Immunity

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Review

Platelets: Orchestrators of immunity in host defense and beyond

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https://doi.org/10.1016/j.immuni.2024.04.008

SUMMARY

Platelets prevent blood loss during vascular injury and contribute to thrombus formation in cardiovascular disease. Beyond these classical roles, platelets are critical for the host immune response. They guard the vasculature against pathogens via specialized receptors, intracellular signaling cascades, and effector functions. Platelets also skew inflammatory responses by instructing innate immune cells, support adaptive immunosurveillance, and influence antibody production and T cell polarization. Concomitantly, platelets contribute to tissue reconstitution and maintain vascular function after inflammatory challenges. However, dysregulated activation of these multitalented cells exacerbates immunopathology with ensuing microvascular clotting, excessive inflammation, and elevated risk of macrovascular thrombosis. This dichotomy underscores the critical importance of precisely defining and potentially modulating platelet function in immunity.

INTRODUCTION

Platelets were first described as normal constituents of blood that are important in mediating clotting in 1882. Since then, it has become increasingly clear that these anucleate cells released from multinucleated megakaryocytes are crucial not only to protect from hemorrhage but are also critical players in thrombosis. Because thrombosis represents the common final pathway of vascular diseases—resulting in stroke, myocardial infarction, and peripheral vessel occlusion[1]—platelets are at the forefront of pharmacological intervention to fight these diseases, particularly in secondary prevention.[2] Millions of individuals worldwide take anti-platelet medication such as aspirin or P2Y12-receptor inhibitors (i.e., clopidogrel).[3] Beyond their established role in clotting, these cells are also important in modulating acute and chronic inflammation and contributing to host defense against bacteria. However, depending on the context, platelets can also be responsible for misguided and exuberant immunopathology.[4–6] A better understanding of immune programs orchestrated by platelets will open new avenues for the treatment of a wide range of diseases beyond cardiovascular diseases.

This review summarizes the current knowledge and overarching concepts in the field, ranging from the platelet immune armamentarium to their interaction with innate and adaptive immunity, their role in tissue healing, and lessons learned from the clinic.

CLASSICAL ROLE OF PLATELETS: CLOT FORMATION

Platelets are the second most abundant cell type in blood—after red blood cells—and are ideally suited to rapidly detect and respond to vascular injury. They do so by engaging specific receptors that recognize extracellular matrix proteins, in particular von Willebrand factor and collagen.[7] Recognition of these ligands signifies a breach in vascular integrity, and platelets use their high-shear resistant glycoprotein (GP) Ib-V-IX complex to arrest at sites of injury.[8] Rapid signal transduction machinery allows activation in milliseconds, as platelets increase affinity of additional receptors such as GPIIbIIIa (a process termed inside-out signaling), and release para- and autocrine activation signals such as ADP and thromboxane.[9] This in turn recruits additional platelets, which will crosslink via GPIIbIIIa-Fibrin(ogen) to form a thrombus. Thrombus formation leads to GPIIbIIIa-mediated further activation, termed outside-in signaling.[10] Individual platelets can generate significant forces of up to 70 nN, a force per volume two orders of magnitude greater than that exerted by myoblasts. These mechanical properties further stabilize the forming thrombus.[11,12] In parallel, strong agonists and cooperative signaling drive procoagulant transformation, which flips negatively charged phospholipids including phosphatidylserine to the exoplasmic surface, and allows binding of coagulation factors and formation of the pro-thrombin complex.[13] This drives subsequent fibrin formation and cross-linking, ultimately stabilizing the clot.[14]

A breach in vascular integrity also represents a potential entry point for pathogens. In invertebrates, clotting and innate immune functions are expedited by a singular nucleated cell type, the hemocyte.[15] After evolutionary separation of the two functions, it is well conceivable that on one hand, platelets have retained some of their immune effector functions. On the other hand, tight integration with innate immunity in guiding immune cells to sites of injury after formation of a hemostatic thrombus has remained fundamental in vertebrates as well. Moreover, due to their large number, rapid response, and expression of immune receptors, platelets can serve as ideal sentinels to detect pathogens at the vascular interface, supporting their role in systemic infections and sepsis.[16] These drivers

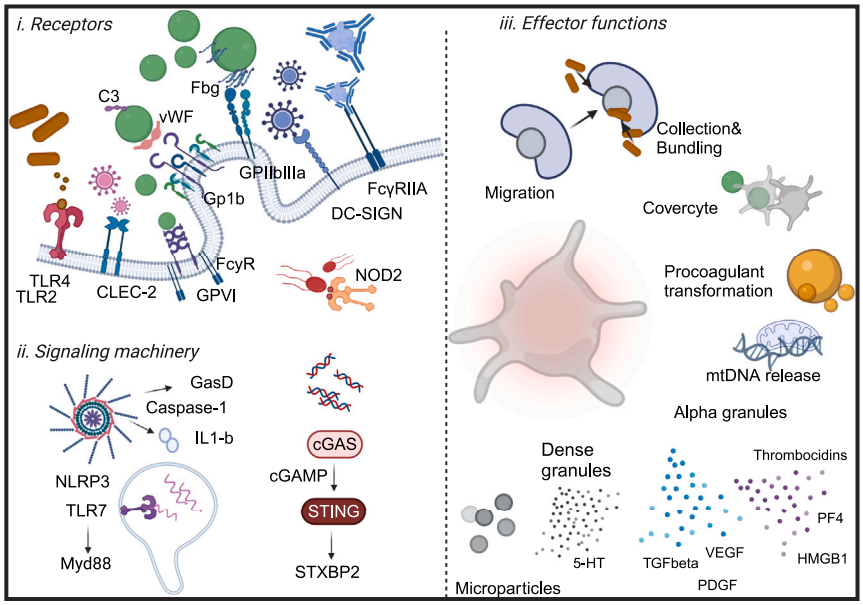

Figure 1. Receptors and signaling pathways in immune responsive platelets

Platelets possess a range of receptors, which are either exclusively used for pathogen interaction, i.e., TLR4 and NOD2, or are primarily important in hemostasis function but can directly or indirectly bind pathogens, like Gp1b or GPIIbIIIa. Downstream of these receptors, platelets also contain the required innate immune signaling machinery, i.e., NLRP3 inflammasomes, and components of cGAS-STING. Upon engagement, platelets can activate multiple effector functions, including migration, collection, and bundling of bacteria; procoagulant transformation; mtDNA release and granule as well as microparticle release. All these functions can contribute to host defense, but also mediate tissue damage in hyperinflammation. Figure created using BioRender.

of platelet immune function—evolutionary conserved effector functions, tight integration with innate immunity, and sentinel function in the vasculature—jointly explain why platelets take center stage in (vascular) inflammation, as detailed below.

PLATELET IMMUNE ARMAMENTARIUM AND SECRETED INFLAMMATORY EFFECTORS

For innate immunity, it is crucial to recognize invading pathogens. Platelets have multiple strategies to discover, bind, and elicit a host response to intravascular pathogens (Figure 1).

First, they express a plethora of receptors that can directly interact with the surface structure of potential invaders. For example, highly glycosylated serine-rich repeat (SRR) proteins, like GspB expressed by *Streptococci*, bind to Gp1b.[17] *Staphylococcus aureus* expresses iron-regulated surface determinants, which can directly engage GPIIbIIIa.[18] But direct interaction is not restricted to bacteria as it also extends to viruses. Uptake of human immunodeficiency virus (HIV) by platelets is mediated mainly by DC-SIGN and CLEC-2 receptors.[19] This interaction can serve as a viral reservoir for HIV during combination anti-viral treatment and correlates with poor $CD4^+$ T cell responses.[20] Platelet inhibition could potentially limit transfer of virions from platelets to other cell types.[21] In dengue virus (DENV) infection, thrombocytopenia is a hallmark of severe disease. This arbovirus is also able to bind and activate platelets via CLEC-2 and DC-SIGN, which leads to apoptosis and release of microparticles. Microparticles can in turn cause innate immune cell activation via TLR2 and CLEC5A and thereby drive immunopathology.[22] This interaction might also be crucial in other viral infections causing hemorrhagic fever, as thrombocytopenia and platelet dysfunction are hallmarks of this syndrome and contribute to bleeding tendency.[23] Along these lines, hantavirus can bind platelets directly via GPIIbIIIa.[24]

The interaction of platelets with adenoviruses has been scrutinized, as *Adenoviridae* used as vectors for gene therapy in animal models have severe thrombocytopenia as an important side effect.[25,26] Indeed, platelets seem to bind adenoviruses directly via β3 integrins and might also express the coxsackievirus and adenovirus receptor (CAR), although conflicting data exist on the latter. This interaction leads to platelet activation and viral clearance.[26] While viremia is most likely restricted to severe COVID-19 cases, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA is seen in circulating platelets of some of these patients.[27] It remains unclear whether uptake is mediated by ACE2 and TMPRSS2 as most studies failed to prove expression of these receptors on platelets.[28] Platelets express CD147 and CD26, which might serve as alternative receptors; however, their role has not been investigated robustly.[29] In conclusion, platelets repurpose receptors central to clot formation to detect and bind a wide range of pathogens.

Innate immunity depends on specialized receptors recognizing conserved pathogen signatures—so called pattern recognition receptors (PRRs) —which sense pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). Platelets express all major classes of PRRs—Toll-like receptors (TLRs), C-type lectin receptors (CLRs) like DC-SIGN mentioned above, and NOD-like receptors (NLRs)[30] (Figure 1). Most data are available on TLR4, which recognizes lipopolysaccharide (LPS), an outer membrane component of Gram-negative bacteria. Platelets can be primed by bacteria in a TLR4-dependent manner, which leads to neutrophil activation and NETosis, but not classical aggregation.[31] Although TLR4 mainly signals through Myd88 in nucleated immune cells, platelet-specific deficiency in Myd88 did not affect outcomes in murine *Klebsiella pneumoniae* infection models. This suggests that the importance of platelet TLR4 signaling depends on context or might be mediated via a Myd88-independent pathway.[32] TLR2 stimulation leads to platelet aggregation via phosphoinositide 3-kinase and can aid in detection of bacteria.[33,34] TLR7 is an intracellular, endosomal receptor that recognizes single-strand RNA. Platelets react to influenza virus infection in a TLR7-dependent manner, leading to the release of complement factor 3 (C3).[35] C3 in turn triggers NETosis by neutrophils, which might contribute to acute lung injury, as well as

thrombotic sequalae of influenza infection.[36] In experimental encephalomyocarditis virus (EMCV) infection, this mechanism limits pathogen spread.[37] NOD-like receptor NOD2 recognizes muramyl dipeptide (MDP), a peptidoglycan motif present in bacteria, and is expressed by platelets. NOD2 can mediate its effects trough Rip2 and contribute to platelet responses in sepsis, but also enhances thrombus formation in a model of arterial thrombosis.[38]

Beyond classical PRRs, platelets are also specialized in recognizing opsonized pathogens. Human platelets express immunoglobin G (IgG) Fc receptor FcγRIIA (CD32a), which has a low affinity for monomeric IgG but binds IgG-coated pathogens and immune complexes with high avidity.[39] This has relevance for interaction with influenza H1N1, *Streptococci*, and *Bacillus anthracis*.[40–42] FcγRIIA received most attention for its central role in heparin induced thrombocytopenia (HIT) pathology, as it can recognize anti-PF4/heparin immune complexes and cooperates with GPIIbIIIa to mediate activation of platelets in a Src/Syk dependent process ultimately leading to thrombosis in this disease.[40] von Willebrand factor (vWF) receptor Gp1b can also recognize complement factor 3 and therefore opsonized bacteria, as has been highlighted for intravascular Listeria monocytogenes.[43]

Beyond these specialized receptors and direct receptor interactions, platelets also utilize their abundant extracellular matrix receptors such as integrin GpIIbIIIa to cross-bridge pathogens, as many bacterial invaders, most prominently *S. aureus*, bind soluble plasma fibrinogen or fibronectin.[44] vWF is also an important intermediate allowing for Gp1b binding of pathogens, as shown for staphylococcal virulence factor clumping factor A.[45]

Platelet immune motif activating and inactivating (ITAM and ITIM, respectively) receptors have gained increased interest for their specific and unexpected roles in health and disease. GPVI is an ITAM receptor recognizing collagen and has been implicated mainly as a signaling receptor.[46] GPVI is also involved in host defense against Gram-negative sepsis after lung infection with *Klebsiella pneumoniae*, most likely by affecting innate immune cell activation.[47] CLEC-2 is a transmembrane receptor recognizing podoplanin and potentially other, so far unrecognized ligands. It is key in platelet-mediated blood-lymph separation during development and, interestingly, limits inflammation in experimental peritoneal sepsis, most likely through interaction with macrophage podoplanin and induction of an anti-inflammatory state in this cell type.[48] In contrast, systemic *Salmonella typhimurium* infection leads to increased expression of hepatic podoplanin in the subacute phase. This in turn triggers CLEC-2 infection-driven thrombus formation, showing that detrimental and protective effects depend on timing and stimulus.[49]

Upon recognition of non-self, nucleated cells possess an intricate signaling machinery to activate cellular and global host defense mechanisms. Increasing evidence is showing that platelets express and use a range of these innate immune pathways as well. For example, stimulator of interferon (IFN) genes (STING) regulates platelet activity via STXBP2, which contributes to granule release via SNARE complex formation.[50] Platelet-specific STING deficiency reduces NET formation and intravascular thrombosis in experimental sepsis, and blocking STING-STXBP2 interplay could replicate these protective effects.[51] Inflammasomes are key cytosolic multiprotein oligomers that mediate immune responses across cell types. Platelets express the NLRP3 inflammasome, which mediates Caspase-1 activation and splicing of pro-interleukin (IL)-1β into IL-1β.[52,53] This pathway is important in mediating platelet responses to inflammation; however, its effects on host defense against bacteria requires further investigation.[54,55]

After recognition and recruitment, innate immune cells need to migrate toward sites of infection and eliminate the recognized pathogen via lethal effector functions such as phagocytosis, release of soluble factors or toxic reactive oxygen species (ROS), as well as DNA and histones, in the form of extracellular traps (ETs). Surprisingly, platelets also show remarkable abilities in this regard (Figure 1). In inflammation, they tend to be recruited as single cells to the vascular wall.[56] This depends on fibrinogen deposition on the inflamed (micro)vasculature. They then engage an inflammation-specific effector program, migration, which requires shape change and sheet-like lamellipodia formation to foster fibroblast-like migration.[56,57] Lamellipodia formation depends on polarization and actin branching, mediated by actin related protein (ARP) 2/3. Platelet-specific deficiency of ARP2/3 affects immune function of platelets while sparing hemostatic/thrombotic ability, underlining that platelets engage specific programs depending on the challenge.[58] Leukocyte function depends on directed migration toward chemotactic triggers. Platelet migration seems to be mainly driven by substrate gradients, a process termed haptotaxis. Haptotaxis allows platelets to identify and reposition toward sites of injury, increasing the probability of pathogen capture.

Upon encountering pathogens, immune cells—most prominently neutrophils and macrophages—use phagocytosis as an important effector function. Platelets have rather been recognized as "covercytes": using their ability to migrate and thereby to greatly increase their surface area by extending their open canalicular network, they can effectively cover up, collect, and bundle bacteria and present them to professional phagocytes.[57,59] Consequently, genetic ablation of Arp2/3-dependent platelet migration leads to increased hematogenic spread of bacteria in an *S. aureus* infection model.[56]

A second important defense mechanism exerted by innate and adaptive immune cells is the release of granule contents. Platelets possess two types of granules: alpha and dense granules. Alpha granules contain >300 biologically active substances that contribute to clot formation but also support host defense. For example, they can release stored defensins, which can directly inhibit *S. aureus* growth.[4,56] In addition, differential proteolytic cleavage of pro-platelet basic protein can generate a range of platelet microbicidal proteins.[60] Thrombocidins are C-terminal deletion products of CXC chemokines[61] and have broad activity ranging from fungi to bacteria.[62] Kinocidins are cytokines that exert direct antimicrobial activity on top of their signaling function. For example, CXCL7 (NAP-2) can attract neutrophils to sites of injury and aid in defense against *Legionella*.[63,64] A very abundant alpha granule kinocidin is platelet factor 4 (PF4)—involved in direct lysis of red blood cells infected with *Plasmodium falciparum* in malaria infection.[65] This finding extends to all major *Plasmodium* subtypes.[65,66] Mechanistically, PF4 is released upon contact with infected erythrocytes, which then requires erythrocyte Duffy-antigen receptor (Fy) to bind and kill parasites.[67] Yet, the importance of this cascade has

been called into question, as a study using a murine model of malaria infection showed no significant anti-parasitic role of platelet but rather a platelet-mediated pathogenic effect on the immune response.[68,69] Alpha granules are heterogeneous and contain diverse cargo beyond defensins and kinocidins.[70] For example, they also contain molecules that contribute to resolution of inflammation and healing processes like transforming growth factor β (TGF-β), VEGF, and PDGF. These proangiogenic mediators are organized in separate granules than anti-angiogenic content.[71] Although the regulatory processes are still incompletely understood, platelets can release their alpha granules differentially based on VAMP subtype expression and potentially other factors.[72]

Dense granules are the main source of circulating serotonin (5-HT). Serotonin exerts pleiotropic functions outside of the central nervous system. Platelet-derived serotonin aids in innate immune cell recruitment in inflammation.[73] In a murine model of immune complex disease, platelets that are activated through immune complexes binding to FcγRIIA liberate pathogenic serotonin causing circulatory shock. Interestingly, platelets are able to reenter the vasculature after degranulation, rendering the animals unresponsive to a second challenge with immune complexes.[74]

Platelets are also an important source of high-mobility group box 1 (HMGB1), a central DAMP able to activate immune responses via receptor for advanced glycation endproducts (RAGE) and TLR receptors. Platelet-derived HMGB1 is instrumental for host defense in bacterial peritonitis by fostering a protective neutrophil response, helping to limit systemic spread of bacteria. It is important to note, though, that platelet HMGB1 is also a critical mediator of thrombosis.[75]

Neutrophils exert one of their most powerful defense mechanism by expelling their nuclear and mitochondrial content in a tightly regulated process termed NETosis.[76] Neutrophil extracellular traps (NETs) are weblike structures containing DNA, histones and granule proteins with antimicrobial function, thereby able to effectively trap and kill pathogens.[77] Platelets do not contain a nucleus, but they can release their mitochondria upon activation. Mitochondria are released as free organelles and in microparticles, which in turn can be hydrolyzed, leading to an inflammatory reaction through released proinflammatory lipid mediators and mitochondrial DNA (mtDNA).[78] mtDNA stimulates thrombin generation via the extrinsic pathway and neutrophil activation.[79,80] Importantly, platelets contribute to accumulation of extracellular mtDNA and recognition by antibodies in systemic lupus erythematosus (SLE) via platelet FcγRIIa stimulation, likely driving immunopathology in this autoimmune disease.[81] Although beyond the scope of this review, it is important to note that platelets can release platelet microparticles (PMPs) that can, on one hand, modulate inflammation, but intriguingly can also reach sites usually inaccessible for platelets like synovial and lymph fluid (reviewed in Puhm et al.[82]). The role of PMPs in host defense remains insufficiently understood, which is partly due to the lack of a PMP deficient mouse model.

Ultimately, platelets can undergo a unique cell death program termed procoagulant transformation. This occurs upon cooperative signaling through strong activation signals, leading to cytosolic supramaximal calcium levels, mitochondrial depolarization, cell swelling (termed platelet ballooning), and exposure of phosphatidylserine, which fosters thrombin generation.[13] Procoagulant platelets are elevated in a range of inflammatory diseases and seem to contribute to thrombo-inflammatory complications.[83–85] However, the exact role and function of procoagulant platelets in immunity and host defense remain unclear.

PLATELET COLLABORATION WITH INNATE IMMUNITY

The platelet arsenal of effector functions enables an intimate interplay with innate immune cells, particularly neutrophils. Due to their rapid response and large number, as well as prowess to adhere under shear stress, platelets arrive first to sites of inflammation and attach to the activated endothelium. This ideally positions platelets to orchestrate the accruing innate immune response in a temporally and spatially controlled manner. Interestingly, their interplay with innate immunity is Janus-faced—on the one hand, platelets are powerful activators of innate immune responses, on the other, they also pose critical checkpoints that control inflammatory responses (Figure 2).

In addition to the proinflammatory agonists discussed in the previous section, platelets recruited to the inflamed vessel wall possess multiple receptors and/or ligands that can directly interact with neutrophils. Thus, they act as landing pads for incoming neutrophils and foster transmigration and extravasation.[86,87] This is an essential function, as depletion of platelets strongly diminishes or even abolishes extravasation of immune cells in various murine inflammatory models.[88–91] Accordingly, thrombocytopenia impairs host defense, most prominently neutrophil responses, in Gram-negative and Gram-positive pneumonia, leading to increased bacterial loads and mortality.[92,93] Direct interaction of these two cell types seems to be crucial, mediated by a growing number of receptor-ligand pairs, most notably P-selectin—PSGL1, ICAM2-LFA1, and Gp1b and Jam3-Mac-1 interplay.[4,94,95] Platelet CD40L also interacts with neutrophil CD40, promoting integrin activation and release of ROS.[96,97] Platelets are also key inducers of NETosis. This process is in part dependent on platelet TLR4 signaling and P-selectin and Gp1b expression, as well as the release of HMGB1, PF4, and CCL5.[31,98,99] NETs are critical for driving intravascular thrombin formation and platelet clotting to limit systemic spread of bacteria in a process termed immunothrombosis (see Box 1).[100]

A recently discovered regulator of NETosis is heat shock protein 47 (HSP47), which is expressed by platelets across species and is strongly diminished in hibernating brown bears as well as long-term immobilized patients with spinal cord injury, correlating with protection from venous thromboembolism.[107] HSP47 is involved in intravascular activation of innate immunity and NET formation, and pharmacological or genetic ablation reproduced the protective effects observed.[107] Its role in immunothrombosis and host defense remains unclear. Beyond neutrophils, platelets can also recruit and activate eosinophils, triggering eosinophil extracellular trap (EET) formation to support clotting.[108]

Platelets and neutrophils also cooperate directly to ensure clearance of pathogens (Figure 2). If migrating platelets encounter bacteria, they can collect and bundle these *in vitro* and *in vivo*, marking them for phagocytosis by neutrophils.[57] Moreover, platelets form touch and go interactions via Gp1b and vWF expressed on Kupffer cells (KCs), liver resident

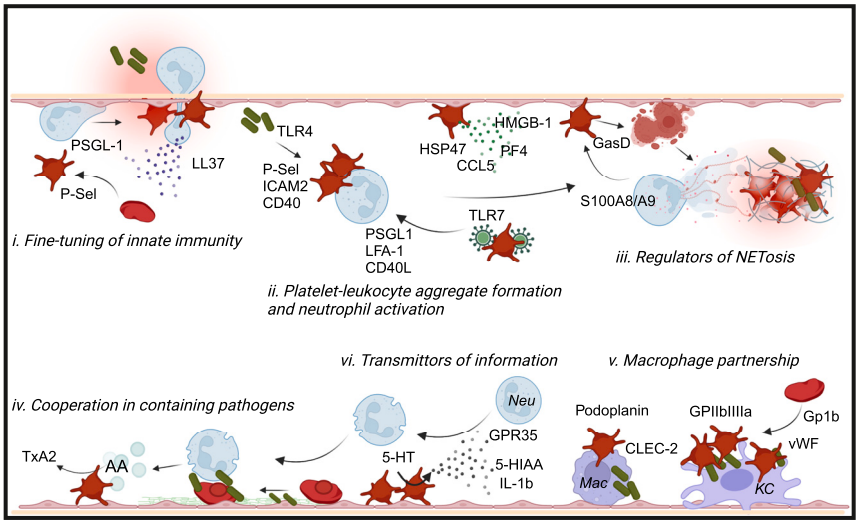

Figure 2. Interplay with innate immune cells
Platelets take central stage in regulating innate immune responses upon pathogen challenge. Their tight interplay with neutrophils allows for fine-tuning of innate immunity by introducing immune checkpoints, which require activation and reciprocal signaling of both cell types for a full immune response. Their interplay with neutrophils ranges from activating these cells indirectly, via PF4 and HMGB-1 release, to directly by forming platelet-leukocyte aggregates. This, in addition to Gasdermin D-dependent pyroptosis, positions platelets as important regulators of NETosis. Platelets also directly cooperate with neutrophils to contain and kill pathogens at sites of inflammation. Moreover, platelets process gut-derived serotonin to 5-HIAA, thereby transmitting information from tissues to neutrophils. Lastly, they partner with Kupffer cells (KCs) in the liver to capture bacteria but also modulate macrophage function via CLEC-2. Figure created using BioRender.

macrophages, under homeostatic conditions; once KCs capture bacteria in systemic infection, as shown for methicillin-resistant *Staphylococcus aureus* (MRSA) and *Bacillus cereus*, this immunosurveillance program leads to platelet activation and stable adherence via GPIIbIIIa, which assists KC-mediated killing of these pathogens.[109]

In addition to its protective roles in bacterial and fungal pathogen containment, platelet-mediated neutrophil activation and NETosis can also be harmful and contribute to immunopathology in a wide range of disease models.[110] Platelet migration contributes to hyperinflammation in severe sepsis and bacteremia, as platelet myosin heavy chain 9 (Mhy9)-deficient mice, which show a defect in platelet migration and bundling, showed reduced organ damage and mortality.[57] In COVID-19, circulating platelets show a distinct activation profile, which in turn drives neutrophil activation and NETosis, contributing to end-organ damage and a systemic pro-thrombotic state.[83,105]

Interplay of platelets and innate immune cells is frequently bidirectional. For example, neutrophil-derived cathelecidins like LL-37 are strong activators of platelets, and its mouse homologue CRAMP drives platelet reactivity via Src-kinase-dependent signaling, thereby contributing to thrombus formation as well as pathological inflammation by reciprocal neutrophil activation.[111] Platelet sensing of S100A8/A9 released by neutrophils leads to Gasdermin D-dependent platelet pyroptosis in mouse model of abdominal sepsis. Pyroptosis triggers the release of oxidized mitochondrial DNA and thereby potentiates NETosis, forming a vicious cycle of inflammation propagation.[112] S100A8/A9 also drives formation of procoagulant platelets dependent on Gp1b signaling in COVID-19, which enhances the systemic pro-thrombotic state in this disease.[113]

Neutrophils also prime platelet release in the bone marrow by physical contact with megakaryocytes, which might also enable direct membrane exchange between these cell types.[114,115] Neutrophils are recruited toward bone marrow megakaryocytes by CXCR4-SDF1 signaling and show pulling behavior on proplatelets, which activates ERK- and myosin II-mediated cytoskeletal changes in MKs necessary for effective proplatelet release. Interestingly, this contributes to the release of young, reticulated platelets with heightened reactivity, and ablation of this pathway via neutrophil specific CXCR4 deficiency can reduce venous and arterial thrombosis.[115] The role in host defense remains unclear; however, neutrophils induce CXCR4 expression upon activation and aging, and CXCR4^{hi} neutrophils migrate back to the bone marrow after localized inflammatory challenges.[116] This pathway might therefore be involved in thrombocytosis frequently observed after resolution of inflammation, which is hypothesized to contribute to tissue healing and recovery.[116,117]

Platelets may also serve as sensitive relays to transmit information to innate immunity: the intestinal epithelium releases IL-33, which regulates serotonin release from enterochromaffin cells, which is in turn taken up by platelets.[118,119] In the case of disturbed epithelium—for example, observed in chronic inflammatory bowel diseases (IBDs) —IL-33 release is elevated, leading to heightened platelet serotonin uptake, driving increased clotting and intestinal neutrophil recruitment.[118] Platelets process serotonin to 5-HIAA, which in turn mediates neutrophil recruitment via G-coupled chemotactic receptor GPR35.[120,121] This mechanism is important in a range of murine inflammatory/infection models. Interestingly, platelet derived 5-HIAA also contributes to eosinophil recruitment in fungal infection.[120] In summary, platelets and nucleated innate immune cells are intricately linked via multiple, bidirectional signaling events that support immune effector function.

But beyond boosting innate immunity and platelet function, crosstalk of innate immune cells and platelets can also fine-tune and/or even limit host immune responses (Figure 2). Activated platelets tether to neutrophils already adherent to the vasculature and are required to instruct these cells to transmigrate in a PSGL-1 manner.[122] This pathway contains a regulatory element: upon strong activation, leading to release of cathepsin G or neutrophil elastase, these enzymes mediate PSGL-1 proteolysis, effectively abolishing PSGL-1 interplay with platelet P-selectin, acting as a negative feedback loop.[123]

An interesting reciprocal checkpoint was identified regarding prostaglandin synthesis: activated platelets foster extracellular vesicle release by neutrophils, which contain arachidonic acid, allowing for cyclooxygenase 1 (Cox1)-dependent thromboxane

Box 1. Immunothrombosis

If pathogens have breached epithelial and endothelial barriers to gain access to the vasculature, it is pivotal for the host to prevent pathogen spread via hematogenous dissemination. This is achieved through initiation of intravascular clotting, predominantly in the microvasculature, effectively trapping and containing invading pathogen.[101,102] Activated monocytes express tissue factor and can therefore trigger the extrinsic coagulation cascade, and neutrophils expel serine proteases as well as NETs that stabilize the forming intravascular clot through coagulation activation and platelet and vWF recruitment, as well as exerting direct microbicidal function. Platelet-innate-immune-cell interplay is critical in initiation and propagation of immunothrombosis through reciprocal activation signals.[6] While this process has been identified to be protective in influenza and *E. Coli* bacteremia,[102,103] it needs to be tightly controlled as micro- and macrovascular thrombosis can lead to tissue hypoxia and cell death. Indeed, arterial and venous thrombosis, the leading causes of death worldwide, share crucial pathways with pathogen-elicited immunothrombosis. The relevance of this pathomechanism in human disease was further demonstrated during the COVID-19 pandemic. Patients with severe SARS-CoV-2 infection show systemic organ dysfunction beyond respiratory failure and a high rate of thrombotic complications.[104] Extensive research revealed that this heterogeneous presentation is linked through dysregulated immunothrombosis, which leads to microvascular thrombosis and organ damage, as well as a systemic prothrombotic state predisposing to cardiovascular complications.[105] Importantly, immunothrombosis is partly resistant to standard anticoagulant treatment, underlining the unmet need for specific, anti-thromboinflammatory drugs.[106]

A2 synthesis by platelets, which in turn elicits a full-fledged neutrophil response.[124] This mechanism is critical in host defense against *E. coli* and proposes compartmentalized substrate-enzyme pairs that restrict inflammation under steady state.[124] It is important to note, though, that long-term inhibition of platelet Cox1 with low-dose aspirin is not associated with increased (or decreased) rates of sepsis or infection, which points toward a minor effect of thromboxane A2 in physiological human host defense.[125,126] Platelets are also crucial in regulating IL-1β production, a key cytokine in systemic inflammation. They license NLRP3 inflammasome expression in innate immune cells, through a so far not-defined signaling pathway.[127] This proposes an additional layer of regulation to the already tightly controlled inflammasome function.

Outside these insights from mechanistic studies, clinical data also support an important role of platelets as checkpoints or even negative regulators of innate immunity. In patients with sepsis, thrombocytopenia is independently associated with increased mortality and associates with a dysregulated immune response.[128] Platelets protect from experimental septic shock by regulating macrophage polarization, as depletion of platelets led to high mortality and a proinflammatory cytokine profile in plasma, which could be rescued through platelet transfusions.[129] Platelet-derived prostaglandin PGE_2 is involved in anti-inflammatory M2-type reprogramming of macrophages.[129] Similarly, NBEAL2 knockout mice deficient in alpha granules showed similar pathogen spread but increased markers of host damage, pointing toward the idea that bactericidal cargo might be less relevant than alpha granule mediated immunomodulatory effects in *Klebsiella pneumoniae* sepsis.[130] One key immune-modulatory platelet receptor is CLEC-2, which binds to podoplanin. Podoplanin is mainly expressed on kidney and lymphatic endothelial cells, but also to some extent on mononuclear cells.[131,132] It represents an immune-modulatory axis regulating cytokine release and leukocyte recruitment in models of endotoxemia, peritoneal sepsis, and lung injury.[132,133] Interestingly, interfering with the CLEC-2-podoplanin axis leads to both increased inflammation and inefficient pathogen control, highlighting the importance of this pathway.

In summary, platelets can be viewed as bona-fide components of innate immunity, regulating key aspects of the first wave of defense against pathogens.

PLATELET AND ADAPTIVE IMMUNITY: FROM T CELLS TO ANTIBODY COMPLEXES

Effective host defense is a multi-tier process, in which first line defense by innate immune cells is followed by cellular and humoral immune cell memory. The latter is mediated by T and B cells, respectively, and ensures a specific and lasting response against the causative agent. This adaptive immune process takes days to develop and is critical for long-term protection. Platelets influence multiple steps of adaptive immunity—from antigen trafficking and presentation mediated by dendritic cells (DCs) to T and B cell signaling, maturation, and polarization (Figure 3).[134] The two key platelet receptors implicated in various studies and disease models are CD40L and IC receptor FcγIIa.

Lymph nodes are key secondary lymphoid structures for antigen presentation and lymphocyte trafficking. CLEC-2 expressed by platelets is required for the development and maintenance of lymph nodes. Constitutive, platelet-specific CLEC-2 deletion causes blood-filled lymph nodes and lymph node fibrosis; these dysfunctional fibrotic lymph nodes lead to impaired antibody formation.[48,135] Beyond maintaining lymph node function as a prerequisite for mounting an effective adaptive immune response, platelets can also directly affect the involved cell types, most notably antigen-presenting DCs. For example, they induce DC differentiation from monocytic cells via the P-selectin-PSGL-1 axis and can boost type I interferon production via CD40L.[136,137] CD40L drives DC maturation *in vitro* and *in vivo*, and platelet CD40L mediated DC activation and interferon production contributes to autoimmunity in lupus pathophysiology.[136] In this disease, innate immune cell activation and crosstalk with coagulation is further enhanced by endothelial protein C receptor (EPCR) and tissue factor signaling.[138] On the other hand, platelet CD40L is required for protection against a secondary viral challenge, as platelet depletion reduces antibody production.[139]

Platelets contain the molecular machinery to process and directly present antigen via major histocompatibility complex

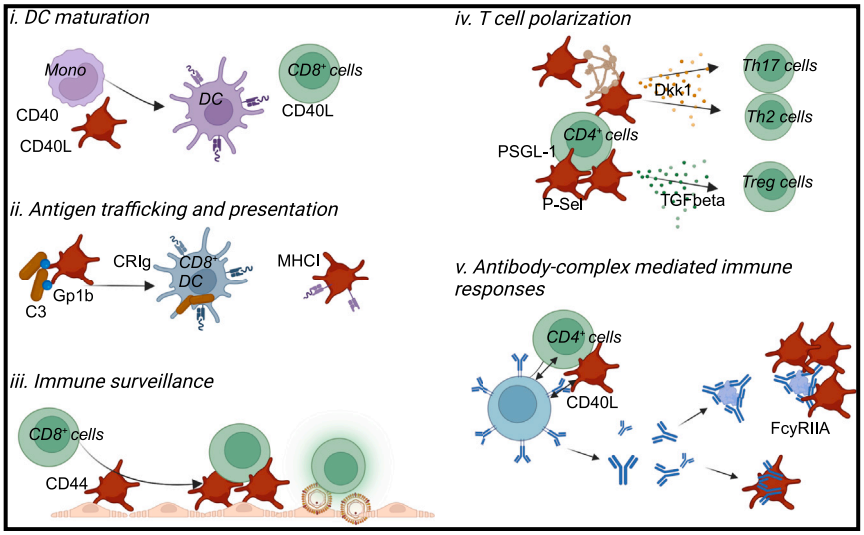

Figure 3. Interplay with adaptive immunity

Platelets influence multiple steps of the adaptive immune response. They are key in mediating dendritic cell (DC) maturation and fostering antigen presentation. Crucially, platelets influence intravascular antigen trafficking, for example to the spleen. They contribute to $CD8^+$ T cell immune surveillance in the liver via CD44 and influence $CD4^+$ T cell polarization, a key process in determining the ensuing immune response. Lastly, platelets mediate antibody responses and can recognize and be activated by immune complexes via FcγRIIA receptors. Figure created using BioRender.

class I (MHC class I).[140] Using platelet-specific MHC class I deficiency, it was shown that platelet MHC class I controls T cell counts and phenotype in sepsis; however, its requirement for mounting an effective adaptive immune response remains unanswered.[141] Even more crucial than antigen presentation might be the role of platelets in antigen trafficking. Platelets bind complement factor 3 (C3) loaded blood-borne *Listeria monocytogenes* and shuttle the pathogen to antigen-presenting $CD8^+$ DCs in the spleen, which triggers an adaptive immune response.[142] Depletion of platelets or prevention of aggregate formation by blocking Gp1b or deficiency in C3 speeds up clearance of the pathogen by KCs in the liver, forfeiting the development of protective antibodies.[142,143] This highlights platelets as important mediators of intravasal antigen trafficking. Whether shuttling to the spleen involves additional platelet specific signals or is solely due to "protecting" antigen from KC-mediated fast clearance, thereby enhancing the probability of capture via CRIg in the spleen, is unclear.[143] Similarly, platelets also traffic adenovirus to the spleen, eliciting an adaptive immune response.[25,26]

Platelets also aid in recruitment of lymphocytes to lymph nodes by fostering rolling on high endothelial venules through P-selectin.[144] Platelet-mediated immune surveillance in the liver by cytotoxic $CD8^+$ T cells is crucial for adaptive immune responses to hepatitis B.[145] Hepatic recruitment of $CD8^+$ T cells is mediated by direct interaction with platelets, which attach to hyaluronic acid-expressing liver sinusoids via CD44. This mechanism causes tissue damage in hepatitis B,[146] and aspirin/clopidogrel treatment in chronic hepatitis B infection blunts inflammation and hepatocellular carcinoma development in mice.[147]

Activated T cells are the predominant cell type expressing CD40L. This receptor is critical for T cell-dependent isotype-switched antibody production, as well as $CD8^+$ T cell function, and orchestrates adaptive immunity. The discovery that platelets also express CD40L raised the question of whether platelets can contribute to this crucial signaling axis.[148] Indeed, transferring wild-type platelets into CD40L-deficient mice challenged with adenovirus enhances $CD8^+$ T cell lytic activity, and platelet depletion reduces cytotoxic T cells in adenovirus- and lymphocytic choriomeningitis virus-infected mice.[149] Moreover, antibody production against adenovirus can be partially rescued by transfusing wild-type platelets, and co-transfusion of platelets and T cells leads to an additive effect on IgG production.[139] Intriguingly, platelet-enhanced signaling dependent on CD40L is particularly relevant for an effective adaptive immune response under conditions of low antigen exposure.[150]

$CD4^+$ T helper (Th) cells differentiate into various subsets, showing remarkable diversity. As master regulators of the immune response, these subsets govern immune trajectories in host defense, autoimmunity, and immunopathology. The cytokine environment is critical in determining T cell polarization, and platelets can contribute to this substantially[151] (Figure 3). For example, platelets sense the toxin candidalysin, secreted by the fungal pathogen *Candida albicans*, via Gp1b. This leads to the release of dickkopf1 (Dkk1), which in turn triggers Th2 and Th17 polarization and an antifungal immune response.[152] However, this might also contribute to allergic asthma development[172]. Regulatory T (Treg) cells are critical in preventing unwanted inflammatory responses. Platelets can foster polarization of T cells toward Treg cells via TGF-β, and $CD25^+$ Treg counts are decreased in thrombocytopenic patients.[153] *In vitro*, platelet-derived microparticles inhibit IL-17 and IFN-γ production by Treg cells and thereby promote Treg cell stability, which was confirmed in an inflammatory environment *in vivo*. Mechanistically, platelet-derived microparticles inhibit Treg cell plasticity in a P-selectin- and partially CXCR3-dependent manner.[154] Platelets also interact with Treg cells and instruct them to release IL-10 and TGF-β in resolution of inflammation.[155]

Beyond cellular immunity, platelets can also aid adaptive immune responses by interplay with antibodies. Of note, platelets can take up preformed antibodies that they can release upon interaction with viral pathogens *in vivo*. Transfusion of influenza A virus-experienced platelets into naive mice results in the transfer of protective antibodies and can recapitulate the protective effect observed in seropositive mice.[156] Importantly, platelets also directly contribute to host defense by reacting with antibody-antigen immune complexes mediated by FcγRIIa receptor and killing opsonized bacteria.[157,158] This can be mediated by specific antibodies against pathogens, or anti-PF4 complex antibodies. Due to its high relevance in human disease, renewed interest has focused on the latter, representing a link between adaptive and innate immunity orchestrated by platelets. As

mentioned above, platelets store PF4, a chemokine with strong affinity to negatively charged polyanions. Prokaryotes are thought to use negative charge to separate each other, a function that was deleterious during evolution of multi-cellular organisms.[157] Therefore, negative charge density is an important separator between eukaryotic and prokaryotic cells. Upon interaction with bacteria, platelets release PF4 and effectively opsonize bacteria. This then leads to neoepitope exposition through conformational changes and co-presentation and formation of anti-PF4 antibodies, which can now be widely employed to recognize PF4-opsonized pathogens.[157] This mechanism, bridging pattern recognition with adaptive immunity effector pathways, is also central to HIT pathogenesis, as heparin-PF4 complexes elicit an antibody response, and the resulting immune complexes are recognized by platelets, triggering activation, thrombocytopenia, and thrombosis.[159] Human polymorphisms in the FcγRIIa receptor that enhance IgG immune complex (IC) affinity predispose to thrombotic HIT, underlining the central role of this receptor.[160,161] Similar mechanisms might also contribute to vaccine-induced thrombosis and thrombocytopenia (VITT), although the mechanisms remain insufficiently understood.[162] Unexpectedly, IgG-FcγRIIa interplay also seems to contribute to anaphylaxis, potentially offering new therapeutic approaches.[163]

These data highlight a complex and multifaceted role of platelets in shaping humoral and cellular adaptive immune responses, ranging from antigen presentation and $CD4^+$ as well as $CD8^+$ function and phenotype to antibody-mediated immunity.

TWO SIDES OF PLATELET IMMUNE FUNCTION: WOUND HEALING VS. IMMUNOPATHOLOGY

The complex interactions of platelets with innate and adaptive immunity shape acute inflammation, ideally leading to effective pathogen clearance. But beyond directly fighting pathogens, it is crucial to maintain tissue integrity and later pave the way for reconstitution of sustained tissue injury. Platelets take over a key role in these tasks.

Platelets already hold an important role in maintaining vascular patency under steady state conditions.[164] In inflammation, single platelets seal off microinjuries without forming a clot, a process termed inflammatory hemostasis (reviewed in Kaiser et al.[165]). Indeed, this is critical for pathogen defense, as thrombocytopenia leads to high mortality in experimental *Aspergillus fumigatus* infection due to pulmonary hemorrhage, which has also been confirmed in viral infection and bacterial pneumonia models.[165–167]

Signals that lead to resolution of inflammation remain insufficiently understood.[168] Soluble mediators like resolvins play an important role. Platelets express resolvin receptors GPR32 and ALX, and they moderate their immune effector functions and immunothrombotic propensity upon exposure to resolvins annexin A and maresin-1.[169,170] Interestingly, platelets can themselves synthesize a precursor of maresin-1, which is transformed into the active compound by neutrophils in murine acute lung injury, exerting organ protective functions.[171] Depletion of platelets after initial neutrophil recruitment in *Klebsiella pneumonia* leads to delayed resolution of inflammation.[155] This is in part mediated by platelet-dependent Treg cell recruitment and licensing for anti-inflammatory cytokine production via PSGL-1-P-selectin and CD40-CD40L.[155] In experimental sepsis, IL-3-dependent platelet production in the spleen increases after 5 days, and these platelets show increased expression of CD40L.[172] Transfusion of these $CD40L^{hi}$ platelets is protective compared to unprimed platelets in sepsis, pointing toward the production of specialized platelets with enhanced immunomodulatory function.[172]

Platelets are well recognized regulators of wound healing and angiogenesis.[173] Their granules contain multiple pro-angiogenic and growth factors, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and TGF-β.[174] For the latter, a slow release system might enable TGF-β secretion to peak in the resolution phase.[175] Indeed, release of factors from alpha granules is involved in wound healing, as NBEAL-deficient mice showed impaired closure of skin wounds.[176] This role of platelets might be therapeutically enhanced by interfering with the anti-angiogenic axis of C5a receptor 1 (C5aR1)-mediated PF4 liberation.[177] Release of mitochondria by platelets can aid in wound healing by transfer of these to mesenchymal stem cells through endocytosis in a clathrin/dynamin manner, which fosters metabolic remodeling.[178] This has prompted the use of platelet-containing plasma as an adjunct therapy to promote wound healing in chronic skin wounds, although there is insufficient data to prove clinical utility.[179]

While these data clearly position platelets at the nexus of tissue homeostasis and repair, the multiple proinflammatory tools at their disposal can cause or contribute to hyperinflammation as outlined in detail above. A prime example of this is infective endocarditis, a disease in which bacteria exploit pathways of platelet activation, recruitment, and coagulation activation to form an immunothrombotic biofilm resistant to immune-mediated clearance.[180] Similarly, the culmination of dysregulated immunothrombosis is uncontrolled intravascular clot formation. This syndrome, named disseminated intravascular coagulation (DIC), is a feared complication of sepsis and other systemic inflammatory syndromes and carries a high mortality with so-far-limited treatment options.[181] Moreover, as they bridge inflammation and thrombosis, platelets are also crucial drivers of complications in and after infections—most prominently thrombotic events. Risk of thrombosis is increased up to 20-fold after infection, and this effect may be partially mediated by platelets.[182,183] Hospitalization for pneumonia is associated with increased short-term and long-term risk of cardiovascular disease.[184] Thrombotic risk is driven by the severity of infection, as seen with acute COVID-19 and influenza, is predicated on strong platelet activation and vascular immunopathology, only developing if a certain threshold of tissue injury or pathogen spread is surpassed.[185] This is again highlighted in the wake of the COVID-19 pandemic, which reveals a substantial, attributable burden of cardiovascular events post COVID-19 infection, which correlates with initial disease severity.[186] Along these lines, influenza vaccination in the aftermath of myocardial infarction results in a lower risk of all-cause death and cardiovascular death.[187]

Therefore, platelet activation during infectious but also non-infectious inflammatory diseases is essential for host protection but may also induce substantial thrombotic and inflammatory collateral damage.

PLATELETS FROM A CLINICAL PERSPECTIVE: DISEASE AND THERAPY

From a clinical perspective, platelets remain of minor interest in infectious diseases. This can be attributed to the fact that most likely low platelet numbers are sufficient for these cells to carry out their function, and very severe thrombocytopenia is relatively uncommon. However, patients with immune thrombocytopenia, a disease with severely diminished platelet counts in some patients, have an increased risk of infection, which inversely correlates with platelet counts.[4,188] In systemic infections, poor outcome corresponds with (severe) thrombocytopenia, but a threshold for "platelet immune function" in humans remains to be defined.[128,189]

A second, emerging line of evidence supporting the critical role of platelets in immunity is platelet transfusions: these blood products must be recognized as immunomodulatory treatments. This was elegantly shown in neonates. These patients receive fractionated adult platelets in severe thrombocytopenia, and a more liberal transfusion trigger (<50,000/μL compared to <25,000/μL) led to paradoxical increase in bleeding and mortality.[190] Basic and translational research revealed that adult platelet transfusions in neonates increase cytokine levels and foster inflammation in a mouse model.[191,192] This seems to be of particular relevance in neonates, as this cohort physiologically harbors hyporeactive platelets. However, even adults on anti-platelet therapy with intracranial hemorrhage fare worse if they receive platelet concentrates, possibly because of boosted thromboinflammation in the brain.[193] Additional research is needed to better define the protective and harmful effects of platelet-based transfusion products.

Moreover, the use of distinct anti-platelet therapies allows conclusions regarding the role of specific signaling pathways in platelets for pathogen containment and tissue damage. In a prospective, randomized, controlled, and double blinded study, patients were enrolled with community acquired pneumonia and randomly assigned to receive either placebo or P2Y12 inhibitor ticagrelor.[194] This leads to a decrease in platelet-leukocyte aggregates and NETosis markers as well as a reduced need for oxygen supplementation and an improved lung function,[194] indicating reduced tissue damage. In line, low-dose aspirin intake in human volunteers reduces polymorphonuclear leukocyte as well as macrophage accumulation in experimental skin blisters.[195] These immunological effects of COX-1 or P2Y12 inhibitors can at least in part be ascribed to their effects on PLA formation and the respective sequelae for leukocyte function and behavior, as extensively reviewed elsewhere.[196]

Jointly, the findings summarized here paint a complex picture of platelets and show that while they might represent an attractive pharmacological target in infection and inflammation, it is necessary to modulate rather than block their function. Moreover, the available anti-platelet therapies, widely used in primary and secondary prevention of cardiovascular disease, including P2Y12 receptor antagonists (i.e., clopidogrel) and Cox1 inhibitors (aspirin), target platelet aggregation. As aggregation is frequently dispensable for physiological platelet functions in host defense,[4] therapies influencing platelet aggregation do not necessarily affect immune responses. Beyond aggregation, the research summarized above points toward novel targets: blockade of GPVI by antibodies or antagonists shows promise in preventing thromboinflammation in stroke with limited effects on bleeding in animal models.[197,198] This has translated to promising data in human trials, with a large phase II/III trial ongoing (ACTISAVE, NCT05070260).[199,200] Interfering with platelet-neutrophil interplay could also be an attractive pharmacological intervention.[201] HSP47, predisposing to thromboinflammation in bear and man, could represent a target to lower the risk of venous thrombosis.[107] P-selectin antibodies like inclacumab and crizanlizumab, blocking PSGL-1- P-selectin interplay, show promising effects on myocardial recovery after myocardial infarction, and are efficacious in preventing vasoocclusive clots in sickle cell disease.[202,203] How these drugs might be used to limit hyperinflammation in infection remains to be investigated. Given the central role of FcγRIIa in immune-complex-mediated immunopathology, targeting this receptor could be of relevance as well.

CONCLUDING REMARKS

In cardiovascular disease, platelets represent ideal pharmacological targets due to their unique set of receptors, their relatively short half-life, and their limited ability for *de novo* protein synthesis. The emerging picture of platelets as central regulators in host defense and inflammation that deploy specialized receptor-signaling axes underscores the potential to achieve major clinical benefit by targeting this cell type beyond thrombosis. To achieve these goals, we must better understand the intricate interplay of platelets and the immune system across disease states, thereby identifying recurring patterns. Moreover, it is crucial to perform meaningful translational studies, including the use of omics technologies, to better understand platelet phenotype and function in human disease.

ACKNOWLEDGMENTS

This work was funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation - SFB 1123 [S.M. and L.N. project B06]; SFB 914 [S.M. projects B02 and Z01), by the DZHK (German Center for Cardiovascular Research) (MHA 1.4VD [S.M.]) and Corona Foundation (L.N.). This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement IMMUNOTHROMBOSIS, no. 833440 to S.M.). Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or the European Research Council Executive Agency. Neither the European Union nor the granting authority can be held responsible for them.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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