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Urinary tract infections (UTIs) are mainly caused by uropathogenic strains of *Escherichia coli* (UPEC) and they induce a cellular innate immune response that is characterized by the activation of Toll-like receptors (TLRs). Now, Jaillon *et al.* show that TLR-mediated signalling during UTIs leads to the production of the soluble pattern-recognition molecule pentraxin-related protein 3 (PTX3), which is crucial for protection against UTIs.

PTX3 is an acute-phase protein that is highly conserved between mice and humans, and can protect against bacterial and fungal infections. To explore the role of PTX3 in UTIs, the authors analysed the susceptibility of *Ptx3*^{-/-} mice to UPEC infections that were contained in the bladder or that had spread to the kidneys (pyelonephritis). Bacterial burdens were similar in the bladders of *Ptx3*^{-/-} and wild-type mice 1 day after UPEC infection but

at 5 days after infection, *Ptx3*^{-/-} mice had substantially increased bacterial burdens compared with control mice. After 1 day of UPEC infection, the bacterial burdens were considerably higher in kidneys from mice with pyelonephritis that lacked PTX3 than in control mice and this difference was maintained for 5 days after UPEC infection. Thus, PTX3 is expressed locally during UTIs and has an important role in the defence against UPEC infection.

Next, the authors investigated the origin and action of PTX3 during UTIs. Using immunohistochemical analysis, the authors found little or no PTX3 expression in the bladder and kidneys of non-infected mice, but 1 day after UPEC infection PTX3 was produced by epithelial cells from the kidneys and bladder, and by infiltrating inflammatory cells. By contrast, intraperitoneal injection of lipopolysaccharide (LPS) did not induce PTX3 expression in the bladder and kidneys. Furthermore, the authors found that PTX3 functions as an opsonin that binds UPEC and promotes its uptake by neutrophils; this opsonization accelerated phagosome maturation in these cells compared with in phagocytes bearing uncoated UPEC. This suggests that PTX3 is produced locally by uroepithelial cells and leukocytes during UTIs and that PTX3 promotes increased intracellular killing of UPEC by neutrophils.

To determine the signalling pathways that are responsible for production of PTX3, the authors

used a human uroepithelial cell line that expresses TLRs and the TLR signalling adaptors MYD88 and TRIF. The induction of PTX3 expression in response to UTI was only abolished when the genes that encode TLR4 and MYD88 were silenced. Furthermore, mice that lacked MYD88 showed decreased levels of PTX3 expression both in the kidneys and in the bladder. Hence, the PTX3 response to UTI seems to be regulated by the TLR4–MYD88 axis.

Finally, the authors investigated the clinical relevance of PTX3 in UTIs. Immunohistochemistry of bladder sections from patients with UTIs showed substantial PTX3 expression, whereas samples from uninfected donors showed no or very low expression of PTX3. In addition, urine and serum levels of PTX3 were increased in patients with UTIs compared with healthy donors, and patients with acute pyelonephritis showed the highest levels. Interestingly, the authors found that two genetic variants of *PTX3* — that have previously been associated with bacterial colonization — were associated with increased susceptibility to UTIs.

In summary, these results suggest that PTX3 contributes to resistance against UTIs that are caused by UPEC, which indicates a role for the humoral arm of innate immunity in protection against UTIs.

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ORIGINAL RESEARCH PAPER Jaillon, S. *et al.* The humoral pattern recognition molecule PTX3 is a key component of innate immunity against urinary tract infection. *Immunity* **40**, 621–632 (2014)

“serum levels of PTX3 were increased in patients with UTIs”

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