blood advances

COUNTERPOINT Platelets as immune-sensing cells

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This article has a companion Point by Brass et al.

Platelets have classically been well recognized for their crucial role in hemostasis; however, it is increasingly evident that platelets are more versatile than originally thought because they possess a large variety of nonhemostatic immunologic functions as well.[1] Crosstalk exists between these 2 major functions as inflammation influences both coagulation[2] and the immune functions of platelets.[3] In this report, we will focus on and advocate for the emerging role of platelet immune functions in a nonhemostatic and inflammatory setting. This includes the ability of platelets to battle invading pathogens during inflammation and to communicate with a large variety of effector cells through an array of different mechanisms.

Platelets initiate their antimicrobial host defense by sensing the presence of pathogens or inflammation through, for example, their multiple immune receptors such as immunoglobulin or complement receptors and Toll-like receptors (TLRs).[4] This enables them to bind and recognize invading pathogens and/or their derived microbial products. For instance, platelet TLR4 can bind lipopolysaccharide (a bacterial gram-negative endotoxin) and was shown to induce thrombocytopenia in vivo.[5-11] In addition, platelet TLR7 has been suggested to mediate host survival and platelet counts during infection with encephalomyocarditis virus in mice, independently of thrombosis.[12]

Platelets are also able to retain pathogens by harboring viruses, bacteria, or parasites on their plasma membrane or intracellularly.[13-19] Activated platelets were shown to inhibit the growth of the bacterium *Staphylococcus aureus* through encapsulating the bacteria and secreting the anti-microbial peptide β-defensin to promote the formation of neutrophil extracellular traps (NETs).[20] Alternatively, bacterial trapping of methicillin-resistant *S aureus* and *Bacillus cereus* has also been shown to occur on hepatic Kupffer cells through a mechanism dependent on engagement of the platelet adhesion receptor glycoprotein (GP)1b.[21] In addition, during sepsis, platelet TLR4 was shown to activate neutrophils causing them to release NETs, thereby trapping bacteria in hepatic and pulmonary blood vessels.[22]

Platelets cannot only detect and retain the pathogens they encounter, they are also able to eliminate them. An elegant example of this was illustrated in studies showing that activated platelets killed the intraerythrocytic malarial parasite *Plasmodium falciparum*[14] through a mechanism involving platelet factor 4 (PF4 or CXCL4) and the erythrocyte Duffy antigen receptor (Fy).[23] In another study, it was demonstrated that platelet TLR2 was required for the formation of platelet–neutrophil aggregates that enhanced the phagocytosis of periodontopathogens.[24] Furthermore, platelets were found to redirect the course of the blood-borne bacteria *Listeria monocytogenes* from less immunogenic phagocytes toward the more immunologically active splenic $CD8\alpha^+$ dendritic cells (DCs) in a GPIb- and complement C3–dependent manner.[25] Taken together, platelets have the ability to increase the clearance rate of infectious agents and strongly enhance the development of immunity to the infection.

Another way that platelets can actively modulate immune responses is through release of several immune mediators such as platelet CD40L, which is released into the circulation on platelet activation. CD40L can trigger T-cell responses following infection with *L monocytogenes*[26,27] and is able to bind to DCs, thereby impairing DC differentiation, suppressing proinflammatory cytokines, and increasing the secretion of the anti-inflammatory cytokine interleukin-10 (IL-10).[28] Through CD40L, platelets are also able to stimulate B-cell differentiation and antibody class switching.[29,30] Furthermore, platelets have the ability to secrete a plethora of cytokines and chemokines,[4] which not only affects hemostasis and wound repair[31] but also various pro- and anti-inflammatory immune responses. For example, the platelet-derived immunosuppressive cytokine transforming growth factor-β is present at low levels during active immune thrombocytopenia; however, on successful treatment of immune thrombocytopenia, the levels of transforming growth factor-β were observed to normalize.[32] This correlated with normalized T-regulatory cell numbers and suppression of the immune response.[33] In addition, platelet-derived IL-33 was recently suggested to induce eosinophilic airway inflammation.[34] On the other hand, PF4 was found to be a negative regulator of Th17 differentiation, thereby limiting cardiac allograft rejection in a murine cardiac transplant model.[35]

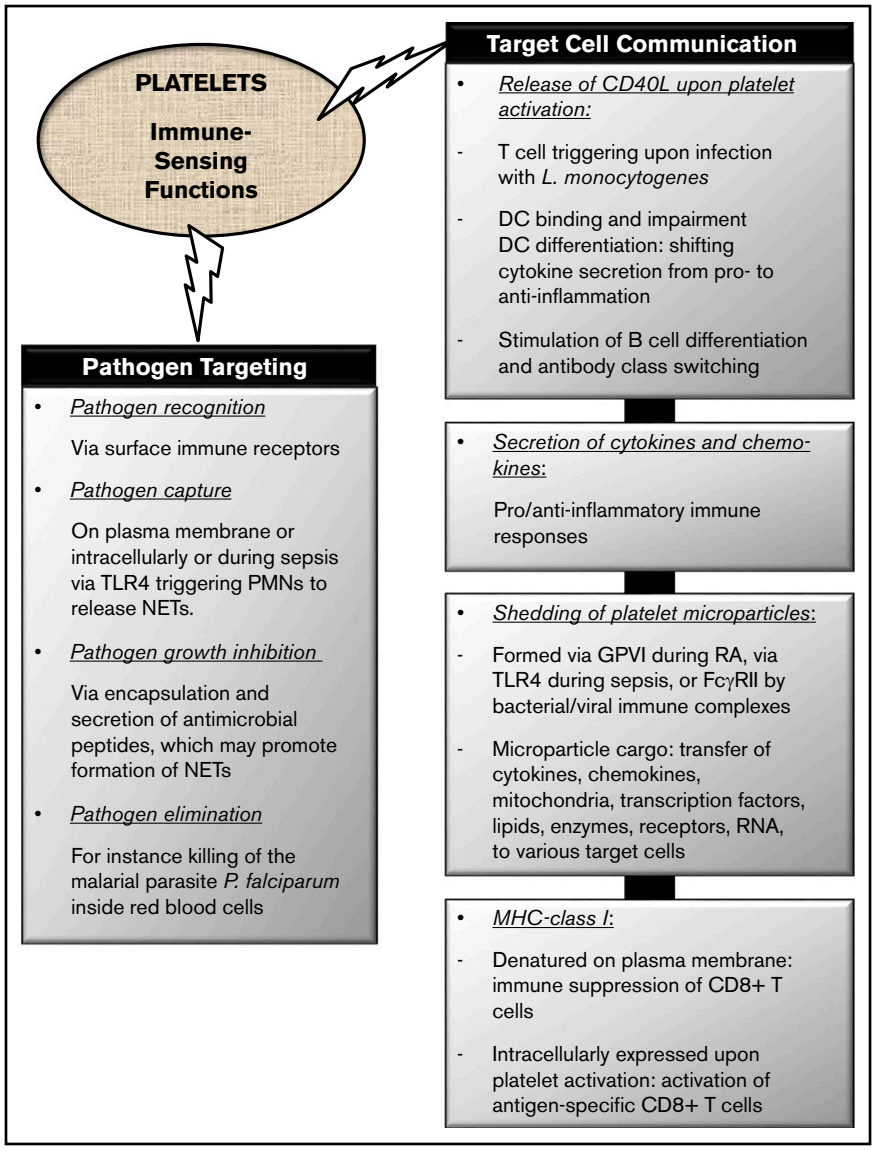

Figure 1. Immune-sensing functions of platelets. The nonhemostatic immune-sensing functions of platelets are generally depicted as pathogen targeting and target cell communication. RA, rheumatoid arthritis.

Platelets also release microparticles, which are small extracellular vesicles (the majority are ~200 nm in diameter) produced via blebbing and fission of the plasma membrane. Although several cells can produce microparticles, platelets appear to be highly effective in their production compared with other cell types.[36] Platelet microparticles express membrane phosphatidylserine[37] but express only modest levels of tissue factor and appear to have a less defined role in coagulation compared with monocyte-derived microparticles, which express both phosphatidylserine and tissue factor on their surface.[38] Platelet microparticles have been associated with immunologic conditions such as platelet activation during inflammation.[39,40] For instance, an elevation of platelet microparticles was observed in the blood and synovial fluid of patients with rheumatoid arthritis.[41] Several platelet surface receptors have been shown to trigger the formation of platelet microparticles such as GPVI during rheumatoid arthritis,[41] TLR4 signaling via lipopolysaccharide during sepsis,[42] and FcγRIIa, which may be targeted by immune complexes (of bacterial components or influenza viral epitopes).[43,44] The GPVI- and TLR4-mediated signals were also associated with increased IL-1 levels, illustrating their proinflammatory effects. Functionally, platelet microparticles can facilitate communication of platelets with other cells as they can carry a large variety of substances such as various cytokines or chemokines (eg, IL-1, RANTES), lipid mediators, enzymes, surface receptors like CD40L, autoantigens, transcription factors, and respiratory competent mitochondria, all of which can regulate immune functions.[3,39,40,45-48] In addition, anucleate platelets contain significant amounts of RNA including mRNA, microRNA, ribosomal and transfer RNA, and antisense RNA (noncoding RNA).[49-65] Interestingly, platelets carry the molecular machinery for mRNA translation into proteins and the RNAs may also be transferred to target cells such as endothelial cells via platelet microparticles.[49,61-63,65] The interaction between platelets and endothelial cells is complex and well described in the literature, particularly in the setting of atherosclerosis, an inflammatory disease state characterized by immune cell interactions with the vascular wall.[29,66]

Platelets contain 2 different types of major histocompatibility complex (MHC) class I molecules: plasma-membrane bound or intracellular.[67] The plasma-membrane–bound platelet MHC class I is denatured as it is adsorbed from the plasma and induces an immunosuppressive effect on $CD8^+$ T cells during, for example, skin graft rejection.[68] On the other hand, the intracellular MHC class I molecules are intact but are only expressed upon platelet activation and can activate antigen-specific $CD8^+$ T cells, as was demonstrated in vivo using an experimental mouse model of cerebral malaria.[69]

In conclusion, platelets have prominent capabilities in antimicrobial host defense and in regulating the immune functions of a large number of immune cells through their diverse surface receptors and secretion of several mediators. They can also traffic their shed platelet microparticles carrying a heterogeneous immunoregulatory cargo. The immune-sensing functions of platelets are schematically summarized in Figure 1. We therefore strongly encourage further research into the immune-sensing capacity of platelets, which may potentially open up new therapeutic avenues to explore in various disease settings.

Acknowledgments

This work was supported by grants from Health Canada and Canadian Blood Services (J.W.S.). R.K. is the recipient of a postdoctoral fellowship from the Canadian Blood Services.

Authorship

Contribution: R.K. wrote the first draft and edited the manuscript; and J.W.S. edited the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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DOI 10.1182/bloodadvances.2016000067