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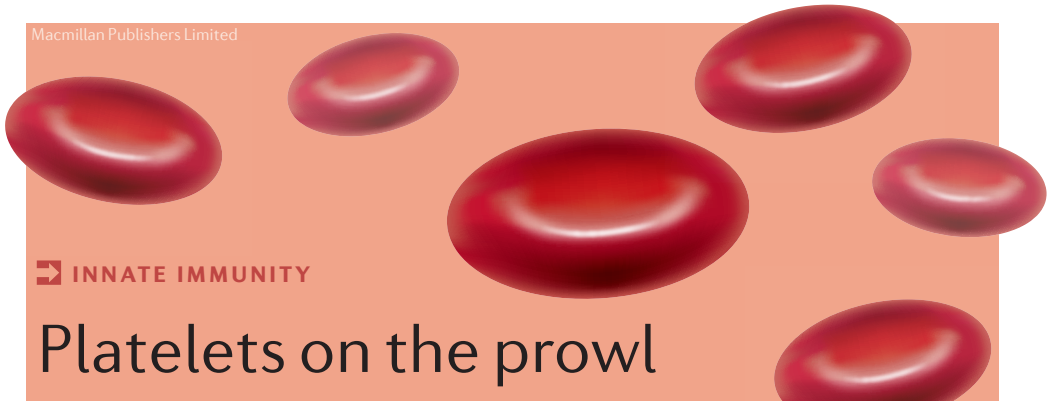

INNATE IMMUNITY

Platelets on the prowl

In addition to their well-defined roles in haemostasis and thrombosis, platelets contribute to immune defence by releasing antimicrobial mediators and initiating immune cell recruitment to injured sites. As anucleate cells, platelets are considered to be stationary outside of the blood circulation; however, Gaertner *et al.* now report that platelets can actively migrate at inflamed sites and are able to collect and bundle bacteria.

The authors generated a multicolour platelet reporter mouse to track individual platelets by intravital two-photon microscopy. In a model of needle-induced vascular injury, they observed adherent platelets in the periphery of the injured site that remained motile and seemed autonomous from the thrombus. The platelets were able to migrate against the blood flow and their motility was not affected by migrating leukocytes, suggesting an active process.

Using an *in vitro* system in which platelets were added to coverslips pre-coated with fibrillar collagen and plasma, the authors found that platelets contacting immobilized collagen fibres formed immotile micro-aggregates. By contrast, platelets that did not contact collagen fibres became motile, first spreading to show a 'fried egg' morphology and then polarizing by protruding one side of the lamellipodium and retracting the opposite side. Polarization was associated with movement of the pseudonucleus to the rear of the platelet and the adoption of a half-moon shape. Inhibition of actin polymerization or actin branching blocked platelet migration, which confirms that this is an active process.

Additional experiments showed that collagen-activated platelets promote the migration of non-adherent platelets by releasing ADP and thromboxin A2. Furthermore, platelet migration was associated with clustering of αIIbβ3 integrin along the lamellipodium and could be inhibited by blocking this integrin. Fibrinogen, which is the physiological ligand of αIIbβ3 integrin, was found to induce spreading of platelets, but their migration was dependent on additional serum components, such as albumin and calcium. Extracellular calcium was shown to support intracellular calcium oscillations and the activation of myosin IIa, thereby generating contractile forces in platelets that enabled adhesion release and autonomous locomotion. Notably, the authors found that platelets migrating on fibrinogen substrates function as mechano-scavengers, removing fibrinogen, transporting it towards the pseudonucleus and depositing it there within internal membrane invaginations (known as the open canalicular system). In addition to scavenging soluble fibrinogen, platelets were shown to migrate on and scavenge large immobilized fibrin strands, as well as latex particles bound to fibrinogen matrix.

The authors found that platelets also scavenged various species of fibrin-bound bacteria *in vitro*. Moreover, *in vivo*, motile platelets could collect and bundle bacteria in the liver sinusoids of mice infected systemically with *Escherichia coli* or methicillin-resistant *Staphylococcus aureus* (MRSA). Following scavenging, platelets did not directly kill bacteria; instead, the authors visualized migrating neutrophils slowing down, arresting and undergoing phagocytosis and the release of neutrophil extracellular traps (NETs) when they encountered the bacterial bundles formed by platelets. In MRSA-infected mice, NETs promote liver pathology and, consistent with this, abrogation of platelet migration in this model reduced neutrophil activation and liver damage without compromising the clearance of MRSA from the liver. Consequently, mice with defective platelet migration were protected against lethal MRSA-induced sepsis.

This study shows that, despite the absence of a nucleus, platelets possess all the machinery necessary for locomotion and can actively migrate. Following vascular injury, migrating platelets can collect and bundle bacteria and promote neutrophil activation; this may promote immunity to infections but have detrimental consequences during sepsis.

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ORIGINAL ARTICLE Gaertner, F. *et al.* Migrating platelets are mechno-scavengers that collect and bundle bacteria. *Cell* **171**, 1368–1382 (2017)

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