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BRANDX

INNATE IMMUNITY

Neutrophils stem the flow

Neutrophils are an essential part of the innate immune system and rapidly accumulate at sites of infection and injury. They have been linked with blood coagulation, which has been proposed to restrict microbial dissemination during infection, but the mechanisms involved and the physiological relevance *in vivo* are largely unknown. Now, Massberg *et al.* show that neutrophil serine proteases, together with extracellular nucleosomes, degrade the anticoagulant tissue-factor pathway inhibitor (TFPI), thereby enhancing coagulation and thrombus (blood clot) formation. This process promotes bacteria retention in liver microvessels, but can also contribute to thrombosis in large vessels in the absence of infection.

To assess the role of neutrophils in coagulation, the authors used mice that lacked expression of two key neutrophil serine proteases, neutrophil elastase and cathepsin G (*Elane*$^{-/-}$*Ctsg*$^{-/-}$ mice). Chemical or mechanical injury of carotid arteries resulted in reduced fibrin formation and thrombus size in *Elane*$^{-/-}$*Ctsg*$^{-/-}$ mice compared with wild-type mice. Furthermore, *Elane*$^{-/-}$*Ctsg*$^{-/-}$ mice had prolonged tail bleeding times, indicating defective blood clotting in these mice.

The authors next determined the mechanism involved in neutrophil-associated coagulation using numerous lines of investigation. The following series of events were described: neutrophil serine proteases degrade TFPI in thrombi, resulting in unrestrained action of the procoagulant factor Xa, which promotes fibrin formation. This process required the presence of activated platelets, which triggered the release of nucleosomes (nuclear fragments, consisting of DNA and histones, that can form neutrophil extracellular traps) by neutrophils. Neutrophil elastase and TFPI colocalized with these extracellular nucleosomes on the surface of neutrophils; this colocalization was required for TFPI inactivation and thrombus formation at the site of vessel injury.

To assess the role of neutrophil-associated coagulation in an immune response, wild-type and *Elane*$^{-/-}$*Ctsg*$^{-/-}$ mice were infected with *Escherichia coli*. In wild-type mice, systemic *E. coli* infection triggered fibrin deposition in hepatic microvessels, which resulted in partial occlusion by the clots. Most of the bacteria were detected in the lumen of hepatic microvessels and were largely absent from larger vessels and the perivascular tissue. By contrast, fibrin deposition and microvascular occlusion were lower in *Elane*$^{-/-}$*Ctsg*$^{-/-}$ mice, and bacteria were detected mostly in the perivascular tissue parenchyma. TFPI degradation by neutrophil serine proteases and extracellular nucleosomes stimulated coagulation in liver microvessels following *E. coli* infection, trapping the bacteria in small thrombi.

So, neutrophil serine proteases, in addition to their direct antimicrobial functions, promote coagulation, which stabilizes nascent thrombi, prevents blood loss and retains bacteria within the microvasculature, preventing their dissemination into the perivascular tissue. This study shows an important link between innate immunity and coagulation and suggests a physiological role for thrombosis in host defence.

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ORIGINAL RESEARCH PAPER Massberg, S. *et al.* Reciprocal coupling of coagulation and innate immunity via neutrophil serine proteases. *Nature Med.* **16**, 887–896 (2010)
FURTHER READING Ruf, W. & Ruggeri, Z. M. Neutrophils release brakes of coagulation. *Nature Med.* **16**, 851–852 (2010)