

The Role of Platelets Beyond Hemostasis

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Abstract

Keywords

- ▶ platelets
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Platelets, small anucleate cells derived from megakaryocytes, are key drivers of hemostasis and thrombosis. There is accumulating evidence, however, that platelets play roles beyond thrombosis and hemostasis, especially in inflammation, infection, and tissue regeneration. They can recruit, stimulate, and modulate immune cells by direct interaction or via the release of soluble factors. During inflammation, platelets maintain vascular integrity in the lung, skin, and brain through interactions of their GPVI, CLEC-2, and GPIb receptors as well as factors released from α -granules and dense granules. They cooperate with monocytes and macrophages to fight bacteria in the bloodstream and in the liver where they accumulate on Kupffer cell–bacteria complexes to support pathogen destruction. Upon liver damage, platelets adhere to the liver sinusoids and release bioactive molecules like serotonin and fibrinogen to support reparative processes. Here, we provide a review of some of the multiple roles of platelets beyond their classical role in hemostasis.

Introduction

The traditional role of platelets is typically linked to their hemostatic function, yet it has become increasingly clear that their functional range extends far beyond thrombus formation. Acting as rapid responders to vascular and tissue disruption, they link mechanical signals with inflammatory and immune responses, thereby influencing both local and systemic reactions to injury or infection. Recent work has revealed that platelets interact dynamically with endothelial, myeloid, and hepatic cells through a combination of receptor-mediated interactions and the release of a variety of granule-derived mediators. These mechanisms highlight platelets as central regulators of vascular integrity, innate immune defense, and tissue remodeling. In this review, we emphasize the notion of platelets as multifunctional effector cells, focusing on their role in inflammatory bleeding, host-pathogen interactions, and hepatic inflammation, regeneration, and wound repair (▶ [Fig. 1](#)).

Platelets

Platelets—small anucleate cells derived from their gigantic mother cells residing in the bone marrow called megakaryocytes—are key drivers of hemostasis. Upon vessel injury, platelets adhere to exposed extracellular matrix (ECM) proteins and become activated, which allows them to also bind neighboring platelets leading to thrombus formation and restoration of vessel integrity. When this process goes awry, excessive platelet activation can lead to thrombosis and myocardial infarction or stroke.

Their surface receptors and biomechanical properties make platelets excellent guardians of hemostasis. The hydrodynamic shear forces in blood vessels cause platelets to flow close to the vessel wall thus allowing them to respond to vascular injury immediately. Upon injury, platelet adhesion receptors interact with ECM proteins laminin, fibronectin, collagen, and von Willebrand Factor (vWF). Under the high shear rates present in arteries and arterioles, platelet

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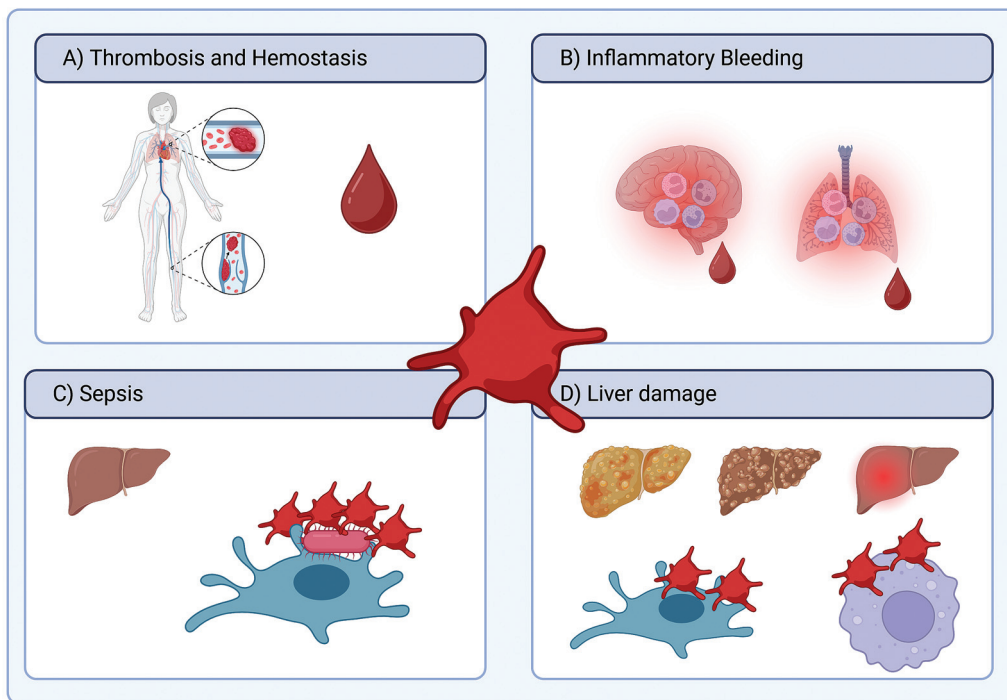


Fig. 1 Overview of platelet functions beyond hemostasis that are reviewed in this article. Platelets play major roles in thrombosis and hemostasis via their surface receptors and factors released from their granules (A), as discussed in the chapter “platelets” of this article. They were also shown to prevent bleeding in settings of inflammation, especially in the lung and brain (B), which is reviewed in the chapter “Maintaining Vascular integrity during inflammation”. Platelets further contribute to fighting infection, mostly by interaction with monocytes and macrophages. Cooperation of platelets with Kupffer cells in the liver has been identified to play a major role in fighting intravascular infections (C) as discussed in the chapter “Platelets in infection”. Lastly, platelets were also shown to contribute to the development of liver damage, e.g., in the setting of MASH (D), which we summarize in the chapters “Platelet Activation and Inflammatory Signaling in MASH”, “Platelet Activation and Liver Regeneration after Partial Hepatectomy” and “Platelets in Hepatic Wound Healing”. (Created in BioRender. Deppermann, C. (2026) <https://BioRender.com/l77e831>.)

adhesion depends on vWF—a large glycoprotein stored in the Weibel-Palade bodies of endothelial cells and α -granules of platelets and megakaryocytes.^{1–3} Shear-induced unfolding of vWF initiates its binding to collagen.⁴ Platelet adhesion to collagen-bound vWF is mainly mediated by glycoprotein Ib (GPIb). This transient interaction causes platelets to roll along the vessel wall, enabling further interactions.^{5–7} This provides an opportunity for the platelet immunoglobulin superfamily receptor GPIIb/IIIa to bind to collagen, thereby initiating intracellular signaling cascades that culminate in the rise of intracellular calcium levels causing the release of platelet granule-derived factors including the secondary mediators adenosine diphosphate (ADP) and thromboxane A₂ (TxA₂) and the shift of integrins to a high-affinity state. ADP and TxA₂ together with thrombin generated by the activation of the coagulation cascade stimulate a variety of G protein-coupled receptors (GPCRs) which together cause full platelet activation and strong crosslinking of individual platelets by activated integrin α IIb β 3.^{8,9}

Platelets possess two major types of granules: α -granules and dense or δ -granules. The more abundant α -granules contain receptors like P-selectin and soluble proteins such as vWF and cytokines, which upon activation are recruited to the platelet surface or secreted into the extracellular space, respectively. Dense granules on the other hand contain

nucleotides such as ADP and ATP as well as serotonin, magnesium, and calcium.^{10–13} Defects in platelet granules can lead to bleeding disorders like the gray platelet syndrome (GPS), which is characterized by enlarged, grayish platelets lacking α -granules, with reduced platelet count, bleeding tendency, and myelofibrosis. Mutations in *NBEAL2* were shown to cause GPS leading to impaired granule packaging inside megakaryocytes and absence of α -granules from platelets in circulation.^{14–16}

Maintaining Vascular Integrity during Inflammation

Immune thrombocytopenia (ITP) is characterized by a significant reduction in the number of circulating platelets caused by platelet destruction through immune cells, mostly by antiplatelet antibodies directed against GPIIb/IIIa and integrin α IIb β 3.¹⁷ ITP causes varying degrees of bleeding including severe bleedings and intracranial hemorrhages (ICH).¹⁸ Studies show that platelet counts may or may not correlate with bleeding severity,^{18–20} suggesting that thrombocytopenia alone might not be sufficient and that an additional trigger—such as inflammation—is needed.

In 2008, Goerge et al showed in a seminal paper that local inflammation in the skin, brain, and lung induces

hemorrhage in thrombocytopenic mice.²¹ In the absence of inflammation, however, they did not observe bleeding in thrombocytopenic mice. In contrast, massive hemorrhage was observed at sites of inflammation during thrombocytopenia. Strikingly, as little as 5% of the baseline platelet count was sufficient to prevent inflammatory bleeding. Further studies showed that platelet ITAM signaling downstream of GPVI and CLEC-2 were crucial in maintaining vascular integrity during inflammation of the skin and lung.^{22,23} Another study also showed that the CLEC-2 ligand podoplanin is upregulated on macrophages and other stromal cells following skin inflammation indicating that in the absence of GPVI, binding of platelet CLEC-2 to podoplanin-positive cells could contribute to preventing inflammatory bleeding in the skin. The study also showed that GPIb contributes to maintaining vascular integrity during lung inflammation. More recently, Kaiser and colleagues have shown that platelet mechanosensing also contributes to inflammatory bleeding in the lung.²⁴

Two mouse models to analyze the role of platelet α -granules and dense granules have been described: the *Unc13d*^{-/-} mouse in which platelets are unable to secrete their dense granules^{25,26} and the *Nbeal2*^{-/-} mouse which lacks platelet α -granules.^{16,27} Both mouse strains did not show signs of spontaneous hemorrhage or in vivo thrombosis models^{16,28} or thrombo-inflammation after ischemic stroke.^{16,25}

Unc13d^{-/-}/*Nbeal2*^{-/-} double deficient animals were used to show that platelet α -granule and dense granule contents are dispensable for preventing inflammatory bleeding in the skin and lung.²⁹ In striking contrast, in a model of ischemic stroke these mice showed increased intracranial hemorrhage and mortality comparable to that observed in mice treated with α IIb β 3 blocking antibodies.³⁰ These results suggest that molecules from both granule types are necessary to maintain cerebral hemostasis after stroke. It is tempting to speculate that angiopoietin-1 or serotonin—which were previously shown to prevent intra-tumor hemorrhage³¹—might play a role in this setting.

Platelets in Infection

Rinder et al described the formation of platelet–monocyte and platelet–neutrophil aggregates upon stimulation of whole blood in vitro.³² Upon activation, P-selectin (CD62P) is exposed on the platelet surface, allowing interactions with its counterreceptor PSGL1 expressed on myeloid cells including monocytes.³³ Further interactions are made through Mac-1 (CD11b/CD18, integrin $\alpha_M\beta_2$) on monocytes binding to platelet GPIb^{34,35} or through CD40L–CD40 interactions.³⁶ Fibrinogen was shown to mediate homo- and heterotypic cellular interactions via α IIb β 3 and other fibrinogen-binding integrins, suggesting this could be another way how platelets interact with monocytes or neutrophils.^{37,38} Indeed, deleting the binding site of fibrinogen on Mac-1 significantly impaired pathogen clearance after intraperitoneal infection with *Staphylococcus aureus*.³⁹ Factors released from platelet granules are the second set of tools in the platelet's toolbox

besides their receptors to influence immune cell recruitment, adhesion, and activation. For example, platelet-derived CCL5 (RANTES) immobilized on inflamed endothelium triggers monocyte arrest under flow.⁴⁰ Upon activation, platelets release large quantities of CXCL4 (PF4),¹³ which enhances monocyte phagocytosis and the generation of reactive oxygen species but has no impact on chemotaxis.⁴¹

Platelet–monocyte aggregates (PMAs) have been studied in a variety of experimental and clinical contexts, especially in diseases characterized by overt immune system activation. Increased numbers of PMAs were found in the blood of patients with acute coronary syndrome and atherosclerosis^{42,43} as well as rheumatoid arthritis and systemic lupus erythematosus.⁴⁴ Increased numbers of PMAs were also found in HIV-infected patients.⁴⁵ In dengue, platelets were shown to form complexes not only with monocytes but also lymphocytes and neutrophils.^{46,47} Increased number of PMAs were found especially in dengue patients showing thrombocytopenia and increased vascular permeability. Co-culture of monocytes from healthy donors with platelets from patients with dengue led to the secretion of IL-1 β , IL-8, IL-10, and MCP-1.⁴⁷

There is increasing evidence that platelets join forces with monocytes or macrophages as part of the host immune response to bacterial infection. When human macrophages were stimulated with LPS and co-cultured with activated platelets, this enhanced macrophage secretion of TNF- α , IL-6, and IL-23, suggesting that activated platelets may exacerbate macrophage activation and secretion.⁴⁸ In a relatively small prospective study, elevated PMA levels were associated with an increased risk of mortality in older septic patients.⁴⁹ A different study showed in an experimental mouse model that platelets provide protection from septic shock via cyclooxygenase 1 signaling.⁵⁰ In a mouse model of *Klebsiella*-induced pneumonia, thrombocytopenia led to impaired survival during pneumonia-derived sepsis.⁵¹ Further, platelets enhanced macrophage uptake and restricted intracellular growth of *S. aureus* through IL-1 β in vitro.⁵²

Carestia et al showed that platelets sequester both pro- and anti-inflammatory cytokines released by monocytes and that LPS-stimulated monocytes were skewed toward M1 type macrophages with increased phagocytic activity by platelets through GPIb–CD11b interactions. In a mouse model of *E. coli* sepsis, platelet transfusion increased the percentage of iNOS⁺ macrophages and improved bacterial clearance and survival rates in a CD11b and GPIb-dependent manner.⁵³

Kupffer cells are liver-resident macrophages, residing within the lumen of the liver sinusoidal endothelium. They have a star-shaped form and extend several pseudopods outside the vasculature. A key function of Kupffer cells is the binding and phagocytosis of circulating pathogens, which they perform with astounding efficiency.⁵⁴ It was previously shown that Kupffer cells catch and destroy intravascular *Borrelia burgdorferi*⁵⁵ as well as methicillin-resistant *Staphylococcus aureus* (MRSA) from the bloodstream. In mice treated with the immunosuppressive drug tacrolimus, Kupffer cells' capacity to capture, phagocytose, and destroy

bacteria was significantly reduced, which could provide a potential explanation for the increased susceptibility of transplant recipients to infection.⁵⁶ MRSA capturing by Kupffer cells is mediated through interaction between complement receptor of the immunoglobulin superfamily (CR1g) and lipoteichoic acid (LTA), a gram-positive bacteria cell wall component.⁵⁷ It was shown that following phagocytosis, a small number of staphylococci were able to overcome the antimicrobial defenses of Kupffer cells and proliferate within this intracellular niche for days.⁵⁸ Using intravital microscopy, Wong and colleagues found that platelets form “touch-and-go” interactions with Kupffer cells mediated by GPIb. Upon intravascular infection with *Bacillus cereus* or MRSA, bacteria were caught by Kupffer cells. This triggered platelets to switch from “touch-and-go” interactions to sustained adhesion to encase the bacteria and support their destruction.⁵⁹ In another study it was shown that *S. aureus* α -toxin causes platelet aggregation in the liver during sepsis, suggesting that there are different responses of platelets to sepsis that have to be taken into consideration also when thinking of potential treatment options.⁶⁰ Interestingly, antiplatelet therapy with acetylsalicylic acid (ASA) in *S. aureus*-infected mice significantly reduced platelet aggregation and NET release, intravascular thrombin activity, and microvascular occlusion as well as liver damage.⁶¹

Platelet Activation and Inflammatory Signaling in MASH

Platelets, traditionally recognized for their pivotal role in hemostasis and thrombosis, have emerged as dynamic immune and signaling cells orchestrating hepatic inflammation, fibrosis, and regeneration. Increasing evidence suggests that platelets not only participate in the early inflammatory responses in liver injury but also directly modulate hepatocellular function, sinusoidal microcirculation, and tissue remodeling. Their multifaceted contribution covers a wide spectrum of hepatic pathologies from sterile surgical injury and partial hepatectomy (PHx) to metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH).

MASLD, previously known as nonalcoholic fatty liver disease (NAFLD), is a hepatic condition primarily defined by the accumulation of fat within liver cells (steatosis).⁶² As the disease advances, it may progress to liver fibrosis and is often accompanied by systemic complications such as increased cardiovascular risk. In cases where hepatic inflammation and cellular injury are present alongside steatosis, the condition is classified as metabolic dysfunction-associated steatohepatitis (MASH). Beyond classical metabolic triggers such as dyslipidemia and insulin resistance, platelet activation has recently been recognized as a key contributor to disease progression.⁶³ In recent years, analysis of platelets from MASLD/MASH patients showed that platelet function correlates with liver disease severity. Harm et al recently described that platelet reactivity correlates closely with hepatic fat accumulation, iron deposition, and liver volume, suggesting a bidirectional relationship between metabolic

stress and platelet hyperactivation.⁶⁴ Notably, treatment with antiplatelet agents mitigated these hepatic alterations, leading to a reduction in hepatic volume, iron overload, and systemic inflammatory cytokines.⁶⁴ In patients with progressive MASH, a specific cytokine profile characterized by elevated levels of profibrotic and apoptotic chemokines is accompanied by enhanced platelet reactivity. Interestingly, Castelli et al described a dual role of integrin α IIb β 3 activity correlating with fibrosis severity. Low-grade fibrotic score caused enhanced reactivity, while high-grade scoring correlated with reduced integrin α IIb β 3 activity. Still, soluble P-selectin in plasma of patients and platelet adhesion on a collagen matrix was enhanced, suggesting an exhausting phenotype of platelets with progressive fibrotic score in patients.⁶⁵ Although reduced platelet aggregation is associated with decreased inflammatory and fibrotic signaling, this indicates that platelet modulation could directly influence the hepatic microenvironment. Circulating platelets from MASH patients show upregulation of inflammatory transcripts, further emphasizing that platelets themselves acquire a proinflammatory phenotype under metabolic stress.⁶⁶ Upon hepatic inflammation, platelets interact with Kupffer cells and sinusoidal endothelium, promoting a pro-fibrotic phenotype.^{67,68} Malehmir et al demonstrated that in both early and advanced stages of steatohepatitis, platelet adhesion is mediated by hyaluronan-CD44 and GPIb α interactions.⁶⁷ Blocking GPIb α significantly reduced inflammatory cytokine release, highlighting the central role of α -granule-derived mediators in leukocyte attraction and activation.⁶⁷ These findings collectively emphasize a mechanistic network in which platelet activation directly connects a systemic metabolic phenotype with intrahepatic immune signaling, thus driving steatohepatitis progression. This interplay underlines that platelets act as active participants rather than passive bystanders in MASH pathophysiology and supports their potential as both biomarkers and therapeutic targets.

Beyond their inflammatory properties, platelets communicate directly with hepatocytes, thereby influencing hepatic gene expression and proliferation. Experimental models have demonstrated that hepatocytes internalize platelets and incorporate platelet-derived RNA, leading to the horizontal transfer of genetic material that promotes hepatocellular proliferation. This transfer occurs both in vitro and in vivo following partial hepatectomy, and enzymatic degradation of platelet RNA reduces hepatocyte proliferation.⁶⁹ Additionally, platelet-derived macrovesicles are an important factor that potentially modulate leukocyte and hepatocyte gene expression in MASH.^{70,71} Thus, platelets act as cellular messengers capable of transferring functional transcripts that initiate regenerative responses. This molecular crosstalk between platelets and hepatocytes is further modulated by the hepatic sinusoidal niche. Recent data highlight the essential role of Kupffer cells as mediators of platelet-hepatocyte communication. Kupffer cells form a structural and signaling bridge, anchoring platelets to sinusoidal walls and facilitating thrombopoietin (TPO) generation by hepatocytes.⁷² Hepatocyte sinusoidal protrusions extend through

fenestrae of liver sinusoidal endothelial cells (LSECs) to interact with platelet-bound Kupffer cells, creating a cell network for maintaining platelet homeostasis and regenerative capacity.⁷² These findings reshape the traditional view of TPO regulation, revealing that platelet–Kupffer cell–hepatocyte interactions are all indispensable for a tightly integrated signaling network in hepatic physiology.

Platelet Activation and Liver Regeneration after Partial Hepatectomy

The liver's extraordinary regenerative potential is orchestrated through a highly coordinated sequence of cellular and molecular events. Within this process, platelets emerge as pivotal modulators that synchronize inflammatory priming with hepatocellular proliferation. Following PHx, platelets accumulate rapidly within the hepatic sinusoids, where they interact with endothelial cells, Kupffer cells, and the ECM to release bioactive molecules like serotonin or fibrinogen.^{69,73,74} These early events initiate the priming phase of liver regeneration, setting the stage for subsequent hepatocellular proliferation.

Within hours after PHx, platelet activation is enhanced by contact with ECM components, particularly fibrinogen and vWF. Fibrinogen-mediated integrin $\alpha\text{IIb}\beta\text{3}$ signaling is indispensable for liver regeneration, as it directs platelet accumulation in the regenerating lobes and triggers hepatocyte proliferation.^{73,74} Similarly, transient vWF-dependent platelet influx into the remnant liver supports early hepatocellular mitogenic signaling.⁷⁵ In addition, podoplanin–CLEC-2 interactions between hepatic sinusoidal cells and platelets further promote regeneration; deficiency of CLEC-2 leads to reduced platelet aggregation and impaired liver regeneration.⁷⁶ These ECM–platelet interactions collectively describe the early phase of regeneration by connecting hemostatic activation to regenerative signaling.

Experimental evidence supports a temporal correlation between platelet activation and regenerative phases. During the priming phase (0–6 hours post-PHx), cytokine signaling through tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) is induced, accompanied by ECM remodeling that facilitates platelet adhesion.⁷⁷ Activated platelets release serotonin and sphingosine-1-phosphate (S1P) from α -granules and dense granules, both stimulating hepatocellular proliferation and endothelial activation.^{78,79} Lesurtel et al described that especially platelet-derived serotonin shows potent liver regenerative capacities and accelerates restoration of liver mass following PHx.⁷⁸ This platelet activation seems to be transient because as hepatocellular expansion progresses into the proliferative phase (6–72 hours), platelet activation declines as platelet activation and adhesion under flow conditions are reduced.⁸⁰ By entering the termination phase (72 hours onward) of liver regeneration after surgical intervention, hemostatic balance is restored.⁸⁰ Thus, platelet activity follows a tightly regulated kinetic pattern that follows major phases of liver regeneration.

The interplay between platelet signaling and hepatic endothelial modulation is also evident in the rapid induction

of endothelial inhibitors such as prostacyclin (PGI₂) and nitric oxide (NO) following PHx.⁸⁰ These mediators could act to regulate platelet activation, preventing excessive aggregation while preserving regenerative signaling. In pathophysiological conditions such as liver fibrosis initiated by cholestasis, however, platelet activation becomes impaired, resulting in bleeding complications and delayed regeneration.⁸¹ Together, these observations highlight the balance between platelet activation, endothelial signaling, and effective liver regeneration.

Platelets in Hepatic Wound Healing

Hepatic wound healing describes the sequence of hemostasis, inflammation, proliferation, and tissue remodeling. In chronic liver injury such as ischemia, toxin exposure or chronic metabolic injury, platelets act as central modulators of each of these phases.⁸² Their role extends beyond promoting clot formation to shaping the cellular and molecular environment of sinusoidal repair and regeneration. Unlike infectious inflammation, which is driven by microbial signals, sterile inflammation is initiated by endogenous danger signals damage-associated molecular patterns (DAMPs), including molecules like ATP and mitochondrial peptides, released from injured cells.⁸³ This distinction is critical for our understanding how platelets orchestrate immune cell behavior and regenerative signaling in the liver.

Following hepatic injury, vascular integrity is disrupted, exposing ECM components and thus promoting platelet adhesion.⁸⁴ Platelets rapidly bind to LSECs and Kupffer cells, promoting immune cell infiltration and regenerative capacities of immune cells. Accordingly, platelets release α - and dense-granule contents such as PDGF, HGF, IGF-1, serotonin, and S1P.^{78,79,85,86} These factors serve as mitogenic and immune-modulatory signals as already described earlier. Their release triggers a variety of downstream signaling (Akt/ERK1/2; IL-6/STAT3 axis primarily in hepatocytes, but also LSECs, Kupffer cells, and hepatic stellate cells).^{87–90} Platelets take on the role of “first responders” in the wound-healing cascade, causing a shift from mechanical and vascular injury signals into regenerative cell signaling. Recent intravital imaging studies of liver tissue have further refined this understanding. Slaba et al demonstrated that platelets rapidly adhere to the sinusoidal endothelium in the area of sterile hepatic injury, creating a supportive milieu for neutrophil crawling into the necrotic area.⁹¹ This interaction is mediated by integrins such as GPIIb/IIIa (CD41) and GPIb (CD42b), and is essential for neutrophil recruitment and subsequent tissue repair. Within this sterile necrosis, released ATP and mitochondrial-derived formylated peptides act as danger signals guiding neutrophils to the injury site via P2Y2 and FPR-1 receptors, but unlike in infectious models do not induce significant NET formation.⁹² Notably, platelet depletion or CD41 deficiency severely impairs neutrophil migration and reduces wound healing, underscoring role of platelets in orchestrating immune cell behavior during sterile inflammation.^{91,92} As shown by several groups, not only the interaction of platelets with LSECs but also with Kupffer

cells at the site of injury is important. Platelets can directly induce LSECs or Kupffer cells to release IL-6, which in turn activates STAT3 in hepatocytes—a crucial step for initiating liver regeneration.^{79,87,93,94} Similarly, platelet-Kupffer cell crosstalk amplifies TNF- α and IL-6 secretion, reinforcing the priming signals required for hepatocyte cell cycle entry.^{95,96} In the context of hepatic injury and regeneration, the communication and regulation of key cytokines with pro- and anti-inflammatory signaling pathways decide upon regenerative signaling or if inflammation and fibrosis is promoted.

Regarding regenerative capacity, an important cytokine released by platelets is TGF- β .⁹⁷ Platelets are the major source of circulating TGF- β .⁹⁸ Upon activation in liver disease and concurrent wound healing, TGF- β is released and acts on hepatic stellate cells and immune cells. In the early phase of wound healing, platelet-derived TGF- β is needed to activate quiescent HSCs, which begin producing ECM components and release growth factors to facilitate regeneration.⁹⁹ Concurrent with these findings, platelet-specific TGF- β knockout mice showed decreased liver regeneration.¹⁰⁰ However, an uncontrolled and exaggerated TGF- β signaling can further promote liver fibrosis. Continued liver injury induces repeated wound-healing signaling, causing a constant release of TGF- β and subsequent initiation of uncontrolled ECM production.¹⁰¹

Therapeutically, the implications of platelet-mediated wound healing are substantial. On one hand, enhancing platelet function or numbers (via thrombopoietin agonists or platelet transfusion) has potential to improve regeneration after hepatectomy or acute liver injury.^{102,103} On the other hand, reducing platelet activation may be beneficial in chronic liver disease settings to prevent fibrosis progression. Thus, platelet-targeted therapies must be context-specific: promoting rapid, effective wound healing after acute insult without tipping the balance toward chronic fibrogenesis. Moreover, measurement of platelet activation markers, granule contents, and associated cytokine profiles may support personalized stratification of hepatic wound healing. In essence, platelets function as both the “first responders” and the “regeneration architects” in the liver’s wound environment, provided their activation is properly timed, spatially confined, and molecularly modulated.

Conclusion

Platelets are the guardians of the vasculature in many ways: They help to maintain vascular integrity during vessel damage where they become activated to form a clot and seal the damaged endothelium, thus preventing further blood loss. Vascular integrity can also be compromised upon inflammation, especially in the setting of thrombocytopenia, thus highlighting the importance of platelets also under these conditions. Another prominent role is their contribution to fighting intravascular infections. Further, they also contribute to different types of liver damage, including fatty liver and MASH as well as tissue restoration following hepatectomy. These findings suggest that antiplatelet therapy might be a useful treatment alternative for some of these diseases.

Indeed, there have been clinical trials evaluating the impact of antiplatelet therapy on sepsis, e.g., a small Brazilian study evaluated if ASA treatment would reduce organ dysfunction in septic patients. Unfortunately, the study had to be stopped prematurely because of a significant number of major bleedings in the treatment group. Further, the authors did not report a difference in Sequential Organ Failure Assessment (SOFA) score.¹⁰⁴ On the other hand, a retrospective cohort study investigating the impact of P2Y12 inhibition with clopidogrel in patients with *S. aureus* bacteremia found significantly reduced mortality.¹⁰⁵ Also for certain liver diseases there have been trials to evaluate the effect of antiplatelet therapy, e.g., a placebo-controlled phase 2 trial run at a hospital in Boston found that aspirin significantly reduced relative hepatic fat content in MASLD patients after 6 months of treatment.¹⁰⁶ Although some of these results are encouraging, bleeding and timing are major concerns as, e.g., in sepsis platelets seem to play a dual role: beneficial at early stages, detrimental at later time points. The ideal drug would therefore selectively target only certain aspects of platelet functions while sparing hemostasis. Thus, more basic as well as clinical research is needed to understand which molecule would make a promising candidate.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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