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INFECTION

Dysregulation of *E. coli* α-hemolysin alters UTI course

The majority of UTIs are caused by uropathogenic *Escherischia coli* (UPEC), which can bind to urothelial cells, after which it is either expelled or invades into the cytoplasm. Exfoliation of the host urothelium can hasten recovery by increasing excretion of bacteria-filled cells via the urine, but can also aid deeper infiltration of UPEC into the urothelium, resulting in persistent infection. The exfoliation process has been shown to be dependent on caspases, but a deeper understanding of the mechanism in *E. coli* has remained elusive.

New research research published in *Proceedings of the National Academy of Science* has shown that UPEC α-hemolysin (HlyA) induces inflammatory cell death in human urothelial cells, and that overexpression of HlyA *in vivo* accelerates exfoliation of of bacteria in acute bladder infection.

HlyA is a pore-forming toxin, highly expressed in *E. coli* isolated from patients with UTI, and previously implicated in urothelial cell toxicity *in vivo*. In this study, the researchers sought to determine the relationship between HlyA and the exfoliation response in UPEC UTI. "Urothelial exfoliation is a critical response of the bladder mucosa to invasive infection," lead author Scott Hultgren told *Nature Reviews Urology*. "We hypothesized that the timing and extent of this innate response could greatly impact the severity and length of UTI in an animal model". Based on previous studies showing that the Cpx two-component system (CpxRA) provides UPEC with a survival advantage in the bladder, Hultgren's team first showed that the response regulator sensor kinase CpxRA regulates *hlyA* and fine tunes HlyA protein levels, thus affecting host cell toxicity. They then investigated whether HlyA could directly induce urothelial cell death pathways *in vitro*. By infecting a human urothelial cell line with UPEC that lacked the Cpx system, they showed that α-hemolysin was upregulated, resulting in an increase in inflammatory cell death (also known as pyroptosis), which was dependent on caspase 1, caspase 4 and NLRP3.

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They went on to study this effect *in vivo*, by infecting mice with mutant strains of UPEC and assessing their bladder bacterial load at 16 h after infection. "We were able to demonstrate that increasing the extent and kinetics of urothelial exfoliation by infecting the bladder with UPEC that overexpress α-hemolysin enhanced bacterial clearance during acute cystitis, and that these effects were reversed when Caspases 1 and 4 were inhibited," explains Hultgren. "These results will have significant implications for our understanding of how UPEC establish persistent colonization."

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Original article Nagamatsu, K. *et al.* Dysregulation of *Escherichia coli* α-hemolysin expression alters the course of acute and persistent urinary tract infection. *Proc. Natl Acad. Sci. USA* doi:10.1073/pnas.1500374112