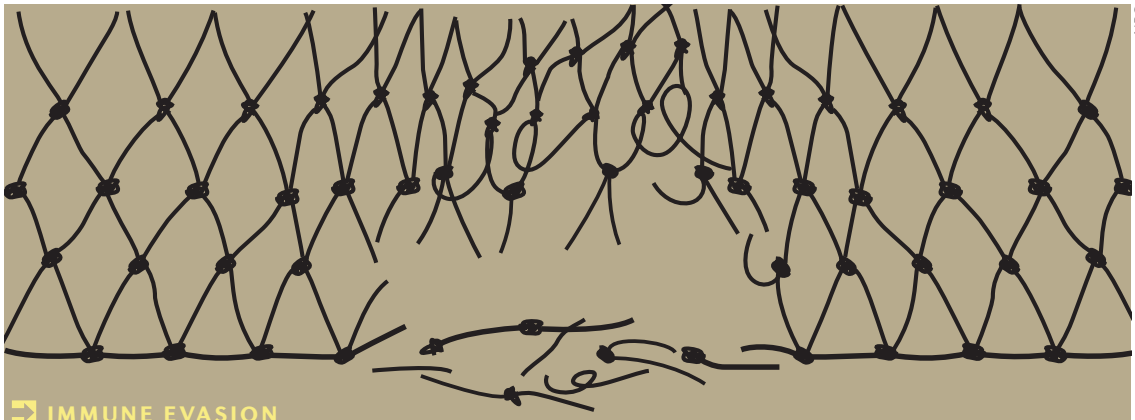
Nature Reviews Immunology | AOP, published online 6 December 2013; doi:10.1038/nri3585



NPG

IMMUNE EVASION

Staphylococcus slips through the net

Staphylococcus aureus infection often leads to the formation of abscesses, which are a host mechanism to contain the pathogen — for example, in neutrophil extracellular traps (NETs). However, *S. aureus* evades this host response by releasing a range of virulence factors that enable it to persist and replicate in the lesions. Although the interaction between *S. aureus* and neutrophils has been well studied, its interaction with macrophages has remained elusive. Now, Schneewind and colleagues identify two new *S. aureus* virulence factors, staphylococcal nuclease (Nuc) and adenosine synthase A (AdsA), which convert NETs to 2′-deoxyadenosine, thus triggering macrophage apoptosis.

When the authors looked at immunohistochemistry images of abscesses in mice that were infected with wild-type *S. aureus*, they noticed that bacteria were primarily surrounded by neutrophils, whereas macrophages only accumulated at the periphery of abscesses. To identify *S. aureus* virulence factors that affect abscess formation, the authors then screened transposon-insertion mutants. They found that, in abscesses that were caused by two *S. aureus* strains with mutations in the genes encoding either Nuc or AdsA, macrophages penetrated the lesions. This suggests that both enzymes are required to restrict macrophages from *S. aureus*-induced abscesses.

To test whether the secretion of these enzymes had a direct effect on macrophages, the authors incubated cultured human or mouse macrophages with *S. aureus*-conditioned medium; however, the cells remained unaffected. By contrast, treatment of macrophages with staphylococcal cultures that have been exposed to phorbol 12-myristate 13-acetate (PMA)-treated neutrophils (which induces the formation of NETs) resulted in increased apoptosis of macrophages. The *nuc* and *adsA* mutants caused less macrophage death, which suggests that *S. aureus* generates a toxic product from host NETs in a process that depends on Nuc and AdsA.

NETs are composed of DNA that is released by neutrophils. Mass spectrometry analysis of NET cleavage reactions showed that NET samples that were treated with staphylococcal culture medium contained a DNA metabolite, 2′-deoxyadenosine, levels of which were decreased in samples that were treated with *nuc* or *adsA* mutants. This, together with the observation that purified 2′-deoxyadenosine decreased macrophage viability, suggests that *S. aureus* Nuc and AdsA release 2′-deoxyadenosine from NETs, which is responsible for the cytotoxic effect on macrophages.

Finally, treatment of macrophages with 2′-deoxyadenosine triggered the conversion of pro-caspase 3 to active caspase 3, which is a potent activator of apoptosis. Consistent with this, inhibition of caspase 3 decreased 2′-deoxyadenosine-induced cell death, and caspase 3 activation was observed in *S. aureus* abscesses but to a lesser extent in lesions that were caused by the *nuc*- or *adsA*-mutant strains.

Together, these results show that *S. aureus* secretes enzymes to convert NETs to 2′-deoxyadenosine, which triggers macrophage apoptosis and thus inhibits phagocytosis of the bacterium by these cells.

> “*S. aureus* generates a toxic product from host NETs”

Andrea Du Toit, Assistant Editor,
Nature Reviews Microbiology

This article originally appeared in *Nature Rev. Microbiology* (http://dx.doi.org/10.1038/nrmicro3179).

ORIGINAL RESEARCH PAPER Thammavongsa, V., Missiakas, D. M. & Schneewind, O. *Staphylococcus aureus* degrades neutrophil extracellular traps to promote immune cell death. *Science* **342**, 863–866 (2013)