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Scientists identify gene vital for rebuilding intestine after cancer treatment

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The stem cells in our gut divide so fast that they create a completely new population of epithelial cells every week. But this quick division is also why radiation and chemotherapy wreak havoc on the gastrointestinal systems of cancer patients - such therapies target rapidly dividing cells. Scientists at the UNC School of Medicine and the UNC Lineberger Comprehensive Cancer Center found that a rare type of stem cell is immune to radiation damage thanks to high levels of a gene called Sox9.

The discovery, which was made in mice and published in the journal *Gastroenterology*, could lead to new ways to protect the gastrointestinal systems of cancer patients before they receive treatment. Such a preventative measure could allow patients to receive higher treatment doses to more aggressively attack cancer cells.

"Not only do we show that Sox9 is responsible for making and maintaining these rare 'reserve' stem cells, but also that the gene has a radio-protective impact on the intestine after radiation damage," said Scott Magness, PhD, associate professor of medicine, cell biology and physiology, and biomedical engineering, and senior author of the paper.

With further exploration of how Sox9 protects reserve stem cells, Magness said it could be possible to use the gene to protect the intestines against the ravages of chemotherapy and radiation.

For decades, scientists have known that 'reserve' stem cells exist, possessing all of the properties of regular stem cells, except they don't

divide rapidly. Regular stem cells divide quickly under normal conditions to supply the gut with enough cells to keep the intestinal lining in working order. But during cancer treatment, the DNA of normal stem cells is mutated so much that the cells die through a process called apoptosis, which causes damage to the intestinal lining. This is why cancer patients experience severe gastrointestinal side effects during treatment.

When cancer therapy kills the regular stem cells, the reserve stem cells wake up and replenish the gut lining. Why or how these cells wake up, no one knows.

Kyle Roche, a fourth-year graduate student and first author of the *Gastroenterology* paper, said, "It hasn't been proven, but there's strong evidence suggesting that when the normal 'active' stem cells are dead and gone, the reserve cells move into the newly opened space, wake up, and begin to divide to replenish the epithelial lining."

Magness, a member of the UNC Lineberger Comprehensive Cancer Center, and Roche wanted to find out how reserve stem cells are generated and maintained in the gut.

Using mice, Roche conducted an analysis of single cells that naturally express a lot of Sox9 to check whether they had an expression pattern consistent with reserve stem cells. He found that some cells had strong stem cell signatures. Roche then removed Sox9 in the mice to see if reserve stem cells relied on Sox9 to live. He found that animals without Sox9 lacked this reserve stem cell population and that these mice did not recover when exposed to radiation.

"If Sox9 is not present, then reserve stem cells are not made and the animals are much more sensitive to radiation damage," said Roche, who noted that humans also have Sox9 in their intestines.

Magness pointed out, "If we can figure out the mechanisms that Sox9 uses to control reserve stem cells - to keep them quiet and poised to wake up - then theoretically we could develop an agent to protect cancer patients against the gastrointestinal side effects of chemotherapy and radiation. This is the kind of idea we are hoping for down the line."

More immediately, Roche said it should be possible to increase Sox9 levels in human epithelial cells and test whether these cells would survive following DNA damage caused by radiation or chemotherapy.

"If so, then this would put Sox9 on the board as a therapeutic target for pharmaceutical agents that can protect the intestine during radiation therapy," Roche said. "We think Sox9 carries a lot of promise in advancing our understanding of how to preserve the intestinal health of cancer patients during treatment."

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