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INFECTION

Impeding UPEC gut colonization

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Antibiotic resistance of uropathogenic *Escherichia coli* (UPEC) results in failure of standard treatments for UTI and recurrent infections in many patients. A new paper in *Nature* describes oral treatment with a mannoside compound that, by specifically blocking host cell binding via the adhesin FimH, impairs UPEC colonization in the gut and the urinary tract of mice without altering the remaining gut microbiota.

UPEC can colonize host environments through adhesion to target cells via chaperone–usher pathway (CUP) pili, such as the type 1 pilus containing FimH, which enables bladder colonization. The gut is a primary reservoir of UPEC strains that can colonize the vagina and periurethral area before ascending through the urethra to cause UTI; however, little is known about the mechanisms by which UPEC is able to establish itself in the gut.

The researchers created a model of UPEC gut colonization in streptomycin-pretreated, conventionally raised female mice. "Mice were co-colonized with the *E. coli* strain UTI89 (a human cystitis isolate) and one of nine isogenic mutant strains, each lacking a single CUP operon normally encoded in UTI89," explains Scott Hultgren, senior author of the study. Deletion of the *fim* or *ucl* pilus operons (encoding type 1 and F17-like pili, respectively) resulted in 100-fold and 1,000-fold reductions in gut colonization, respectively. Combined deletion had an even greater effect, suggesting nonredundant roles of these two pilus types. Mutations of *fimH* are known to abolish UPEC colonization of the bladder; by contrast, deletion of *ucl* had no effect on rate or severity of bladder infections in mice.

The team then investigated whether the two pilus types, which are tipped with either the FimH or UclD adhesin, had differing cellular binding affinities. "Interestingly, UclD binding was restricted to the lower portion of colon crypts, whereas FimH bound to the upper region, suggesting that these pili promote binding to different carbohydrate structures expressed by epithelial cells at different stages of differentiation," summarizes Hultgren.

Phylogenetic analyses of the F17-like pilus encoded by *ucl* showed that it is unique to B2 type *E. coli* strains and is closely related to CUP pili of enteric pathogens, such as enterotoxigenic *E. coli* (ETEC) and enterohaemorrhagic *E. coli*. "This finding suggests that UPEC adapted this subgroup of gut-related CUP pili to maintain gut colonization," Hultgren told *Nature Reviews Urology*. Two X-ray crystal structures of the F17-like adhesin UclD showed that the overall secondary-structure characteristics of the UclD and the F17 adhesin, which is expressed by ETEC, are largely conserved, although sequence identity was only 25%. However, sequence, structure, and tissue binding differences demonstrated that UclD binds a different ligand than the F17 adhesin.

The team also analysed genomes of UPEC strains from women with recurrent UTI and found that the genes encoding F17-like pili are more common in these UPEC strains than in genomes of *E. coli* in a reference database. "Together, these experiments reveal the first known structure and function of F17-like pili, and suggest that UPEC strains benefit by forming host reservoirs in the gut through a F17 family intestinal colonization factor," highlights Hultgren.

The FimH adhesin of type 1 pili recognizes and binds mannose, which is required for bladder colonization in mouse UTI models, and M4284 is a mannoside that binds to FimH with a ~100,000-fold higher affinity than D-mannose. Oral treatment of mice with M4284 reduced the UTI89 population in the gut, urine, bladder, and kidneys by up to 99% (~100-fold). Notably, the treatment did not significantly alter the phylogenetic configuration of the gut microbiota, and was similarly effective in another mouse strain and in mice with different gut microbiota.

"Identification of genes involved in UPEC colonization of the gut provides new avenues for therapeutic development," concludes Hultgren. "If taken to clinical practice, a treatment like mannoside would reduce the exposure of the gut bacterial community to antibiotics. Our ultimate goal is to help patients manage and prevent UTI while also helping to address the worlwide crisis of antimicrobial resistance."

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ORIGINAL ARTICLE Spaulding, C. N. *et al.* Selective depletion of uropathogenic *E. coli* from the gut by a FimH antagonist. *Nature* http://dx.doi.org/10.1038/nature22972 (2017)
FURTHER READING Zowawi, H. M. *et al.* The emerging threat of multidrug-resistant Gram-negative bacteria in urology. *Nat. Rev. Urol.* **12**, 570–584 (2015)