

New mechanism underlying colorectal cancer reveals a crucial role for intestinal microbes

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Cancer—Histopathologic image of colonic carcinoid. Credit: Wikipedia/CC BY-SA 3.0

A collaborative study by research groups from the VIB-UGent Center for Inflammation Research and Ghent University uncovered a new mechanism causing colorectal cancer. The researchers found that abnormal expression of the protein Zeb2 affects the integrity of the

intestinal wall or 'epithelium.' This epithelium normally functions as a barrier to prevent infiltration by intestinal microbes. Zeb2 undermines this barrier and allows infiltrating bacteria to cause inflammation that drives cancer progression. Importantly, the scientists demonstrated that manipulating the immune system or removing the microbiota can prevent the development of cancer. These findings may lead to new treatments and are published in the leading journal *Nature Cancer*.

Colon cancer

Colorectal cancer is the third most common and fourth most deadly type of cancer. Unfortunately, anti-cancer therapies, including immunotherapy, have a relatively low effectiveness in colorectal cancer. In addition to [genetic factors](#), environmental factors linked to a Western lifestyle (such as diet, obesity, and a sedentary lifestyle) also increase the risk for developing colorectal cancer.

The disease originates from the [epithelial cells](#) that line the intestines. These 'barrier' cells accumulate mutations and acquire malignant properties over time. A better understanding of the molecular mechanisms responsible for colorectal cancer development is essential to develop new therapies to effectively combat this [deadly disease](#).

A new mechanism driving colon cancer

A collaboration between the research groups of prof. Geert van Loo, prof. Lars Vereecke, and prof. Geert Berx identified the protein Zeb2 as a possible cause of colorectal cancer. They showed that the abnormal expression of this protein in the epithelial cells of the gut in mice can induce colorectal cancer.

Zeb2 destabilizes the integrity of the intestinal barrier which allows

bacteria to infiltrate the tissue and provoke inflammatory reactions. This causes an abnormal proliferation of epithelial cells which ultimately leads to the development of malignant intestinal tumors. Importantly, by treating mice with broad-spectrum antibiotics to kill intestinal bacteria, or by raising mice in complete sterile conditions, cancer development could be completely prevented.

Prof. Geert Berx (CRIG/UGent) states, "We study the molecular mechanisms that regulate tissue invasion and metastasis in various types of cancer. We knew Zeb2 regulates a molecular process which allows cancer cells to acquire tissue-invasive properties, resulting in malignant disease progression. By using [transgenic mice](#) expressing Zeb2, we can study this process in multiple tissues, including the intestine. This study demonstrates that Zeb2 reprograms the epithelial cells of the intestinal wall, which allows bacteria to pass and cause inflammation that can lead to tumor development."

Prof. Lars Vereecke (VIB-UGent Center for Inflammation Research/CRIG) says, "There is increasing evidence that the microbes in our gut play a central role in human health and disease. Many diseases are associated with distinct shifts in the microbiota-composition, including colorectal cancer. Proving that the microbiota contribute to disease requires functional studies in mice. Recently, we established the first Belgian germ-free mouse facility at Ghent University where we raise mice in completely sterile conditions. Using this new technology, we could prove that removing the intestinal microbes prevents colorectal cancer development in our model. Moreover, by modulating the activity of specific immune cells we could also suppress cancer development. Together, these findings demonstrate that complex immune-microbiota interactions contribute strongly to colorectal cancer development."

New therapies

The new Zeb2 mouse colorectal cancer model represents a unique tool to study tumor-immune-microbe interactions, which is very useful in the search for new therapies targeting colorectal cancer. Since cancer development in these mice is microbiota-dependent, germ-free Zeb2 mice represent a unique preclinical platform for microbiota research to identify cancer-promoting microbes, but also to test new microbiota-based therapies to prevent or treat colorectal cancer.

Prof. Geert van Loo (VIB-UGent Center for Inflammation Research/CRIG) concludes, "We identified a disease-causing mechanism using a new mouse model but also confirmed abnormal Zeb2 expression in human colorectal tumor cells, which proves the clinical significance of our model for human patients. Our results are important from a scientific point of view since they help us understand why and how [colorectal cancer](#) develops. But this knowledge also has therapeutic implications and suggests that altering the microbiota or targeting specific immune components may be effective strategies for developing new treatment options for colon [cancer](#)."

More information: Karolina Slowicka et al. Zeb2 drives invasive and microbiota-dependent colon carcinoma, *Nature Cancer* (2020). [DOI: 10.1038/s43018-020-0070-2](https://doi.org/10.1038/s43018-020-0070-2)

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