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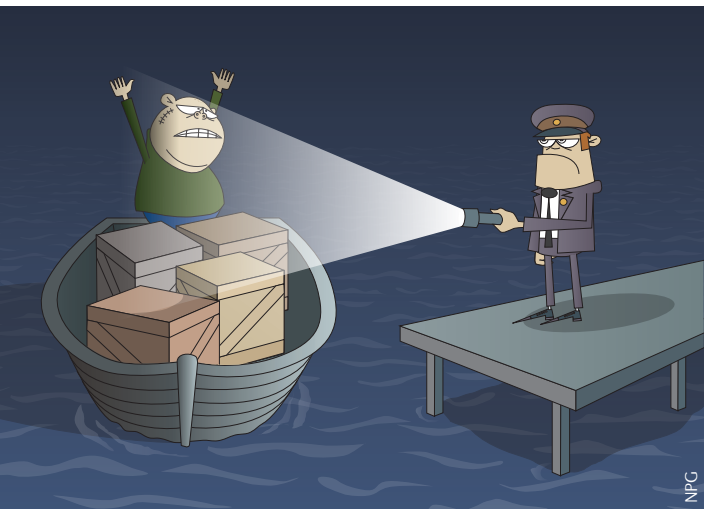
BACTERIAL TOXINS

Exposing the exporter

> discovery of an essential secretion system that is shared by all *Staphylococcus aureus* PSMs

With resistance to traditional antibiotics increasing globally, the targeting of virulence factors has emerged as an alternative strategy to control bacterial infections. Phenol-soluble modulins (PSMs) are a family of cytolytic peptide toxins with key roles in staphylococcal pathogenesis; however, because of their considerable diversity, effective targeting of PSMs is difficult. A new study now reports the discovery of an essential secretion system that is shared by all *Staphylococcus aureus* PSMs, representing a promising new lead for drug development.

S. aureus produces four different PSMα peptides, two different PSMβ peptides and the δ-toxin. Although these proteins display highly variable amino acid sequences, they all lack a signal peptide, which suggests that they use a common mechanism of secretion. Thus, Chatterjee *et al.* set out to determine the mechanism of PSM export. Because accessory gene regulator (Agr) controls PSM production, the authors began by searching for Agr-regulated genes with putative transport functions. Similarly to the *psm* genes, a set of four candidate genes was common to all staphylococcal isolates, and these genes encoded a previously uncharacterized ATP-binding-cassette transporter, which the authors termed PSM transporter (Pmt).



Deletion of the *pmt* locus revealed that all *S. aureus* PSMs were strongly dependent on Pmt for export, and in particular on the conserved Walker A and Walker B boxes, which are required for energy-dependent transport. In the absence of *pmt*, PSMs accumulated in the cytosol and caused a pronounced growth defect, which was accompanied by defective cell division and membrane damage. Conversely, the expression of Pmt protected *S. aureus* from the antimicrobial effects of self-produced PSMs, in addition to PSMs produced by *Staphylococcus epidermidis*, indicating that the system provides immunity to both self and non-self PSMs. This feature is likely to be important during mixed infections, when PSMs could be used as weapons to target other bacterial species competing for the same niche.

The authors went on to evaluate the role of Pmt in virulence and found that biofilm development, as well as lysis of neutrophils and erythrocytes, was severely compromised in the *pmt*-negative strain. A mouse skin infection model was also used to determine the contribution of Pmt to disease progression. Abscesses formed by *pmt*-negative strains were significantly smaller than those formed by *pmt*-positive strains, consistent with a reduced number of viable *pmt*-negative cells in the smaller abscesses.

Collectively, these findings identify the Pmt export system as a crucial component of *S. aureus* virulence. Although this study focused on *S. aureus*, the high similarity of *pmt* genes among staphylococci indicates that the system is likely to be conserved in other species. Finally, considering that Pmt is required for secretion of an entire family of clinically relevant toxins and that the system provides immunity to such toxins, the authors propose that this exporter represents an ideal target for the development of new antibacterial drugs.

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ORIGINAL RESEARCH PAPER Chatterjee, S. S. *et al.* Essential *Staphylococcus aureus* toxin export system. *Nature Med.* 10 Feb 2013 (doi:10.1038/nm.3047)