EndA:
http://ca.expasy.org/uniprot/P0A3S3

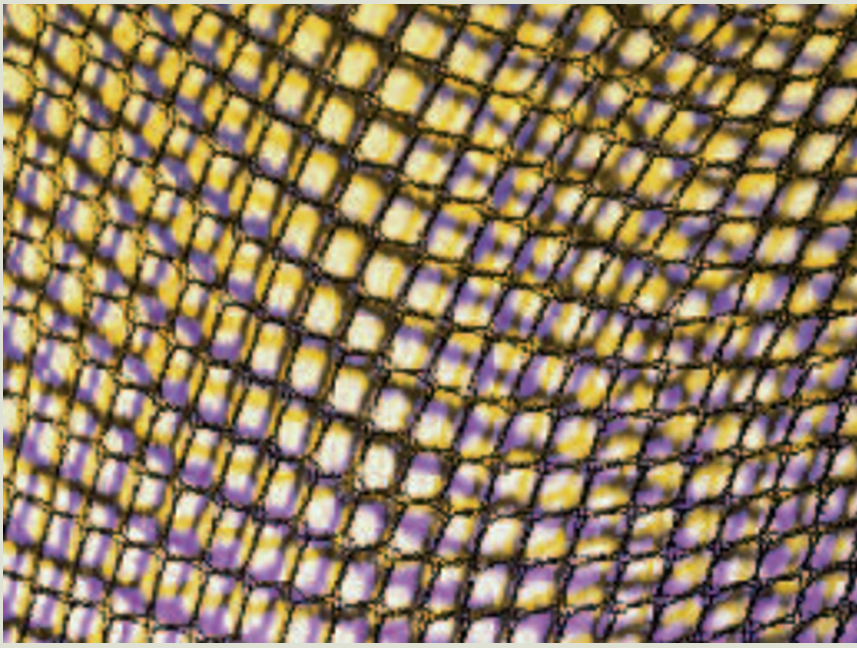
Streptococcus pneumoniae serotype 4 strain TIGR4:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genomeprj&cmd=Retrieve&dopt=Overview&list_uids=277

BACTERIAL PATHOGENICITY

Escaping the net

Many bacterial pathogens produce extracellular DNases, and whether these proteins have a role in bacterial pathogenesis has been a long-standing question. Now, two papers in *Current Biology* prove a role for streptococcal DNases in evading the innate immune response.

James Musser and colleagues began to elucidate the role of DNases when they reported that the extracellular DNase activity of a group A *Streptococcus* (GAS) strain contributes to disease progression and protects from killing by polymorphonuclear leukocytes. They speculated that the protection resulted from bacterial DNases degrading neutrophil extracellular traps (NETs), which are released by activated neutrophils as part of the innate immune response. NETs comprise a DNA scaffold 'decorated' with antimicrobial agents such as histones and components from neutrophil granules. However, until now, no experimental data were available to support this hypothesis.



In the first *Current Biology* paper, Buchanan *et al.* looked at the role of the DNase Sda1 from an M1 serotype GAS strain. Initial *in vitro* work revealed that a Δ*sda1* mutant showed reduced DNase activity and increased killing by neutrophils. A fluorescence-microscopy protocol that allowed live imaging of NET formation by neutrophils indicated that the DNase activity of Sda1 was necessary and sufficient to degrade NETs. Finally, a correlation was made between NET degradation and GAS pathogenicity *in vivo* — in a mouse model of necrotizing fasciitis, the Δ*sda1* mutant was significantly less virulent

than the wild-type strain, and when exudates from abcesses in mice in the early stages of infection were examined for the presence of NETs, it was shown that significantly more NETs were present in mice infected with the Δ*sda1* mutant than in mice infected with wild-type GAS.

The second study looked at the role of the DNase EndA from the *Streptococcus pneumoniae* serotype 4 strain TIGR4. The DNase activity of EndA and a role for this activity in degrading the DNA scaffold of NETs were both confirmed *in vitro*. Beiter *et al*. then established that NETs are present in a C57BL/6 mouse model of TIGR4 pneumococcal pneumonia, and that the removal of *endA* was associated with a decrease in TIGR4 virulence *in vivo*. Further detailed characterization of the competitive index after simultaneous infection with TIGR4 and either TIGR4 Δ*endA* or an *endA*$^+$ revertant showed that the Δ*endA* strain was outcompeted by both the wild-type and the revertant strain in the lungs and bloodstream but not in the upper respiratory tract. As Beiter *et al*. also established that pneumococci are trapped but not killed by NETs and that EndA activity allowed the pneumococci to escape from NETs, these observations suggest that the *S. pneumoniae* DNase EndA has a crucial role in virulence, allowing the bacteria to escape from the innate immune response in the upper respiratory tract and establish an invasive infection.

These papers prove not only that extracellular DNases do have a role in bacterial pathogenicity but also that NETs are involved in the innate immune response *in vivo*. The degradation of NETs might prove to be another general mechanism used by bacteria to escape from the host immune response, and so DNases might be of interest as a novel therapeutic target.

Sheilagh Molloy

ORIGINAL RESEARCH PAPERS Buchanan, J. T. *et al*. DNase expression allows the pathogen group A *Streptococcus* to escape killing in neutrophil extracellular traps. *Curr. Biol.* **16**, 396–400 (2006) | Beiter, K. *et al*. An endonuclease allows *Streptococcus pneumoniae* to escape from neutrophil extracellular traps. *Curr. Biol.* **16**, 401–407 (2006)

FURTHER READING Sumby, P. *et al*. Extracellular deoxyribonuclease made by group A *Streptococcus* assists pathogenesis by enhancing evasion of the innate immune response. *Proc. Natl Acad. Sci. USA* **102**, 1679–1684 (2005) | Brinkmann, V. *et al*. Neutrophil extracellular traps kill bacteria. *Science* **303**, 1532–1535 (2004)