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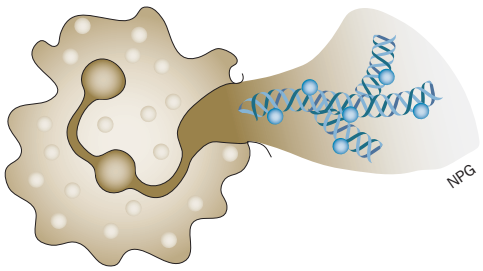
LIVER

Neutrophil extracellular traps mediate bacterial liver damage

A new study in *Nature Communications* reports on the contribution of neutrophil extracellular traps (NETs) to liver damage after methicillin-resistant *Staphylococcus aureus* (MRSA) infection.

Neutrophils are part of the first line of defence during bacterial infection and they have a number of strategies at their disposal to efficiently deal with pathogens. Phagocytosis and degranulation are the mechanisms they are probably best known to use, but they also employ NETs to—quite literally—trap bacteria. NETs comprise DNA webs with attached histones and granule enzymes, such as neutrophil elastase (NE). In addition, peptidyl arginine deiminase type IV (PAD4) also has an essential role in NET formation.



Kolaczkowska *et al.* showed that, after MRSA infection, bacteria accumulated in the liver more readily than in other organs, as they were captured by Kupffer cells residing in the liver. Subsequently recruited neutrophils released NETs into the vasculature in an attempt to eradicate the pathogens; a response that might actually do more harm than good.

"We found that the majority of the injury in the liver was induced by these NETs and not by the bacteria itself," says corresponding author Paul Kubes. Liver damage was attenuated when MRSA-mediated NET release was reduced in mice via elastase inhibition or genetic ablation of *Ne* or *Pad4*.

"We also found that NETs could linger around for quite some time, attached to vessel walls," explains Kubes. The authors identified von Willebrand factor as an anchor that equally helped to reduce liver damage when disrupted.

However, deoxyribonuclease (DNAse) enzymes, which can dissolve NETs by breaking up their DNA backbone, might not be applicable to prevent liver damage. DNAse fails to clear all NET components, leaving histones and NE attached to the endothelium. Despite DNAse treatment, NE retains its proteolytic activity and damages the surrounding tissue.

The authors caution that this effect could have clinical implications as DNAse is used therapeutically. They propose that inhibition of NET formation or shedding of anchor molecules might prove a more effective strategy in damage-prevention than NET dissolution.

Christine Weber

Original article Kolaczkowska, E. *et al.* Molecular mechanisms of NET formation and degradation revealed by intravital imaging in the liver vasculature. *Nat. Commun.* doi:10.1038/ncomms7673