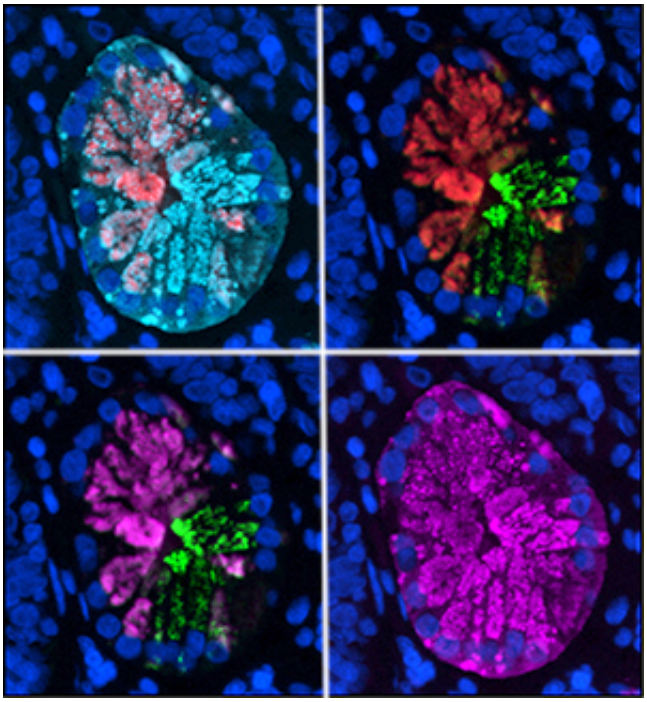
Brain-building gene plays key role in gut repair

April 5 2013, by Michael C. Purdy



Researchers at Washington University School of Medicine in St. Louis have discovered that a gene called mindbomb 1 plays an important role in healing stomach injuries. In the images above, which show cells before injury and at various points in the repair process, the protein made by mindbomb 1 appears green. Credit: Benjamin Capoccia, PhD

(Medical Xpress)—A gene with a colorful name – mindbomb 1 – plays a key role far beyond the brain. New research at Washington University School of Medicine in St. Louis shows that mindbomb 1 may be

involved in repairing cells injured by infection or inflammation in the stomach and pancreas. Researchers also found hints that mindbomb 1 problems may have connections to cancer in those organs.

"Stomach cancer is the fourth most common and second most fatal malignancy worldwide, but we know little about its molecular origins," says senior author Jason Mills, MD, PhD, associate professor of medicine, pathology and immunology and developmental biology. "Our new results indicate that loss of mindbomb 1 function is one of the first molecular steps in the transition from healthy cells in the stomach and pancreas to precancerous cells."

The study is available online in *The Journal of Clinical Investigation*.

Mindbomb 1 first won notice (and its name) when studies in zebrafish showed that deleting the gene wrecked development of the brain and central nervous system.

In the new study, research assistant Benjamin Capoccia, PhD, began by deleting mindbomb 1 from mouse stomach and pancreas cells that make digestive fluids. Mills studies how these secretory cells develop and work to make digestion possible.

"Without mindbomb 1, secretory cells can't make large stores of digestive enzymes any more, and they begin to look the way they do after injury from infection or inflammation," Capoccia says. "But what really struck us was that some of the cells without mindbomb 1 started to take on the appearance of precancerous cells, which could eventually lead to tumor formation."

Other scientists recently learned that when the stomach or the pancreas is injured, secretory cells at the site of the injury slow down their production of digestive juices. The secretory cells temporarily become

more like stem cells and start reproducing rapidly, providing a supply of new cells that can replace cells damaged or destroyed by injury.

Mills and Capoccia looked at mindbomb 1's activities in two different mouse models. One group of mice was infected with Helicobacter pylori, a bacterium linked to ulcers and stomach cancers in humans. The other mice had damaged stomachs due to exposure to a drug.

The scientists showed that mindbomb 1 is essential for secretory cells to store large reserves of the digestive fluids that they make. Researchers think the gene's protein is involved in rearranging and organizing the proteins that make storage of these fluids possible.

Mindbomb 1 becomes less active when the cells decrease digestive juice production during the repair process. Mills and Capoccia think that is because those cells must start reproducing rapidly to fix the injury, and the release of digestive fluids during this repair process would only cause more damage.

Mills is concerned – but cannot yet prove – that frequent activation of this repair process can contribute to cancer. As an example, he notes that H. pylori infections are often difficult for the immune system to eradicate completely. This leads to recurrent flares of conflict between the bacteria and the immune system. Mills and Capoccia suspect that these battles repeatedly activate the repair processes that the researchers linked to mindbomb 1.

"During these processes, many genes that normally are not active in the secretory cells get temporarily switched on," says Mills. "Our theory is that some of these temporarily activated genes may have mutations that can push the cells closer to becoming tumors."

Such mutations usually have little to no effect on the secretory cells

because they're not active when the cells are operating normally.

The researchers are now looking at mindbomb 1's potential contributions in other tumor types.

More information: Capoccia, B. et al. The ubiquitin ligase mindbomb 1 coordinates gastrointestinal secretory cell maturation. *The Journal of Clinical Investigation*, doi:10.1172/JCI65703

Provided by Washington University School of Medicine in St. Louis