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Discovery helps mice beat urinary tract infections

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Scientists at Washington University School of Medicine in St. Louis have found new clues to why some urinary tract infections recur persistently after multiple rounds of treatment.

Their research, conducted in mice, suggests that the bacteria that cause urinary tract infections take advantage of a cellular waste disposal system that normally helps fight invaders. In a counterintuitive finding, they learned that when the disposal system was disabled, the mice cleared urinary tract infections much more quickly and thoroughly.

"This could be the beginning of a paradigm shift in how we think about the relationship between this waste disposal system, known as autophagy, and disease-causing organisms," says senior author Indira Mysorekar, PhD, assistant professor of obstetrics and gynecology and of pathology and immunology. "There may be other persistent pathogens that have found ways to exploit autophagy, and that information will be very useful for identifying new treatments."

The results will be published the week of June 18, 2012, in the early online edition of The *Proceedings of the National Academy of the Sciences*.

Urinary tract infections are very common, particularly in women. In the United States alone, annual treatment costs are estimated to run as high as $1.6 billion. Scientists believe 80 percent to 90 percent of these infections are caused by the bacterium *Escherichia coli* (*E. coli*).

Data from the new study and earlier results have led Mysorekar and her colleagues to speculate that *E. coli* that cause recurrent urinary tract infections may hide in garbage-bin-like compartments within the cells that line the urinary tract.

These compartments, found in nearly all cells, are called autophagosomes. They sweep up debris within the cell, including harmful bacteria and worn-out cell parts. Then, they merge with other compartments in the cell that are filled with enzymes that break down the contents of autophagosomes.

"We think, but can't yet prove, that the bacteria have found a way to block this final step, " Myosrekar says. "This would transform the autophagosome from a death trap into a safe haven where the bacteria can wait, hidden from the immune system, for their next chance to start an infection."

In the new research, Mysorekar teamed with colleagues at the School of Medicine who had developed mice in which both copies of an important autophagy gene, Atg16L1, were impaired. Co-author Herbert W. Virgin, MD, PhD, Edward Mallinckrodt Professor and head of the Department of Pathology and Immunology, and others created the mice to study Crohn's disease, a chronic bowel inflammation associated with mutations in Atg16L1.

Co-lead authors Caihong Wang, DVM, PhD, a staff scientist, and Jane Symington, an MD/PhD student in the Mysorekar group, infected the mice with *E. coli*. The researchers found that bacteria levels in the urinary tracts of the modified mice decreased much more rapidly after infection than they did in normal mice. Cells lining the urinary tract in mice with the mutated gene also had significantly fewer dormant reservoirs of *E. coli* than in normal mice.

The scientists identified structural changes in urinary tract cells of the mice with Atg16L1 mutations that may help explain their unexpected results. These changes may have made it much more difficult for the bacteria to find and break into autophagosomes, Mysorekar says.

The altered gene also was associated with changes in the immune system. In the modified mice, *E. coli* infections in the urinary tract led cells to produce more inflammatory immune factors and prompted additional bacteria-fighting immune cells to come to the site of the infection.

"The immune system appears to be primed to attack at the slightest provocation in the mice with mutations," Mysorekar says. "This may be why mutations in Atg16L1 are also connected with Crohn's disease, which involves immune cells erroneously attacking beneficial microorganisms in the gut."

Mutations in Atg16L1 are quite common, according to Virgin, although not everyone who has a mutated form of the gene will get Crohn's disease.

"These new results may help explain why the mutations have persisted for so long in the general population," he says. "They don't just put the carrier at risk of Crohn's disease, they also may have a protective effect that helps fight infections."

Mysorekar plans to investigate how *E. coli* takes advantage of a fully functioning autophagy system in mice with urinary tract infections.

More information: Wang C, Mendonsa GR, Symington JW, Zhang Q, Cadwell K, Virgin HW, Mysorekar IU. Atg16L1 deficiency confers protection from uropathogenic Escherichia coli infection in vivo. *The Proceedings of the National Academy of Sciences*, early online edition, week of June 18, 2012.

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