Researchers identify a mutation that causes inflammatory bowel disease

February 10 2009

A team of scientists at The Scripps Research Institute has linked a mouse mutation to an increased susceptibility for developing inflammatory bowel disease -- represented in humans as Crohn's disease and ulcerative colitis, which together are estimated to affect more than a million people in the United States. The findings may one day lead to new and better treatments for the disease.

The work was published in the February 6, 2009 Early Edition of the *Proceedings of the National Academy of Sciences (PNAS)*.

Humans have a gene that is very similar to the mouse gene, called Mbtps1, and in certain rare instances, mutations of this gene may contribute to IBD in humans. The disease is associated with painful ulcers and bleeding in people's intestines and can place them at greater risk for colon cancer. Although common, the disease is still somewhat mysterious. The Scripps Research study sheds light on a major mechanism through which it may develop.

"We are just beginning to get a sense of the complexity of inflammatory bowel disease as far as humans are concerned," says Bruce Beutler, M.D., who is the chair of the Scripps Research Department of Genetics.

Scientists have known for a long time that IBD is linked to genetics—it runs in families, for instance. However, there seems to be no single gene responsible. More likely, says Beutler, mutations in many different genes have additive effects and cause people to develop variably severe forms

of the disease. One of the long-term goals of his laboratory is to identify these genes and the main biological processes they control.

In the latest study, Beutler, Research Associate Katharina Brandl, Ph.D., former Research Associate Sophie Rutschmann (now a member of the Faculty of Medicine at the Imperial College, London), and colleagues, discovered how the gene Mbtps1 is linked to ulcerative colitis in mice. What is clear from their studies, says Beutler, is that crippling the protein product of the Mbtps1 gene makes mice prone to colitis.

The Mbtps1 gene codes for the crucial "site-1 protease," or S1P, an enzyme that cleaves other proteins and is required for life. S1P had been known to process transcription factors: proteins that allow the expression of specific genes. By doing so, S1P allows cholesterol synthesis. It also participates in the so-called "unfolded protein response" that is triggered by numerous forms of cellular stress. Without S1P, cellular stress sometimes ends in cell death rather than repair of cell injury.

The team was first alerted to previously unknown functions of S1P through a curious observation. A few years ago, the scientists discovered a mutant mouse they called "woodrat" whose coat turned gray over time—strikingly different from the normal black coat color. It also turned out that the mouse was susceptible to a form of colitis, induced by a chemical called DSS. The scientists turned to a technique called positional cloning to identify the mutation. They were surprised to find that Mbtps1 was the mutant gene. Mbtps1 had not previously been known to support the integrity of the gastrointestinal tract or normal pigmentation of the coat.

Any mouse entirely bereft of the Mbtps1 gene would not survive past the embryo stage. The woodrat mouse, in fact, has a crippled but not entirely worthless version of the gene. The mutation significantly diminishes the capacity of S1P to function. Beutler and his team estimate that the

altered S1P protein has less than half but more than 1/8th the activity of the normal enzyme. The diminished capacity to process unfolded proteins makes the woodrat mouse susceptible to developing colitis. What happens is that when cells lining the lower digestive tract are stressed, they begin to synthesize a set of specific proteins to deal with the stress. Mbtps1 and a number of other genes are needed to help process unfolded proteins by activating the unfolded protein response, but the diminished capacity of Mbtps1 causes unfolded protein to build up. If the cells cannot deal with the excess unfolded proteins, they initiate a process called programmed cell death and quickly die.

When the cells lining the intestines die, they leave open spaces through which bacteria in the gut can invade. Ultimately what leads to the disease is not the bacteria themselves but the mouse immune system, which creates a strong inflammatory response to the bacteria. This response causes the bleeding, ulcers, and other symptoms that are the hallmark of IBD.

This is a new model for how IBD develops, says Beutler—one of the first corner pieces in the puzzle that he and his colleagues are fitting together to reveal how the disease arises in all its manifestations.

More information: "Enhanced sensitivity to DSS colitis caused by a hypomorphic Mbtps1 mutation disrupting the ATF6-driven unfolded protein response" are Xiaohong Li, Xin Du, and Nengming Xiao of The Scripps Research Institute and Bernd Schnabl and David A. Brenner of the University of California, San Diego. See www.pnas.org/content/early/200 … /0813036106.abstract .

Source: Scripps Research Institute