Chronic Inflammation Leaves Long-Lasting Impression on Gut Stem Cells, Increasing Colorectal Cancer Risk

NIH-funded animal study finds heritable memories of damage persisted in cells months after inflammation ceased.

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In a new study, funded in part by the National Institutes of Health (NIH), researchers have uncovered a molecular mechanism that could explain how chronic gut inflammation may increase the risk of colorectal cancer. By simulating chronic colitis in mice and tracking the colon's response during inflammation and recovery, scientists demonstrated that these changes increased the activity of a specific group of proteins, AP-1 transcription factors, and promoted tumor growth.

The link between inflammation and cancer is well established, but the underlying mechanisms have remained unclear.

"By spelling out how repeated cycles of injury in the gut may influence colorectal cancer risk, the authors have potentially opened avenues toward much-needed methods of early evaluation and therapy for a condition that is of increasing concern," said Anthony Letai, MD, PhD, director of NIH's National Cancer Institute (NCI).

The authors, based at the Broad Institute of MIT and Harvard, analyzed the animals and organoids derived from their injured tissue, finding that the damage caused alterations in stem cells, which new cells inherited for more than 100 days after colitis ceased. While an individual's DNA generally stays the same over time, the collection of chemical annotations to their genome — called the epigenome — is dynamic.

This epigenetic flexibility allows cells to adapt to shifting circumstances, such as damaging inflammation, by modulating the expression of certain genes, such as those associated with regeneration. These adaptations can persist as memories in the epigenome, but recent research suggests that they can backfire in the long run, inadvertently increasing cancer risk.

The researchers closely examined more than 52,000 individual cells across the animals, identifying one epigenetic change that stood out from the rest. The results suggested that colitis led to an alteration in colonic stem cells that increased the activity of AP-1

transcription factors, which are known to steer cellular responses to stress. This memory persisted in the epigenomes of cells for more than 100 days after the authors removed colitis-inducing chemicals from the animals.

To better understand how this alteration was sticking around so long, the researchers developed a method to track epigenetic memories as cells divided within an organoid model of colitis, built from injured mouse tissue. They confirmed that the memory of AP-1 was heritable, with colonic stem cells passing it down to new cells as they divided.

They next sought to find out if this enduring effect of chronic inflammation had implications for cancer risk. To achieve this, researchers introduced genes capable of sparking tumor growth into mice that had either recovered from chronic colitis or were previously healthy. The authors found colorectal tumor growth to be far more rapid in the colitis-recovered animals compared to the other group.

“We have known for some time that colitis can accelerate tumor growth after cancer has already begun, but here we show that the effect of chronic inflammation on cancer risk remains well after animals have recuperated,” said Jason Buenrostro, PhD, corresponding author and member of the Broad Institute and professor at Harvard University.

The authors found that a slew of regenerative activities associated with AP-1 were in overdrive within tumors of recovered animals. When they blocked AP-1 activity, the pro-cancer effect of colitis disappeared, suggesting that this group of molecules may be a central player linking chronic inflammation in the gut to increased colorectal cancer risk.

Buenrostro and his colleagues believe that, if this phenomenon plays out similarly in humans, then tests for these epigenetic memories could potentially inform patients of colorectal cancer risk early on. And one day, therapeutics aimed at disrupting the post-colitis activity described in this study may help stall tumor growth.

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