

Bacterial Toxin Tied to Chronic Urinary Tract Infections

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Researchers from the University of Utah have identified a process by which the most common types of urinary tract infection-causing bacteria are able to trigger bladder cell shedding and disable immune responses. According to this new study, published in the Jan. 19, 2012, issue of *Cell Host & Microbe*, α -hemolysin, a toxin secreted by many strains of *Escherichia coli* (*E. coli*), may play an important, unexpected role during both the establishment and persistence of urinary tract infections.

Urinary tract infections (UTIs) are among the most common infectious diseases worldwide. Each year, 15 million U.S. women have a UTI and nearly 50 percent of women will have at least one UTI in their lifetime. Bacteria known as uropathogenic *E. coli* (UPEC) are the leading cause of both acute and chronic urinary tract infections. UPEC invade cells on the surface of the bladder, where it can stimulate exfoliation, or shedding, of bladder cells.

“Exfoliation of bladder cells can be viewed as a double-edged sword since it may benefit both the host and the invading bacteria,” says Matthew Mulvey, PhD, associate professor of pathology at the University of Utah and co-author on the study. “While shedding helps to get rid of infected cells, it can also promote spread of the bacteria both within and outside of the urinary tract. The goal of our investigation was to uncover possible mechanisms by which UPEC might prime bladder cells for shedding.”

Mulvey and Bijaya Dhakal, PhD, U of U postdoctoral fellow in pathology, found that infection of bladder cells with UPEC led to degradation of a protein called paxillin, which helps to regulate cell adhesion. They discovered that paxillin degradation was stimulated by α -hemolysin (HlyA), a toxin secreted by UPEC, which inserts into bladder cell membranes. HlyA itself does not act to break down paxillin, but Mulvey and Dhakal found that HlyA caused increased activation of a protein-degrading enzyme called mesotrypsin.

“Our data indicate that mesotrypsin is at least partially responsible for paxillin degradation in the UPEC-infected bladder cells,” says Mulvey. “This finding is unexpected and intriguing because, although mesotrypsin has been implicated in bladder and other cancers, as well as the shedding of skin cells, its function is still largely undefined.”

When UPEC infect bladder cells, the bacteria either multiply or persist in an inactive state for days or even weeks. This persistence creates intracellular reservoirs of bacteria, which are thought contribute to chronic or recurrent infections. Mulvey and Dhakal found that HlyA triggers not only paxillin degeneration, but also breakdown of key proteins involved in cellular responses to infection. The investigators also discovered that the effects of HlyA are not limited to bladder cells. HlyA stimulated protein degradation in macrophages, key immune cells responsible for destroying bacteria, as well. These disruptions of the normal immune response to bacterial invasion may help to explain why UTIs can persist or recur, even in otherwise healthy individuals and in the presence of antibiotics.

“UTIs caused by UPEC strains that secrete HlyA lead to more severe clinical symptoms and tissue damage,” says Mulvey. “HlyA is also associated with other closely related strains of *E. coli* that cause pneumonia, meningitis or serious bloodstream infections. So, in addition to furthering our understanding of UTIs, this study may help to shed light on the mechanisms of other infectious diseases.”