

FEBRUARY 16, 2007

Adult Stem Cells Decide the Fate of Their Daughters

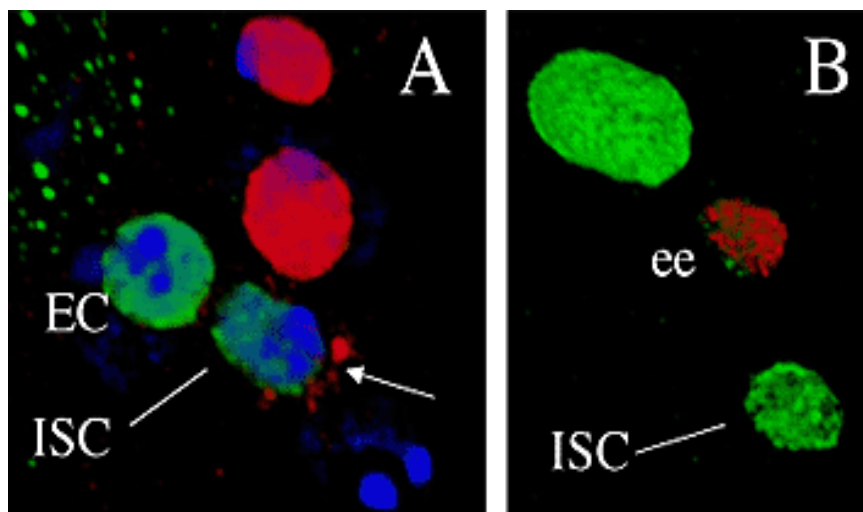


Image Title: The amount of the signaling protein Delta, shown in red, in an intestinal stem cell (ISC) determines the fate of its daughter cells. In panel A, an ISC that has just produced an enterocyte (EC) shows a high level of Delta (arrow). In panel B, an ISC that has just produced an enteroendocrine cell (ee) lacks detectable Delta. - B. Ohlstein and A. Spradling

Adult stem cells call the shots when it comes to their daughters' destinies. That's the take-home lesson for adult stem cells in the intestines of fruit flies, according to new studies by researchers at the Howard Hughes Medical Institute (HHMI).

The researchers found that intestinal stem cells make important decisions about their fate by communicating directly with their daughter cells, instructing them to become one of two possible cell types. The studies bring researchers a bit closer to understanding how adult stem cells decide to make the cell type that best meets the current needs of the organism.

The finding, reported by HHMI investigator Allan C. Spradling and colleague Benjamin Ohlstein in the February 16, 2007, issue of the journal *Science*, is important because it begins to reveal the fine details of how stem

cells replenish damaged or diseased tissues in a particular part of the body. Spradling and his postdoctoral fellow Ohlstein are at the Carnegie Institution of Washington.

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- Allan C. Spradling

Adult stem cells are undifferentiated cells that exist in different parts of the body. When they divide, they create pools of differentiating daughter cells. In vertebrates such as humans, they have been found in blood, brain, bone marrow, skin and many other tissues. Adult stem cells tend to occur in very small numbers, lying low, at times for years, until they are called into service to help replace dead or damaged cells or maintain the health of the tissue where they are found. Unlike embryonic stem cells, which can become any kind of cell in the body, adult stem cells are usually limited to making one or a few types of cells that make up the tissue where they are found.

"Basically, our bodies are constantly undergoing stem cell therapy," said Spradling. "We would live one or two days without (adult) stem cells. It's essential to have these cells doing their thing."

Insight into the molecular mechanisms that control differentiation of stem cells could help scientists develop therapies for some common diseases. The idea, according to researchers, is that adult stem cells found in a healthy region of tissue could be prompted to repopulate and repair diseased or damaged tissue nearby.

Spradling's research group first discovered intestinal stem cells in fruitflies in 2006. He and Ohlstein had found that adult intestinal stem cells make two types of daughter cells: enterocytes, cells that line the intestine and absorb nutrients, and enteroendocrine cells, which belong to a family of hormone-secreting cells.

In the case of fruitflies -- and very likely vertebrates such as humans -- intestinal stem cells make the two types of cells according to cues they receive from other cells in their immediate environment. Those signals trip the switch of a key genetic pathway known as Notch that tells the cell what to become. Notch is a genetic regulatory pathway implicated in multiple differentiation processes.

“You need Notch activity to make the major cell types,” Ohlstein explained, “and these results suggest a simple model for the determination of intestinal stem cell daughter cell fate.”

In the current study, Spradling and Ohlstein were able to track the fate of the stem cells and their daughters by activating genetic markers in the intestinal stem cells of fruit flies and tracing their paths of development: “You can randomly turn on a marker in a cell and once the gene is on, it will be on in all of the progeny of that cell,” said Spradling.

By tracking the cells in this way, Spradling said, it became clear that the intestinal stem cells' differentiation into daughter cells was carefully controlled in response to the needs of the surrounding tissue.

“The stem cells know when the enteroendocrine cells turn over and when they need to make a replacement,” Spradling explained. “If there are happy, healthy enteroendocrine cells nearby, they keep the stem cells from making more.”

Notably, Spradling and Ohlstein found that it is the intestinal stem cells themselves that ultimately control the fate of the daughter cells. By placing a molecule known as Delta on its own cell surface, the intestinal stem cells can switch on the Notch signaling pathway that turns a daughter cell into an enterocyte. When more hormone-producing cells are needed instead, the stem cells reduce the amount of Delta, and their daughters become enteroendocrine cells.

The fruitfly, Ohlstein noted, is a critical model for sorting out the mechanisms that control stem cell differentiation. The same basic cellular and genetic processes, he says, are almost certainly at work in vertebrates, including humans. “You need an in vivo system to know what to really believe,” he said. “What we're seeing in the fly may be true for the mouse or the human as well.”

Spradling and Ohlstein next plan to examine the role of stress on intestinal stem cells. They explained that normal laboratory conditions may prevent the cells from performing some of their most important functions. “We feed these flies very well, very uniformly,” Spradling said. “They hum along under these conditions.”

By imposing stress, it may be possible to see other hidden capabilities of the intestinal stem cell: “Stem cells may be able to move to an area where more are needed,” Spradling said. “We do think there are more sophisticated things they can do than this basic process we've described so far.”