Press Release

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Embargoed until Wednesday, 14 March 2007, 18:00 GMT

Researchers identify molecular basis of inflammatory bowel disease

Scientists decipher a signaling pathway crucially involved in Crohn's disease and Ulcerative Colitis

Cologne/Mainz/Monterotondo, 14 March 2007 - Inflammatory bowel diseases, such as Crohn's disease and Ulcerative Colitis, severely impair the lives of more than four million people worldwide. The development of effective therapies against these diseases requires an understanding of their underlying molecular mechanisms. Researchers from the Universities of Cologne and Mainz in Germany, the Mouse Biology Unit of the European Molecular Biology Laboratory (EMBL) in Italy and their collaborators, have now deciphered a molecular signal that triggers chronic intestinal inflammation. The study, which is published in the current online issue of *Nature*, shows that blocking a signaling molecule causes severe intestinal inflammation in mice and reveals a molecular mechanism that is likely to also underpin human inflammatory bowel disease.

Our gut is home to an enormous number of bacteria, which live in harmony with us and help in food digestion. If they penetrate the wall of the intestine, however, these bacteria can become harmful and cause diseases. This is why a thin, continuous layer of interconnected cells, called an epithelium, lines the intestinal surface creating a barrier that prevents bacteria from crossing that border. The mechanisms that control the integrity of the epithelium and contribute to maintaining a healthy gut have remained unknown.

Arianna Nenci from the group of Manolis Pasparakis at the University of Cologne and Christoph Becker, a member of Markus Neurath's group in Mainz, investigated the role of NF-κB, a signaling molecule that helps cells cope with stress, in the intestinal epithelium. Using sophisticated genetic methods, they generated a mouse model that does not express NEMO, a protein needed to activate NF-κB, in intestinal epithelial cells. As a result, these mice developed severe chronic intestinal inflammation very similar to Colitis in humans.

"A close look at the mice revealed that their gut epithelium was damaged," says Manolis Pasparakis, who recently moved from heading a lab at EMBL to becoming a professor at the University of Cologne. "NF-κB acts as a survival signal for cells. Without the molecule cells are much more likely to die and this is what happened in the intestines of our mice; individual epithelial cells died disrupting the gut lining."

Through these gaps bacteria could penetrate the intestinal wall. Right behind the gut epithelium lie cells of the intestinal immune system, the biggest immune system of our body. It detects the invading bacteria and generates a strong immune response to fight off the invaders. In the process of combating the bacteria, the immune cells secrete a cocktail of signals that bring about the symptoms of inflammation.

"This is where the vicious cycle closes," explains Markus Neurath, professor at the University of Mainz. "Inflammatory signals also reach the epithelial cells that due to the lack of NF-κB are very sensitive to them and die. The death of more epithelial cells creates bigger gaps in the gut lining so that more bacteria enter. The result is a constant immune response leading to chronic inflammation as we know it from inflammatory bowel diseases in humans."

The finding that defective NF-κB signaling in the gut epithelium initiates the outbreak of inflammation in the intestine provides a new paradigm for the pathogenesis of inflammatory bowel disease. Since the immune systems of mice and humans are very similar, the insights gained through the mouse model are steps towards a better understanding of the mechanisms causing human inflammatory bowel diseases and may pave the way for novel therapeutic approaches.

Source Article

A. Nenci, C. Becker, M. Neurath, M. Pasparakis et al. Epithelial NEMO links innate immunity to chronic intestinal inflammation, *Nature*, 14 March 2007

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About EMBL

The European Molecular Biology Laboratory is a basic research institute funded by public research monies from 19 member states (Austria, Belgium, Croatia, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, the Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and the United Kingdom). Research at EMBL is conducted by approximately 80 independent groups covering the spectrum of molecular biology. The Laboratory has five units: the main Laboratory in Heidelberg, and Outstations in Hinxton (the European Bioinformatics Institute), Grenoble, Hamburg, and Monterotondo near Rome. The cornerstones of EMBL's mission are: to perform basic research in molecular biology; to train scientists, students and visitors at all levels; to offer vital services to scientists in the member states; to develop new instruments and methods in the life sciences and to actively engage in technology transfer activities. EMBL's International PhD Programme has a student body of about 170. The Laboratory also sponsors an active Science and Society programme. Visitors from the press and public are welcome.

About EMBL Monterotondo

The EMBL Mouse Biology Unit based in Monterotondo (Rome), is a basic research center of excellence and innovation in mouse genetics and functional genomics, capturing new opportunities and applications of mouse genetic manipulation and becoming a hub for the international mouse research network. Alliances with other EMBL research units, neighboring facilities in the European Mouse Mutant Archive (EMMA) and Italian national research (CNR) groups, and European academic research and clinical centers has resulted in the participation of EMBL in several EU-wide initiatives to establish an international research and knowledge database, linking information on genetics/genomics, phenotyping/physiology and biomedical features. EMBL Monterotondo currently has six research groups, with a staff of over 80 people.