Newly identified stem cells may hold clues to colon cancer

March 29 2012

Vanderbilt-Ingram Cancer Center researchers have identified a new population of intestinal stem cells that may hold clues to the origin of colorectal cancer.

This new stem cell population, reported March 30 in the journal *Cell*, appears to be relatively quiescent (inactive) – in contrast to the recent discovery of intestinal stem cells that multiply rapidly – and is marked by a protein, Lrig1, that may act as a "brake" on cell growth and proliferation.

The researchers have also developed a new and clinically relevant mouse model of colorectal cancer that investigators can now use to better understand where and how the disease arises, as well as for probing new therapeutic targets.

Colorectal cancer is the second leading cause of cancer deaths in the United States. These tumors are thought to arise from a series of mutations in intestinal stem cells, which are long-lived, self-renewing cells that gives rise to all cell types in the intestinal tract.

For more than 30 years, scientists believed that intestinal stem cells were primarily quiescent, proliferating only rarely in order to protect the tissue against cancer. Then, in 2007, researchers reported finding a population of intestinal stem cells (marked by the molecule Lgr5) that were highly proliferative.

Those findings "really changed the way we think about intestinal stem cells," said Robert Coffey, Jr., M.D., Ingram Professor of Cancer Research, co-chair of Vanderbilt's Epithelial Biology Center and senior author on the study.

"It came to so dominate the field that it raised the question about whether quiescent stem cells even exist…and that's where we enter into the picture."

Coffey's lab studies the epidermal growth factor (EGF) signaling pathway – which includes a family of receptors known as ErbBs – and its role in cancers of epithelial tissues, like the intestinal tract.

Postdoctoral fellow Anne Powell, Ph.D., led the recent experiments showing that Lrig1, a molecule that regulates ErbB activity, is present in intestinal cells that have the qualities of stem cells (self-renewal, and the ability to produce all the cells of the intestine).

"Essentially, what we show is that the Lrig1-expressing cells are stem cells and they are largely quiescent," Powell said. "We also show that they're distinct from the Lgr5-expressing stem cells that had become a sort of 'hallmark' stem cell population…with different gene expression profiles and different proliferative status."

They also showed that Lrig1 is not only a marker of intestinal stem cells, but also acts as a tumor suppressor and inhibits the growth and proliferative signals of the ErbB family – acting as a sort of "brake" on cell proliferation that can lead to cancer.

Postdoctoral fellow Yang Wang, Ph.D., eliminated Lrig1 in mice and showed that nearly all of those mice developed intestinal tumors, providing further evidence suggesting that Lrig1 functions as a tumor suppressor.

The findings underscore the importance of ErbB signaling in the behavior of intestinal stem cells from which colorectal cancer may arise.

Most exciting, said Coffey, is that the mouse model his lab has generated as a part of these studies is one of the only mouse models to develop tumors in section of the intestines where most human tumors develop: the colon. One additional advantage of this model, in contrast to others, is that the tumors develop quickly and can be easily monitored with endoscopy, which will make it easier to assess how therapeutic interventions are working.

"We are fairly confident that this will be the 'go-to' model to study colon cancer in mice for the foreseeable future," Coffey said.

Provided by Vanderbilt University Medical Center