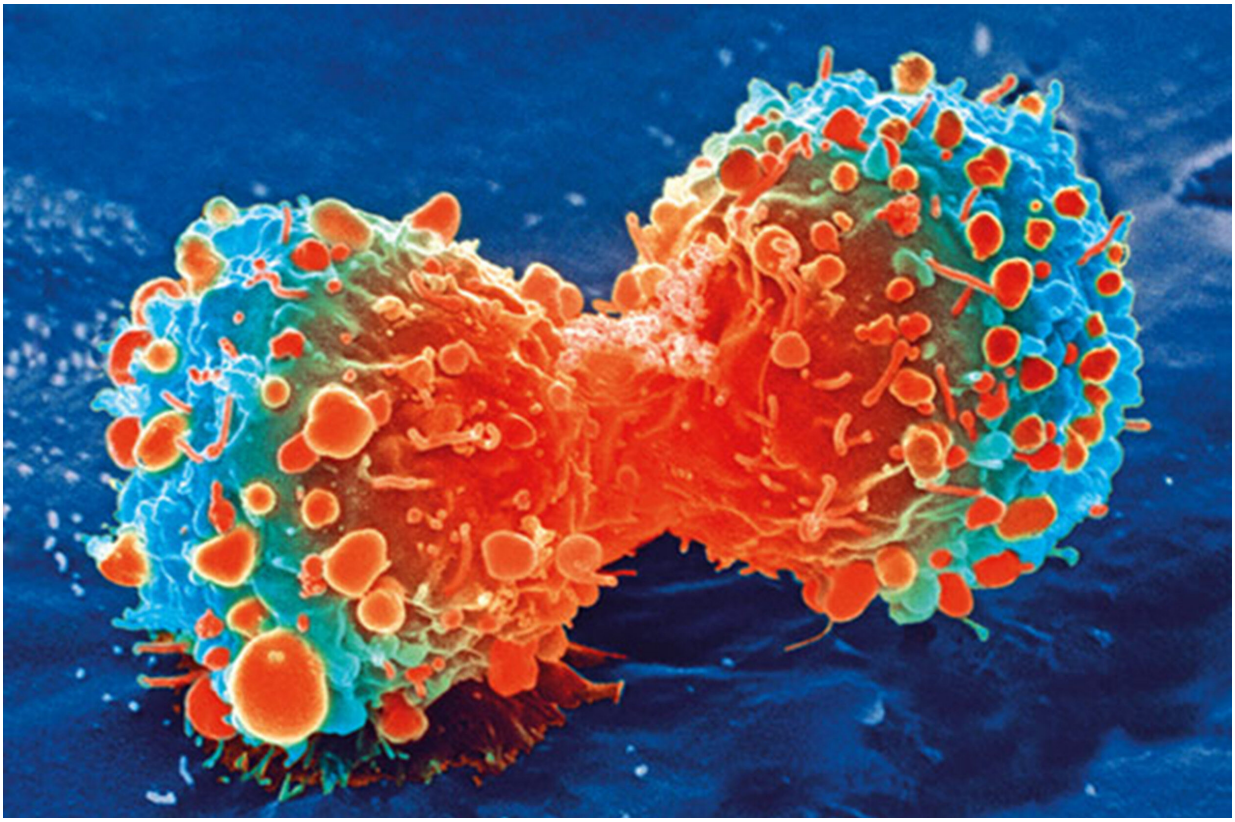

Cancer cell during cell division. Credit: National Institutes of Health

Researchers at Michigan Medicine and in China showed that a type of bacterium is associated with the recurrence of colorectal cancer and poor outcomes. They found that Fusobacterium nucleatum in the gut can stop

chemotherapy from causing a type of cancer cell death called apoptosis.

Colorectal cancer is the third most common cancer and the second leading cause of cancer-related death worldwide. The two most widely used drugs to treat colorectal cancer act to either inhibit enzyme activity of cancer cells or arrest tumor cell growth. But a bacterium can make them ineffective.

"We treat patients with chemotherapy so that it will ultimately induce tumor cell apoptosis. But some cancer cells have a way to avoid apoptosis that is induced by chemotherapy. Those cells escape from the apoptosis process by activating a cell-survival mechanism called autophagy. That mechanism protects cancer cells from destructing," says Weiping Zou, M.D., Ph.D., professor of surgery at Michigan Medicine.

This collaborative study between Michigan Medicine and China is published in *Cell*. The research was led by two teams, Weiping Zou, M.D., Ph.D., at Michigan Medicine, and Jing-Yuan Fang, M.D., Ph.D., in Shanghai. Fang is a professor in Renji Hospital, Shanghai Jiao Tong University School of Medicine.

"Once autophagy is active, the cancer becomes resistant to chemotherapy. Then Fusobacterium nucleatum keeps autophagy turned on. That's how the tumor cells may be able to avoid the induced apoptosis," says Zou.

"Typically, autophagy can be turned on or off. However, the bacterium prevents the expression of two microRNAs so that autophagy doesn't turn off. The loss of these microRNAs keeps the autophagy turned in the 'on' position," says Zou.

The idea to check the role of the bacterium associated with innate immune signaling in chemotherapy resistance was linked to earlier work

done by this researcher team. Their study was published in *Cell* in 2016. In the previous research, they studied adaptive immunity, specifically the impact of T cells on chemoresistance. They found that adaptive immunity is reversely associated with resistance of cisplatin, the drug used for ovarian cancer. This means if you have a strong T cell immunity, then the cancer cells are more sensitive to chemotherapy.

In the current study in *Cell*, they researched whether bacterium-mediated innate immune signaling regulates chemotherapy resistance in colon cancer.

The innate immune system refers to the front-line defenders—the cells and molecular mechanisms that attack pathogens. The adaptive immune system refers to the body's response to specific antigens, such as foreign substances from bacteria or tumor-associated antigens from tumor cells.

Adaptive immunity is mediated by T cell signaling. Innate immunity is mediated by innate signaling including proteins called Toll-like receptors (TLR)."We knew that the body uses both systems, adaptive and innate, to fight cancer and infectious pathogens. That gave us the inspiration to look further at bacterium associated with innate immune signaling.

"The results of the research were a surprise. We did not expect bacterium to contribute to chemoresistance," says Zou.

There are other factors that are unknown about *F. nucleatum*. For example, what would happen if the bacterium were reduced or blocked? Would other prevalent bacterium create a similar problem with chemoresistance?

"Right now, we don't have a specific approach to selectively treat or control Fusobacterium nucleatum. Also, we don't know if an abundance of this bacterium is found in any other types of cancer chemoresistance,"

says Zou. "Still, based on our studies, we think that if we deal with this bacterium, we may be able to delay and prevent chemoresistance in colorectal cancer."

More information: *Cell* (2017). DOI: 10.1016/j.cell.2017.07.008