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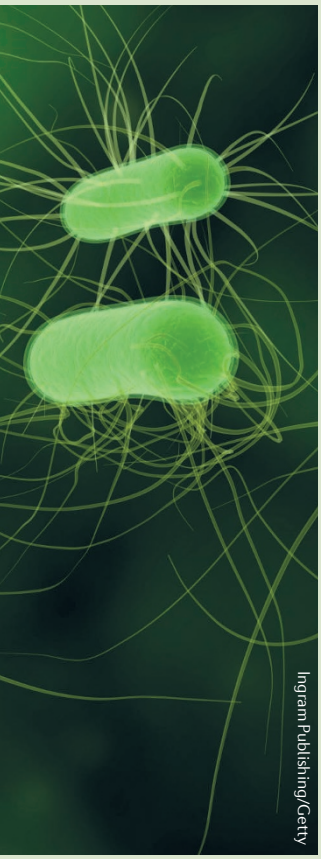

INFECTION

Transcriptome remodelling explains UTI recurrence

A history of ≥2 incidences of UTI is an independent predictor of recurrent UTI; however, the mechanisms of this effect remain largely unknown. Now, researchers have established the existence of substantial changes in the urothelial morphology and transcriptomes of mice that are sensitized following initial infection with uropathogenic *Escherichia coli* (UPEC), compared with mice that remain resistant despite initial infection. Researchers were also able to demonstrate some success with systemic vaccination with the bacterial adhesion protein FimH in mice that are sensitized to recurrent UTI.

In this study, infection of mice with the UPEC isolate *utI89* resulted in one of two distinct outcomes: spontaneous resolution or persistent infection. When exposed to a range of bacterial isolates from women with recurrent UTI, mice with spontaneous resolution of the initial infection were almost entirely insensitive to these strains, while a significant number of mice that were sensitive to initial infection became reinfected.

The urothelial morphology of these sensitized mice was investigated using electron microscopy, and several notable differences were observed. These included significant changes in the expression of several marker proteins, including a reduction in Krt20, indicating a reduction in the level of terminal differentiation and a significant increase in the size of the intermediate and basal cell layers, suggesting the presence of urothelial hyperplasia. These differences were confirmed by RNA-sequencing analysis of the bladders of resistant and sensitized mice during recovery from infection: significant differences in the expression of 837 different genes were observed, with changes in expression of genes involved in immune-related pathways, cellular development and proliferation among the most common observations.

Researchers also demonstrated the central role of cyclo-oxygenase-2 (COX2) enzymes in recurrent UTI: treatment of sensitized mice with a COX2 inhibitor resulted in a significant reduction in bacterial burden, this effect was not observed in resistant mice, most likely reflecting a lack of COX2 upregulation. Furthermore, recurrent infection upon exposure of sensitized mice to *ut189* was also prevented by vaccination with the bacterial adhesion protein FimH, although further research will be required prior to implementation.

These findings provide valuable mechanistic insights on the unexplained variations in vulnerability to recurrent UTI. Furthermore, data on the clinical effectiveness of COX2 inhibition and fimH vaccines in patients with recurrent UTI are eagerly anticipated.

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ORIGINAL ARTICLE O'Brien, V. P. *et al.* A mucosal imprint left by prior Escherichia coli bladder infection sensitizes to recurrent disease. *Nat. Microbiol.* http://dx.doi.org/10.1038/nmicrobiol.2016.196 (2016)