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ANTIMICROBIALS

Modified sugar compound can clear intestinal colonization by UPEC

> This novel strategy … may represent a valid alternative to antibiotic treatments

The gastrointestinal tract represents the natural habitat for both pathogenic and commensal bacterial species that constitute the gut microbiota. Uropathogenic *Escherichia coli* (UPEC) is a commensal bacterium that colonizes the gut, but becomes pathogenic in the bladder and causes urinary tract infections (UTIs). UPEC strains in the gut cause UTIs after being shed in the faeces and colonizing the vagina and urethra, before ascending through the urethra and accessing the bladder. Despite antibiotic treatment, these infections are often recurrent and are increasingly caused by antibiotic-resistant UPEC strains. Bacterial pili are known to have vital roles in host–UPEC interactions, by mediating adhesion to epithelial cells that are present at distinct infection sites, such as the bladder and kidneys. However, little was known about the mechanisms that enabled the colonization and persistence of UPEC in the gut.

In a new study, Spaulding *et al.* investigated and showed that chaperone–usher pathway (CUP) pili have a role in the colonization of the gut by UPEC strains. In particular, the authors generated nine single-deletion mutants that each lacked a CUP pilus operon and tested the effect of these mutations in a mouse gut colonization model. They found that single deletion of two operons, *fim* and *ucl*, which encode type 1 pili and F17-like pili, respectively, caused a marked reduction in the ability of the bacterium to colonize the gut. Moreover, the deletion of both operons in a single strain generated a greater fitness defect than either single deletion, which proves that their roles are not redundant. The *fim* and *ucl* operons each encode adhesins that are located at the distal tip of each pilus, FimH and UclD, respectively, which mediate binding to host cells. By testing purified fragments of these two adhesins in *in vitro* binding assays, the authors showed distinct binding specificities to glycans present on the surface of host epithelial cells distributed along intestinal crypts; FimH bound preferentially to *N*-linked glycans that contain mannose, whereas UclD domains bound to *O*-linked glycans. In addition, loss of the type 1 pilus adhesin FimH mirrored the defect caused by the deletion of the full *fim* operon. Previous studies found that the loss of type 1 pili abolished the ability of UPEC to colonize and invade the bladder; by contrast, the authors found that F17-like pili had no identifiable role in UTIs. To try to prevent the binding of type 1 pili to epithelial cells of the gut, the authors tested the M4284 mannoside, which is a synthetic small molecule that is linked to mannose and binds with high affinity to the type 1 pilus adhesin FimH. Mice that were treated orally with this compound showed decreased gut colonization by UPEC strains compared with untreated mice, demonstrating that this mannoside could effectively compete for binding to mannose on host surfaces and thus directly interfere with host–pathogen interactions. The authors also show that the administration of M4284 could decrease the likelihood of developing a UTI by simultaneously removing UPEC from the gut and treating an active bladder infection. Moreover, this treatment did not cause substantial alterations in the composition of the gut microbiota, which contrasts with the antibiotic treatments that are currently in use. This novel strategy shows that anti-adhesive therapies can reduce colonization of specific bacteria from pathogenic and commensal habitats, and may represent a valid alternative to antibiotic treatments, thereby overcoming the limitations of antibiotics, such as the disruption of the commensal communities that are present in the microbiota and emergence of antibiotic resistance.

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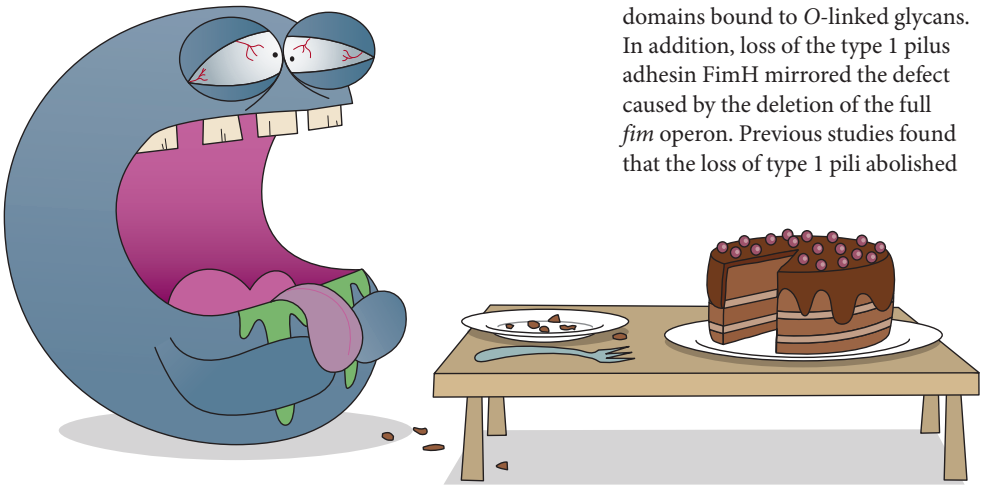

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