# The making of an intestinal stem cell

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Researchers have found the factor that makes the difference between a stem cell in the intestine and any other cell. The discovery reported in the March 6th issue of the journal *Cell*, a Cell Press publication, is an essential step toward understanding the biology of the stem cells, which are responsible for replenishing all other cells in the most rapidly self-renewing tissue in mammals. It may also have implications for colon cancer, according to the researchers.

The report finds evidence that a transcription factor called Achaete scute-like 2 (Ascl2) switches on the stem cell program in intestinal cells. Transcription factors are genes that control other genes.

"This transcription factor makes these stem cells tick," said Hans Clevers of Hubrecht Institute-KNAW & University Medical Center Utrecht, The Netherlands. "It activates a small program of genes essential to gut stem cells." In other words, if the Ascl2 gene turns on, any dividing cell in the intestine would turn into a stem cell capable of producing any other cell type in that tissue, he added.

The lining of the intestine is made up of peaks known as villi and valleys called crypts. The crypts contain stem cells and so-called Paneth cells, which serve to protect those stem cells.

Intestinal stem cells are rather unique among adult stem cells, Clevers said. In most tissues of the body, stem cells divide only rarely -- perhaps once a month. That's not true of the rapidly dividing stem cells of the intestine.

"Their entire life, intestinal stem cells make tissue every day," he said. That's because approximately every five days, the intestinal lining is replaced in its entirety, leaving only the stem cells and their Paneth cell defenders constant. The stem cells produce an impressive 200 to 300 grams of new cells every day, Clevers added.

"That's an enormous buildup of tissue. These stem cells are responsible."

While there has been some controversy in the field over the identity of intestinal stem cells, Clevers team earlier showed that tiny cells intermingled with the Paneth cells of the intestine do have the characteristics of stem cells. Each crypt bottom harbors around six of those cells, which divide daily to produce every other type of cell in the intestinal linings of mice over the course of their lifetimes. These cells are defined by the expression of a gene called Lgr5.

In the new study, the researchers wanted to further explore the genes that distinguish the Lgr5 stem cells from other intestinal cells. After examining 200 or so genes, they landed on a handful that differed between stem cells and all other cells. Of those, Clevers said Ascl2 was the only transcription factor, a class of genes that are generally important to setting the fates of cells.

When they induced the activity of the Ascl2 transcription factor throughout the intestinal lining of mice, it caused the overgrowth of crypts and the development of additional crypts on surfaces of the villi, they report. In intestines of adult mice lacking Ascl2, the Lgr5 stem cells disappeared within days. All together, those findings led the researchers to conclude that Ascl2 is the key to intestinal stem cell fate.

While he said the findings may not have any immediate practical implications, they could yet yield some insight into the cancer stem cells that give rise to other colon cancer cells.

"In colon cancer tumors, there are a very limited number of cells that express this transcription factor," Clevers said. "It's likely that the same gene turns cancer cells into cancer stem cells."

Source: Cell Press