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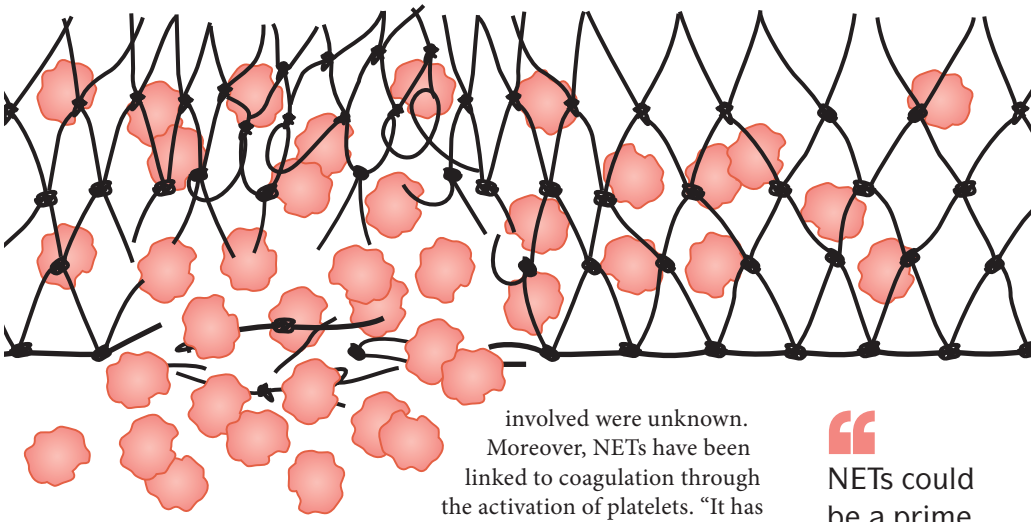
SEPSIS

NET-induced coagulation induces organ damage in sepsis



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Current understanding of the pathophysiology of sepsis is limited and sepsis remains a major cause of morbidity and mortality in the intensive care unit. Now, researchers show that neutrophil extracellular traps (NETs) contribute to organ dysfunction in sepsis by inducing widespread intravascular thrombosis, resulting in impaired tissue perfusion and end-organ damage. "Perhaps most importantly, we observed that removing NETs can prevent this intravascular coagulation and organ damage, indicating that NETs could be a prime therapeutic target to treat the microvascular dysfunction of sepsis," explains researcher Braedon McDonald.

NETs are networks of extracellular fibres released by neutrophils that can trap and kill micro-organisms and activate other immune cells. Previous work had identified an important role for NETs in the development of organ dysfunction in animal models of sepsis, but the mechanisms involved were unknown. Moreover, NETs have been linked to coagulation through the activation of platelets. "It has been known for many years that interplay between the immune system and the coagulation system is fundamental to the pathophysiology of sepsis, but little was known about how this actually occurs *in vivo*, and how it results in organ dysfunction," says McDonald. "Our study used multi-colour confocal intravital microscopy to visualize the activity of immune cells, platelets, and coagulation within the microvasculature of septic animals *in vivo*. This technology enabled direct evaluation of the interplay between neutrophils and NETs with platelets and members of the coagulation cascade, providing a versatile platform to understand the pathophysiology of disease within the vasculature."

Using *in vivo* imaging, the researchers observed that activation of intravascular thrombin and platelet aggregation colocalized with NETs in the liver vasculature of mice with sepsis. Genetic or pharmacological ablation of NET activation achieved by deletion of *PAD4* or intravenous administration of DNase, respectively, led to a significant reduction in intravascular thrombin activity in response to lipopolysaccharide, *Escherichia coli* or *Staphylococcus aureus* compared to levels in control mice, demonstrating a critical role for NETs in the development of sepsis-induced intravascular coagulation. Notably, the effect of NET removal on coagulation was independent of the bacterial stimulus used to induce sepsis, indicating that sepsis-induced coagulation is a consequence of a dysregulated host-response and not of the type of inciting pathogen. Further analyses demonstrated key roles for histone H4 — likely exposed by NETs — and inorganic polyphosphate — likely released from platelets — in the coagulation response to NET formation.

> "NETs could be a prime therapeutic target to treat the microvascular dysfunction of sepsis"

The induction of coagulation by NETs led to vessel occlusion and reduced microvascular perfusion in the liver, as well as a systemic coagulation response. Moreover, genetic ablation of NET formation led to a 59% reduction in serum creatinine levels compared to levels in wild-type septic mice, although inhibition of thrombin alone did not reduce creatinine levels. "Together, these data suggest that inhibition of NETs reduces both intravascular coagulation and organ damage, whereas anti-coagulation alone does not significantly impact organ pathology," say the researchers.

McDonald plans to continue investigating the mechanisms that allow NETs and platelets to collaborate in the vasculature. "Our ultimate aim is to uncover treatments to improve the lives of patients with diseases such as sepsis."

Susan J. Allison

ORIGINAL ARTICLE McDonald, B. *et al.* Platelets and neutrophil extracellular traps collaborate to promote intravascular coagulation during sepsis in mice. *Blood* http://doi.org/10.1182/blood-2016-09-741298 (2017)