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Feedback loop explains inflammatory effect on intestinal lining

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Signals released by immune cells during a bout of inflammatory bowel disease interfere with intestinal cells' ability to regenerate. Yet people with inflammatory bowel diseases have a significantly higher risk of developing colon cancer: a hyper-activation of growth in those same intestinal cells.

Researchers at Emory University School of Medicine have identified a feedback loop involving a growth-regulating circuit in intestinal cells, which helps explain these apparently contradictory observations. The findings also suggest that interfering with one component of the feedback loop—a protein called "dickkopf 1" —may aid in controlling inflammatory bowel diseases.

The results are published online and scheduled for publication in the March 26, 2010 issue of the journal *Immunity*.

Senior author of the paper was Asma Nusrat, MD, Emory professor of pathology and laboratory medicine. The research was conducted by postdoctoral fellows Porfirio Nava, Stefan Koch and Mike Laukoetter. Laukoetter is now at the University of Münster in Germany.

The cells lining the intestine, or intestinal epithelial cells, are normally able to repair breaks in the lining by dividing and migrating until the wound has been healed, Nusrat explains. In inflammatory bowel diseases such as Crohn's or ulcerative colitis, immune cells release signals that prevent this repair and cause epithelial cells to die.

Nusrat and her colleagues examined mice treated with a chemical, dextran sulfate, which gives them colitis. The most prominent signaling molecules given off by immune cells in inflamed intestinal tissue were the cytokines ("cell movers") interferon-gamma and tumor necrosis factor-alpha. When the researchers treated intestinal cells by themselves in dishes with these cytokines, the cells had a burst of growth but then started to die out after three days.

"We were puzzled when we saw that cytokines induced activation of a pathway that should lead to cell division and cell survival, not cell death. It was not immediately clear to us why the epithelial cells were dying after exposure to cytokines despite stimulation of this survival pathway," Nusrat says.

A set of proteins together making up a regulatory circuit, collectively known as the Wnt pathway, controls the growth of intestinal epithelial cells. Most colon cancer cells have mutations in their DNA that push this circuit into overdrive. However, the circuit has to work at a moderate level or intestinal cells will not grow.

Nusrat's team found that prolonged exposure to the cytokines induces intestinal cells to give off a protein called dickkopf, which quenches the Wnt pathway and eventually kills the cells.

In mice with a bout of colitis, activity by the intestinal epithelial cells comes in two phases: mild growth for a few days, followed by cells dying out and then growth in areas next to ulcers in the intestinal lining, the authors found.

"Some areas of the intestinal epithelium are able to overcome inhibition of the Wnt pathway, perhaps by inactivating dickkopf," Nusrat says. "Our studies suggest that hyper-stimulation by inflammatory cytokines may be one of the mechanisms making patients with inflammatory

bowel diseases significantly more susceptible to cancer development."

The authors speculate that the experimental chemotherapy drug triciribine, which could prevent cells from making dickkopf, could be useful in controlling specific stages of active inflammation in colitis. Another potential tool for controlling inflammation can be antibodies to dickkopf, they say.

Provided by Emory University