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Immune system overreaction may enable recurrent urinary tract infections

The immune system may open the door to recurrent urinary tract infections (UTIs) by overdoing its response to an initial infection, researchers at Washington University School of Medicine in St. Louis have found.

Researchers showed in mice that severe inflammatory responses to an initial UTI cause bladder damage and allow infection to persist longer. After one to two weeks of infection, the bladder wall undergoes additional changes that leave mice more vulnerable to later infection. Suppressing the immune system during initial infection decreases these vulnerabilities, they report Aug. 12 in *PLoS Pathogens*.

"We found markers in the mice that may one day help us identify patients vulnerable to recurrent infection and refine our treatment strategies," says lead author Thomas J. Hannan, DVM, PhD. "There were infection-fighting elements in the immune responses of some mice that we may, for example, one day be able to trigger with vaccines for vulnerable patients."

The research was conducted at the Center for Women's Infectious Disease Research at the School of Medicine.

UTIs affect millions of people each year. Although antibiotics are the primary treatment, antibiotic resistance is a growing concern, according to Scott Hultgren, PhD, the center's director. Symptoms include frequent, painful urination, blood or cloudiness in the urine and fatigue.

"Women and infants are at greatest risk for UTIs, and chronic and recurrent infections are common," says Hultgren, the Helen L. Stoeber Professor of Molecular Microbiology. "The diagnosis and treatment of UTIs in the United States is estimated to cost \$1.6 billion annually."

Hultgren's lab has shown that bacteria can cause multiple bouts of UTI symptoms by going into a dormant state in the host and reactivating months later.

In the study, researchers infected mice with UTIs for a month. Some mice spontaneously resolved their infections; others developed a persistent infection that Hultgren's group calls chronic bacterial cystitis.

These mice persistently had high levels of bacteria in their urine and bladder and high levels of inflammation in the urinary tract.

"Chronic bacterial cystitis is an infection that is actively reproducing, has established a persistent and significant foothold in the host's bladder and has prompted a sustained response from the immune system," says Hannan, a research instructor in pathology and immunology. "Despite all this, the infection is still well-tolerated by the mice."

In one experiment, mice were treated with antibiotics after four weeks of UTI to eliminate the bacteria. Researchers then exposed mice to other UTI-causing bacteria that they could distinguish from the initial infectious bacteria to see how the mice would respond to a subsequent infection.

Forty percent of mice that had signs of chronic bacterial cystitis in the initial challenge developed it again. Mice who never progressed to chronic cystitis or defeated the infection on their own did not develop chronic bacterial cystitis in the second challenge.

Symptoms were more severe in mice with recurrent chronic infections than in recurrent infections that were rapidly cleared.

In mice more vulnerable to recurrent chronic infection, inflammatory immune cells had infiltrated bladder tissues. Inflammatory cells were still visible up to a month after infections were treated and cleared.

"We repeated the experiment, shortening the initial infection time to 14 days and then to one day," Hannan says. "Two weeks of initial infection produced a similar effect, but one day of infection, which is not long enough to progress to chronic bacterial cystitis, did not."

Mice that had chronic bacterial cystitis in the first round of infection but avoided it in the second had little or no bacteria in their urine during the second test. Hannan says this suggests that they may have antibodies in their urine directed against UTI-causing bacteria. Hultgren and colleagues are currently testing vaccines designed to provoke a similar mouse immune response.

Investigators in Hultgren's laboratory are also collaborating with researchers at the University of Washington and Duke University to see if the mouse results can lead them to markers of vulnerability to recurrent infection in humans.

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Hannan TJ, Mysorekar IU, Hung CS, Isaacson-Schmid ML, Hultgren SJ. Early severe inflammatory responses to uropathogenic *E. Coli* predispose to chronic and recurrent urinary tract infections. *PLoS Pathogens*, Aug. 12, 2010.

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