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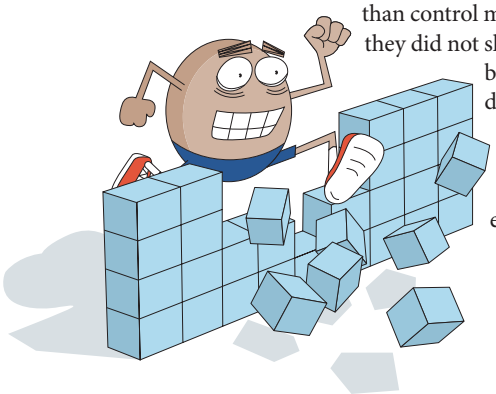
BACTERIAL TOXINS

Breaking the barrier

> it is possible that the activity of ADAM10 is usurped by a broad range of bacteria

α-haemolysin, a pore-forming toxin produced by *Staphylococcus aureus*, was recently shown to bind the host cell metalloproteinase ADAM10 (a disintegrin and metalloproteinase domain-containing protein 10). Bubeck Wardenburg and colleagues now find that this interaction is key to barrier disruption in epithelial cells during infection.

To investigate the role of ADAM10 in *S. aureus*-mediated pneumonia, the authors generated mice that lacked this protein specifically in the respiratory epithelium. On infection with *S. aureus*, these mice did not develop severe pneumonia, showing greater preservation of lung tissue and less inflammation than control mice. However, they did not show a reduced bacterial burden, indicating that ADAM10 has a role specifically in epithelial injury.



ADAM10 triggers the cleavage of E-cadherin, leading to breakdown of cell–cell junctions, so the authors reasoned that this may be the mechanism by which α-haemolysin promotes epithelial barrier disruption. Accordingly, epithelial cells treated with α-haemolysin showed increased metalloproteinase activity, E-cadherin cleavage and rapid loss of barrier function *in vitro*. By contrast, metalloproteinase activity in cells lacking ADAM10 was markedly reduced and barrier function was normal.

The authors assessed the relevance of their findings *in vivo*. In contrast to mice infected with wild-type *S. aureus*, those infected with α-haemolysin-deficient bacteria showed decreased levels of barrier disruption and had lower levels of the E-cadherin amino-terminal fragment (generated following cleavage of the full-length protein) in the lungs. Moreover, α-haemolysin treatment did not induce E-cadherin cleavage in mice lacking ADAM10 in the respiratory epithelium, confirming that ADAM10 has a key role in mediating the effects of the toxin. Importantly, treating mice with an ADAM10 inhibitor following challenge with α-haemolysin prevented E-cadherin cleavage; this inhibitor also protected mice from lethal pneumonia following infection with *S. aureus*.

This study reveals a crucial role for ADAM10 in mediating pathogenesis during *S. aureus* infection. Interestingly, the authors report that ADAM10 can also be used by pneumolysin, a *Streptococcus pneumoniae* toxin, to trigger E-cadherin cleavage. Therefore, it is possible that the activity of ADAM10 is usurped by a broad range of bacteria, making it a potential therapeutic target.

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ORIGINAL RESEARCH PAPER Inoshima, I. *et al.* A *Staphylococcus aureus* pore-forming toxin subverts the activity of ADAM10 to cause lethal infection in mice. *Nature Med.* 18 Sep 2011 (doi: 10.1038/nm.2451)