Zebrafish study shows key enzyme in gut is a peacemaker

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University of Oregon scientists, using zebrafish to study the gastrointestinal tract, say that an enzyme long assumed to be involved in digestion instead is a detoxifying traffic cop, maintaining a friendly rapport between resident gut bacteria and cells.

A deficiency of the enzyme, intestinal alkaline phosphatase (Iap), said Karen Guillemin, a professor of molecular biology, appears to change the playing field inside the gut. Without Iap, an endotoxin called lipopolysaccharide (LPS), which resides in abundance on the gut, gains strength.

The UO pioneered the use of zebrafish as a model biological system for studying vertebrates, opening research windows on a growing list of human diseases. These new findings, reported in the December issue of the journal Cell Host & Microbe, are based on manipulations made in young, germ-free zebrafish and build upon key developmental discoveries involving the zebrafish gut that were published in 2006.

The implications, Guillemin said, could involve human inflammatory bowel diseases, including Crohn's disease, ulcerative colitis and necrotizing enterocolitis. The latter is a common gastrointestinal emergency in premature infants.

"We've shown that the bacteria that reside in our gut play an active role in modulating our immune response to them and help to prevent excessive inflammation," said Guillemin, who is a member of the UO's

Institute of Molecular Biology. "There exists a give-and-take mutual co-existence of our resident bacteria and the cells of our gut."

In a 2006 study, Guillemin and colleagues showed that alkaline phosphatase is induced by LPS, a constituent of the outer membrane of all Gram-negative bacteria, in the early development of the gut's microbiota. The new study found that fish bred without Iap quickly become highly sensitive to LPS toxicity as do wild-type zebrafish when exposed to high levels of LPS. When Iap exists at sufficient levels the enzyme removes phosphates from LPS and turns it into a non-toxic molecule.

The new study is the first to show that LPS exposure in zebrafish causes symptoms that resemble septic shock in mice and humans. UO researchers also identified at least two cytokine genes involved in inflammation in the zebrafish. Cytokines are chemicals normally made by immune cells that boost the immune system to fight infectious pathogens and kill cancer cells.

While the ramifications to human gut diseases are speculative, Guillemin said, there is a lot of interest in connecting inflammatory bowel diseases with microbial changes. "At this point, there is no good understanding as to whether inflammation is caused by a shift in the bacteria present or the disease state changes the balance," she said. "We are not sure which may come first. And no one has looked at the normal variation of alkaline phosphatase in human intestines."

The possibility that the Iap-LPS balance may be contributing to necrotizing enterocolitis in premature babies is intriguing, she said. "So far, there is no real evidence for the involvement of a pathogen causing an infection," she explained. "The best predictor is how old premature infants are. This could represent the fact that this enzyme has not yet been expressed to protective levels."

Source: University of Oregon