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RESEARCH NEWS

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Gene Triggers Stem Cell Differentiation

A gene that governs development of neuronal cells has now been shown to be involved in regulating differentiation of stem cells into secretory cells in the intestine.

The research team, which included Howard Hughes Medical Institute investigator Huda Zoghbi , Qi Yang, Nessan Bermingham and Milton Finegold at Baylor College of Medicine, showed that the *Math1* gene — which codes for a gene-activating protein called a transcription factor — is necessary for the differentiation of three kinds of intestinal cells from stem cells. The team published its findings in the December 7, 2001, issue of the journal *Science* .

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— Huda Y. Zoghbi

Previous work by Zoghbi and her colleagues revealed *Math1's* role in governing differentiation of neuronal cells, including sensory cells in the inner ear. "In the course of those earlier studies, we detected *Math1* expression in the intestine," said Zoghbi. "Its function there was unknown. However, we knew that the gut has a nervous system of its own, so we thought *Math1* might be important for components of that system," she said.

To pinpoint the gene's activity, the researchers genetically engineered mice in which the coding region of the *Math1* gene was replaced by an enzyme that would stain the cells expressing the gene in developing mouse embryos. They first examined mice with one copy of the functional *Math1* gene, along with the stain-producing gene, to determine which cells expressed *Math1* .

"To our total surprise, we could not detect expression of the gene in the nervous system of the gut, but instead found it in the intestinal epithelium," said Zoghbi. These studies revealed that three kinds of secretory cells expressed *Math1* . These were goblet cells that secrete mucous important for

food movement; enteroendocrine cells that secrete regulatory peptides, and Paneth cells that secrete microbe-fighting peptides. The researchers did not find *Math1* expression in other intestinal cells, called enterocytes, which also arise from a common stem cell lineage. In contrast to secretory cells, enterocytes play a role in absorbing nutrients.

"When we studied the mutants with no *Math1* , we found that all three secretory cell types were missing," said Zoghbi. "This told us that *Math1* was important for basic stem cell differentiation, and that *Math1* -negative progenitor cells gave rise to the enterocytes, whereas *Math1* -expressing cells give rise to goblet, enteroendocrine and Paneth cells," she said. "Researchers knew from previous work that one type of stem cell gives rise to all these cell types, but now we know that Math1 likely plays a key role in the decision whether to become a secretory or an absorptive cell."

Additional studies revealed that the protein produced by the *Math1* gene appears to regulate the Delta-Notch signaling pathway that governs endocrine cell differentiation. According to Zoghbi, the discovery of *Math1's* role constitutes a significant step toward understanding how intestinal stem cells differentiate.

"A few months ago all we knew was that in the gut there is a stem cell that is self-renewing and that gives rise to a variety of cell types," she said. "We had no clue what happens to make this stem cell into a mucous-secreting cell or a peptide-secreting cell, or an absorptive cell. Now we have *Math1* to help us begin to build a framework of understanding of the cascade of events, involving many genes, that governs this process."

Such an understanding could have considerable clinical importance, said Zoghbi. "These cells are important in our handling of metabolites absorbed from food and our response to infections," she said. "So, one could imagine a basic understanding of them leading to new treatments for such diseases as irritable bowel syndrome and other abnormalities of gut motility. Also, since these intestinal cells depend on these regulatory pathways to signal them to stop proliferating, understanding those pathways could yield insights into the mechanisms of colon cancers." In the longer term, said Zoghbi, understanding the regulatory control of intestinal stem cells could lead to treatments to regenerate damaged intestinal tissue.

"While it will take considerable work to get to that point, one could envision providing dormant stem cells with some regulatory factors to push them to proceed down a path of differentiation, to replace cells lost to injury," she said. Finally, she said, discoveries about intestinal stem cells could be generalizable to other stem cells.

"What we can learn about the molecular events that trigger intestinal stem cells to differentiate could likely prove applicable to many other stem cells in other parts of the organism," Zoghbi said.