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Gut microbes govern cancer

by Eliran Kadosh[1] | Postdoctoral Research Fellow; Yinon Ben-Neriah[1] | Professor

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[1]: Lautenberg Center for Immunology and Cancer Research, The Hebrew University of Jerusalem, Jerusalem, Israel

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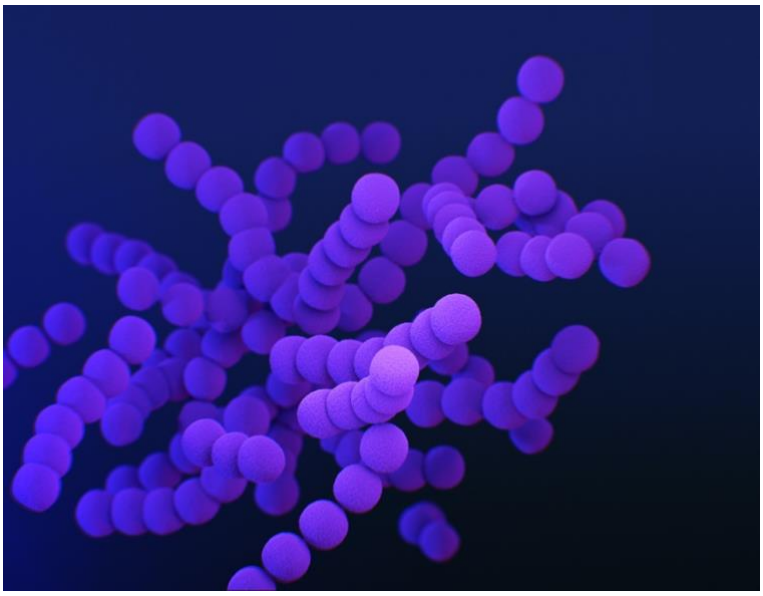
Cancer rarely develops in the small intestine compared to in the large intestine, but its reason remains mysterious. A new study reveals that certain microbes predominantly inhabiting the colon promote cancerous tumor development via a unique metabolite, which may explain the rarity of small intestinal



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Our body is made of trillions of cells. Each of these tiny building blocks has its defined role, and together they create organs. While different cells in our body may look different in size and shape, they all share one common thing – DNA. DNA is a molecule that stores our genes: instruction manuals for creating proteins that are so-called 'functional machines of life', which mainly build cells.

Cells divide, grow, or die in response to environmental cues. When they encounter intense stress, such as heat or UV irradiation, DNA gets damaged and this 'error' can turn the cell into cancerous. The 'abnormal' cancer cells divide quickly and uncontrollably, creating a tumor that can eventually spread to other organs. In a new study, we discovered that gut microbes play an important role in intestinal cancer development.

Innumerable microbes live with us – bacteria, viruses, parasites and fungi communicating with human cells and affecting their health. The gut is the most heavily microbe-populated tissue in our body. Gut microbes are present in an increasing gradient from the upper (small intestine) to the lower (colon) segments of the digestive tract. These microscopic creatures mostly assist in food digestion and gut disease protection.

Cancer tumor often develops in the lower gut. This so-called colorectal cancer has been the second most common cause of cancer-related death. Intriguingly,

tumors much less frequently develop in the upper gut compared to in the lower gut, despite the small intestine being three times longer than the colon. This paradox implies that the enriched microbe population in the lower gut may somehow be involved in cancer development.

To address this question, we generated genetically engineered mice. A mouse is a widely used animal model as its genetic background is very similar to human's, meaning that what happens in mice most probably occurs in humans. These engineered mice were designed to develop intestinal tumors by genetic mutations (alterations in genetic information) that regulate two biological pathways known as cancer hallmarks: namely Wnt and p53.

We found that these mutations caused mice to develop tumors only in the lower gut. Surprisingly, we detected almost no tumors in the upper gut of p53 mutant mice, even better than normal mice. This is paradoxical because the mutant p53 is usually thought of as a cancer driver. Our further investigation revealed that the mutant p53 blocked the hyperactivation of the Wnt pathway – which accelerates cancer development – and prevented tumor development in the upper gut.

This striking difference in consequence of the p53 mutations in the two intestinal parts prompted us to investigate the characteristic difference between them – microbe populations. To do so, we treated our mice with antibiotics that allowed eliminating the gut microbes. This gut cleaning treatment completely abolished the tumor-driving activity of mutant p53, which, in turn, prevented tumor development in the entire gut. This suggests that gut microbes uniquely present in the lower gut help develop tumors by modulating p53 activity.

Next, we aimed to identify the microbe species that cooperate with mutant p53 to turn it into a cancer driver. By screening numerous microbial metabolites, we identified gallic acid as the key metabolite that microbes likely use to regulate mutant p53 activity. Interestingly, two gallic acid-producing bacteria in humans – Lactobacillus plantarum and Bacillus subtills – were also identified in our mice with higher levels in the lower gut than in the upper gut. Moreover, supplementing gut microbe-free (antibiotics-treated) p53-mutant mice with gallic acid was sufficient to allow them to develop tumors in the entire gut. These findings demonstrate that gallic acid – which intestinal cells receive from gut microbes – changes the nature of mutant p53 into a tumor-promoter.

Overall, our study explains the paradox in the mutant p53's function in intestinal cancer development: its tumor-suppressive trait is turned to the tumor-promoting by the gallic acid-producing gut bacteria. As the gallic acid-producing bacteria predominantly live in the lower gut, our discovery possibly explains why cancer is relatively rare in the bacteria-sparse parts of the gut. Based on our findings, doctors may look in the future into patients' microbe patterns to diagnose the risks of specific cancer mutations and consider possible microbe-based therapy. This will expand the horizons of personalized cancer therapy – from only targeting patients' mutations to looking beyond.