Bacteria that cause urinary tract infections invade bladder cells

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Scientists at Washington University School of Medicine in St. Louis have found definitive proof that some of the bacteria that plague women with urinary tract infections (UTIs) are entrenched inside human bladder cells.

The finding confirms a controversial revision of scientists' model of how bacteria cause UTIs. Previously, most researchers assumed that the bacteria responsible for infections get into the bladder but do not invade the individual cells that line the interior of the bladder.

"Our animal model of UTIs has allowed us to make a number of predictions about human UTIs, but at the end of the day, we felt it was critical to show this in humans, and now we've done just that," says senior author Scott J. Hultgren, Ph.D., the Helen L. Stoever Professor of Molecular Microbiology at the School of Medicine.

The results appear in the December issue of *Public Library of Science Medicine*.

Fully understanding what bacteria do in the bladder is critical to developing better diagnoses and treatments for UTIs, Hultgren says. The bacterium Escherchia coli is thought to be responsible for 80 percent to 90 percent of UTIs, which occur mainly in women and are one of the most common bacterial infections in the United States. Scientists estimate that more than half of all women will experience a UTI in their lifetimes, and recurrent UTIs will affect 20 percent to 40 percent of those patients.

"Recurrence is one of the biggest problems of UTIs," says Hultgren. "Even though we have treatments that eliminate the acute symptoms, the fact that the disease keeps recurring in so many women tells me that we need to develop better treatments."

Prior to the work of Hultgren and his colleagues, most microbiologists and urologists believed for a variety of reasons that E. coli wasn't getting into bladder cells.

"For example, there is a barrier in the bladder that prevents toxins and other things in your urine from leaking back into the body," notes David Rosen, an M.D./Ph.D. student at the School of Medicine and lead author of the paper. "And it was thought that bacteria could not penetrate that barrier."

A biopsy could reveal the presence of bacteria in bladder cells, but taking a tissue sample in an infected bladder incurs an unacceptable risk of allowing bacteria to spread into the bloodstream, a dangerous condition called sepsis.

Scientists also thought that if the bacteria were getting into bladder cells, they would replicate and spread rapidly, sometimes leading to sepsis. But after Hultgren first discovered that bacteria are able to invade bladder cells in 1998, he later found evidence in his animal model that bacteria could establish residence inside those cells. He showed that this process involved several behavioral changes that allow the bacteria to form cooperative communities known as biofilms. By working together, bacteria in biofilms build themselves into structures that are more firmly anchored in infected cells and are more resistant to immune system assaults and antibiotic treatments.

To prove that the model correlates with human infections, Rosen led an analysis of human urine samples sent from a clinic at the University of Washington in Seattle. The 100 patients who gave samples were either suffering from an active, symptomatic infection or had previously suffered infections. Researchers analyzing the specimens were not told which group of patients individual specimens had come from.

Using light and electron microscopy and immunofluoresence, scientists found signs of

bladder cell infection in a significant portion of the samples from patients with active UTIs. These included cells enlarged by bacterial infection and shed from the lining of the bladder.

In addition, Hultgren's experiments had previously suggested that some bacteria progress to a filament-like shape when exiting out of the biofilm. Rosen was able to identify bacteria with this filamentous morphology in 41 percent of samples from patients with symptomatic UTIs.

Neither indicator was detected in urine from women who did not have active infections. This was anticipated: Hultgren's animal model work suggests that when women are between episodes of symptomatic infection, intracellular E. coli may be in dormant phases where there would be little cause for bacteria or the cells they infect to be shed into the urine.

Further research is needed to determine if the infection indicators Rosen detected in urine samples from symptomatic women are signs of increased risk of recurrent infection. But looking for those signs using immunofluorescent staining and a variety of microscopy methods is unlikely to be practical on a widespread clinical basis. So to follow up, Hultgren plans a search for biochemical indicators linked to higher risk of recurrent UTIs and of infection spreading to a patient's kidneys. His lab also continues to be involved in many different efforts to develop new vaccines and treatments.

"What we're learning about how bacteria behave in the bladder may also have application to other chronic, treatment-resistant infections such as sinus infections and ear infections," he says. "We're increasingly starting to realize that biofilm formation is generally an important strategy bacteria use to evade host responses and antibiotic therapies. Attacking biofilms is going to be a really important approach as we enter a new era of fighting infectious diseases."

Source: Washington University

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