VACCINES

Ascending to a UTI vaccine?

Researchers at the University of Maryland have developed an intranasal vaccine that protects mice against urinary tract infection by *Proteus mirabilis*.

Escherichia coli is the most common bacterial cause of acute, uncomplicated urinary tract infections (UTIs). However, a high proportion of individuals with anatomically or functionally abnormal urinary tracts and those with indwelling catheters have *P. mirabilis* infections that can ascend the urinary tract and reach the kidney, causing acute or chronic pyelonephritis. *P. mirabilis* is also associated with urolithiasis, the formation of urinary stones, a condition that places a large burden on healthcare resources each year.

Among its virulence factors, *P. mirabilis* expresses four different types of fimbriae on its cell surface. The Mobley lab has focused on one of these — the mannose-resistant *Proteus*-like fimbriae (MR/P) — as a potential vaccine candidate. Previous work has shown that the virulence of MR/P-deficient bacteria is attenuated, and that most of the *Proteus* population present during infection express MR/P fimbriae.

In this work, Xin Li and her colleagues used a mouse model of an ascending UTI to assess the efficacy of vaccination with four different preparations by four different inoculation routes. As initial studies using formalin-killed *P. mirabilis* and purified MR/P fimbriae proved that intranasal inoculation conferred the most efficient protection and was the only inoculation route that elicited a detectable antibody response in vaginal washes, this was the inoculation strategy that was taken forward.

Although the formalin-killed whole bacteria and purified fimbriae were shown to protect mice against *P. mirabilis* infection, Li *et al.* reasoned that a vaccine targeting a *P. mirabilis* adhesin might be more effective as it could block the adherence of the bacteria to host cells. Two further intranasal vaccines were therefore prepared — one comprising the adhesin present at the tip of MR/P fimbriae, the MrpH protein, fused to maltose-binding protein (MBP) and one comprising a fusion between the MrpH amino-terminal receptor-binding domain and MBP. Protection against *P. mirabilis* infection of the bladder and kidneys was most effective (75%) with the truncated MrpH–MBP construct and, importantly, the side effects of this vaccine were significantly reduced compared with the other preparations tested. Analysis of 30 different *P. mirabilis* isolates revealed that MrpH is conserved among diverse strains, indicating that it could provide protection against heterologous strains.

This publication advocates a simple intranasal vaccination route using the receptor-binding domain of the MrpH adhesin for protection against *P. mirabilis* infection in a mouse model of an ascending UTI. Li *et al.* state they might go on to try and further improve the efficacy of their vaccine by adding other adhesin molecules.

Sheilagh Clarkson

References

ORIGINAL RESEARCH PAPER Li, X. *et al*. Development of an intranasal vaccine to prevent urinary tract infection by *Proteus mirabilis*. *Infect. Immun*. **72**, 66–75 (2003)

BACTERIAL PHYSIOLOGY

Unlocking chitin degradation

Chitin — a polymer of *N*-acetyl glucosamine (GlcNAc) — is a highly abundant biological molecule and is present in huge amounts in marine ecosystems in the cuticles of zooplankton. Its degradation by ocean-dwelling bacteria is essential for the cycling of nutrients, and how these microorganisms sense and respond to chitin has long been a matter of interest. Work from Saul Roseman's laboratory now reveals that two vibrio species use a two-component regulatory system to detect chitin and activate the genes that break it down.

Chitin degradation by *Vibrio furnissii* and *Vibrio cholerae* involves dozens of genes, the expression of which Roseman and his colleague, Xibing Li, now show to be controlled by a two-component regulatory system. They used transposon mutagenesis to identify the sensor component of this system by selecting for *V. furnissii* mutants that were able to grow on GlcNAc but were unable to degrade chitin or produce any of the proteins required for its degradation. The *chiS* gene was found to encode the *V. furnissii* sensor component and the homologous gene from *V. cholerae* was identified. The ChiS protein comprises a periplasmic domain that senses the environmental signal and a cytoplasmic domain that transmits this information to activate gene expression.

These studies suggest a model in which ChiS is bound and locked into an inactive state by a periplasmic chitin-oligosaccharide-binding protein (CBP) in the absence of chitin oligosaccharides. According to this model, in the presence of $(GlcNAc)_n$ (which is produced by a chitinase secreted by the bacteria), ChiS is released by CBP and activates gene expression.

To test this, the authors used an assay that measures the activity of β-*N*-acetylglucosaminidases, enzymes in the chitin degradation pathway. In wild-type *V. cholerae*, these enzymes are only induced in the presence of $(GlcNAc)_2$, and this activity is abolished if *chiS* is deleted, consistent with a role of *chiS* in activating genes involved in chitin catabolism. However, when the gene encoding CBP was deleted, β-*N*-acetylglucosaminidases were constitutively activated, even in the absence of $(GlcNAc)_2$, but when both genes were deleted, no activity was detected. This confirms the model in which the sensor is held in the inactive state until the bacteria encounter chitin oligosaccharides, allowing efficient control of chitin catabolic genes.

Louisa Flintoft

References and links

ORIGINAL RESEARCH PAPER Li, X. & Roseman, S. The chitinolytic cascade in Vibrios is regulated by chitin oligosaccharides and a two-component chitin catabolic sensor/kinase. *Proc. Natl Acad. Sci. USA* **101**, 627–631 (2004)

WEB SITE

Saul Roseman's laboratory: http://www.bio.jhu.edu/directory/Faculty/Roseman/Default.html