Nature Reviews Drug Discovery | Published online 15 Jun 2018; doi:10.1038/nrd.2018.100

INFECTIOUS DISEASES

The painful path to avoiding the immune system

Necrotizing fasciitis, or flesh-eating disease, is a painful, life-threatening infection caused by *Streptococcus pyogenes* with a mortality rate of around 30% in developed countries. Now, reporting in *Cell,* Pinho-Ribeiro et al. have found that *S. pyogenes* exploits communication that normally occurs between the nervous and immune systems to avoid clearance by neutrophils. This pain-inducing way to promote bacterial survival offers several approaches to target this difficult-to-treat disease.

The authors had previously found that bacteria can directly activate neurons to produce pain through secretion of pore-forming toxins such as *Staphylococcus aureus* α-haemolysin. To study the role of pain fibres in *S. pyogenes* invasion, the authors subcutaneously injected two *S. pyogenes* strains from human infections in mouse hind paws, which are densely innervated. Both bacterial strains induced hyperalgesia, progressive dermonecrotic lesions and other symptoms that closely resemble human necrotizing fasciitis. The pain was apparent within minutes and was unaffected by treatment with ibuprofen. Moreover, depletion of neutrophils or differentiation of T and B cells did not alter pain after infection, which suggested that this pain could have a nervous, rather than immunological, origin.

> “Local treatment of large lesions with BoNT/A even 48 hours after infection halted the progression of *S. pyogenes* invasion, reduced dermonecrosis and rapidly decreased abscess size”

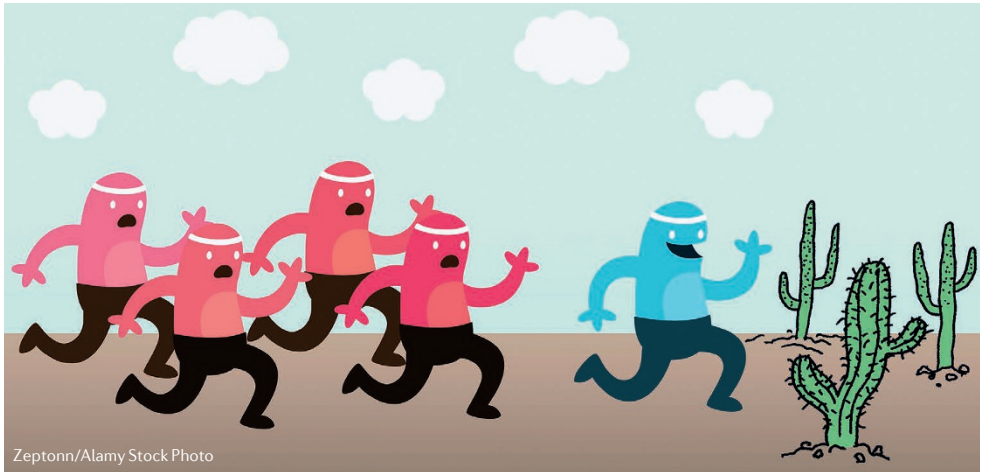
The authors saw that, in vitro, *S. pyogenes* activated nociceptor neurons that expressed transient receptor potential cation channel subfamily V member 1 (TRPV1), a heat-sensitive ion channel, and induced release of calcitonin gene-related peptide (CGRP). Importantly, supernatants from *S. pyogenes* cultures also activated TRPV1$^+$ neurons and further experiments identified the culprit as the pore-forming toxin streptolysin S (SLS), which induces the release of CGRP. Treating cultured neurons with botulinum neurotoxin A (BoNT/A) — a bacterial toxin that blocks neuronal vesicle release — inhibited this CGRP release.

In mice, treatment with a polyclonal antibody against SLS blocked infection-triggered pain. Hyperalgesia was also eliminated in mice that lack neuronal TRPV1. Subcutaneous injection of BoNT/A 6 days before *S. pyogenes* infection prevented the development of dermonecrotic lesions by inhibiting infection-induced CGRP release, which suggested that peripheral release of CGRP is crucial in bacterial invasion, likely by inhibiting neutrophil recruitment. Indeed, in vitro, the presence of cultured nociceptors suppressed the capacity of neutrophils to kill *S. pyogenes*.

Finally the authors explored the therapeutic potential of inhibiting this neuronal suppression of the immune response by targeting neurons using BoNT/A or a CGRP receptor antagonist, BIBN4096. BoNT/A and BIBN4096 increased the recruitment of neutrophils to the infected area compared with infected, untreated mice. Local treatment of large lesions with BoNT/A even 48 hours after infection halted the progression of *S. pyogenes* invasion, reduced dermonecrosis and rapidly decreased abscess size.

Lead author Isaac Chiu now plans “to determine whether Botulinum neurotoxins, including BoNT/A and other serotypes such as BoNT/E that are under clinical development, can be used to treat invasive infections such as necrotizing fasciitis”. Moreover, “CGRP antagonists, which are currently under development or recently approved for treating migraine, can be repurposed to treat invasive infections,” he adds. His group is also interested in determining whether these findings might apply to other types of bacterial pathogens including multiresistant *S. aureus* or Gram-negative bacteria.

M. Teresa Villanueva



Zeptonn/Alamy Stock Photo

ORIGINAL ARTICLE Pinho-Ribeiro F. A. et al. Blocking neuronal signaling to immune cells treats streptococcal invasive infection. *Cell* **173**, 1083–1097 (2018)