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REVIEW

The Crucial Roles of Platelets as Immune Mediators in Sepsis

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Abstract: Sepsis is a life-threatening disease characterized by organ dysfunction resulting from a dysregulated host response to infection, potentially progressing to septic shock. Decreased platelet count and platelet dysfunction serve as crucial clinical markers for assessing the severity and prognosis of sepsis. Historically, platelets have been recognized primarily for their role in hemostasis and thrombosis. However, researches have increasingly demonstrated their significant involvement in innate immunity, contributing to the inflammatory response and coagulation dysfunction in sepsis, mediating sepsis-related complications. The mitigation of the inflammatory response and the suppression of immune mediator release can be achieved through the inhibition of platelet activation, thereby underscoring the therapeutic potential of antiplatelet therapy in ameliorating sepsis. This paper systematically discusses the role of platelets in sepsis, from pathological mechanisms to therapeutic targets, integrating cutting-edge research advances and clinical practice needs to provide a theoretical foundation and translational direction for precision treatment of sepsis.

Keywords: platelets, sepsis, coagulation, inflammatory, antiplatelet therapy

Introduction

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] Infections at localized sites can be triggered by bacteria, fungi, and viruses, activating the immune response. Sepsis ensues when the anti-inflammatory reaction is overwhelmed by an excessive systemic proinflammatory response.[2] The pathogenesis of sepsis is complex. The inflammatory response triggered by infection can activate host immune cells, leading to the release of various inflammatory mediators such as cytokines and chemokines.[3,4] These inflammatory mediators can cause damage and leakage of vascular endothelial cells, leading to circulatory disorders and multiple organ failure. In addition, the activation of immune cells can induce the coagulation system to release platelets and coagulation factors, forming blood clots and exacerbating the inflammatory response, ultimately leading to organ dysfunction and death.[5,6] Significant progress has been made in the treatment of sepsis; however, its prevalence remains high and is expected to continue increasing as the population ages.[7]

Initial research on platelets primarily focused on their hemostasis. However, more recent studies have uncovered its key players in inflammation and immune regulation, particularly in sepsis.[8] Platelet count is an important biomarker for sepsis and helps assess the severity of diseases associated with platelet activation and depletion.[9] During sepsis, platelet activation is continuously stimulated due to ongoing coagulation cascades, inflammatory responses, and endothelial damage. Activated platelets interact with monocytes, endothelial cells, neutrophils, T cells, and B cells through adhesion molecules and the secretion of cytokines, synergistically amplifying inflammatory responses, endothelial damage, immune dysregulation, and coagulation dysfunction.[8] Particularly, platelets have been associated with organ dysfunction in sepsis, including damage to the lung, renal, and liver, and contributing to disseminated intravascular coagulation and

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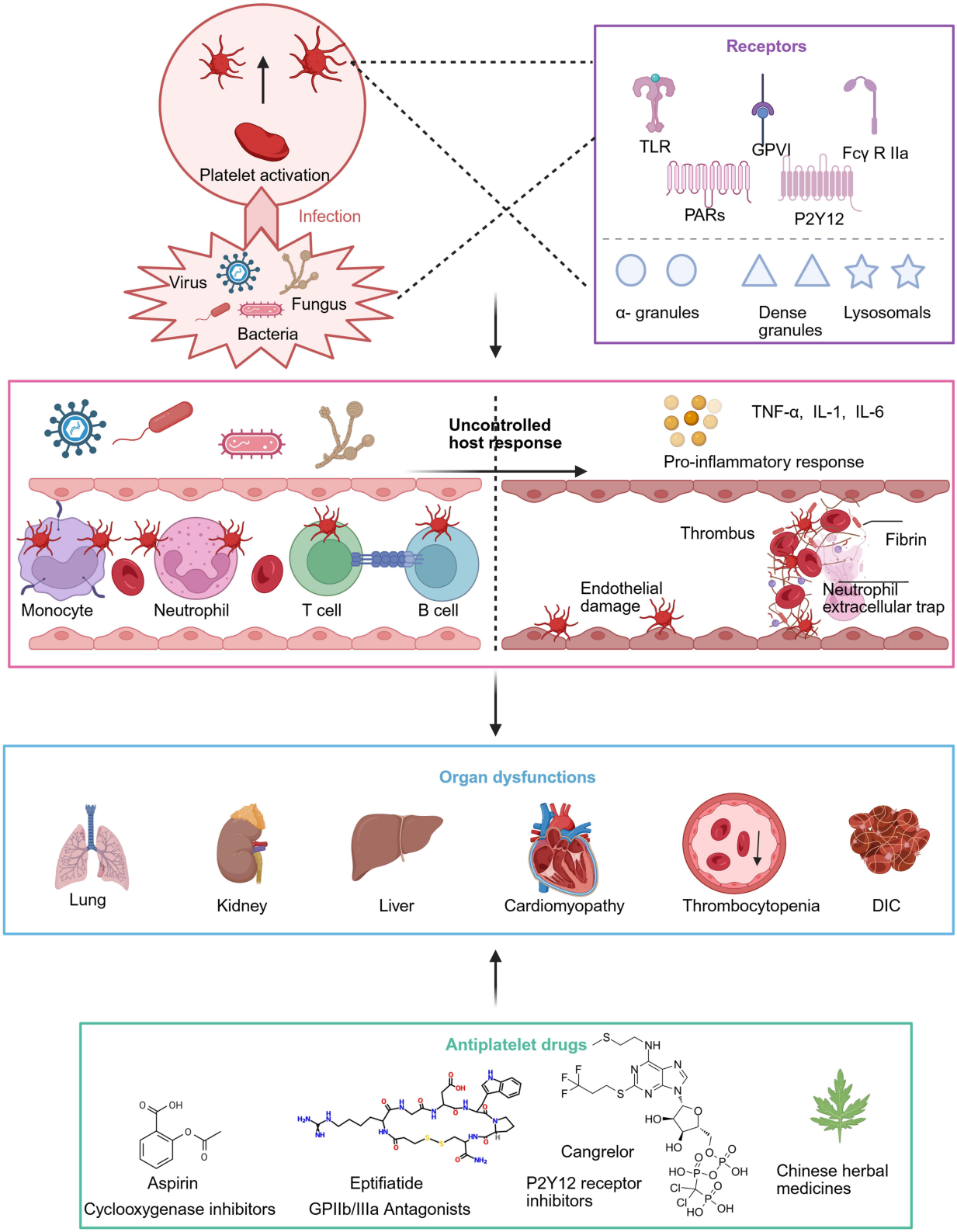
Graphical Abstract



cardiomyopathy.[10] Consequently, this review comprehensively analyzes the multifaceted role of platelets in sepsis and evaluates the therapeutic implications of antiplatelet therapy in sepsis.

The Activation of Platelets in Sepsis

Receptors on the Platelets Surface

Platelets are the smallest non-nucleated cell components in the blood circulation, with 2–4 μm diameter. Platelets are derived from megakaryocytes in the bone marrow and circulate in blood for 7–10 days in humans. Their surfaces are studded with various receptors (Table 1), such as hemostatic receptors (glycoprotein IIb/IIIa [GPIIb/IIIa] and glycoprotein Ib [GPIb]), prostaglandin receptors (thromboxane [TXA2]), G-protein-coupled receptors (like protease-activated receptors 1 and 4 [PAR-1 and −4], and purinergic receptors P2Y1 and P2Y12), and immune receptors (including FcγRIIa, toll-like receptors [TLRs], and C-type lectin-like receptor 2 [CLEC-2]). As shown in Table 1, these receptors play key roles in platelet activation and aggregation during sepsis.[11] In addition, when pathogens invade, these receptors are activated, triggering signaling pathways that lead to platelet activation. Activated platelets release various substances, including cytokines and chemokines, which can attract and activate other immune cells, such as neutrophils and monocytes, thereby enhancing the inflammatory response.[12]

Pathogen Interaction with Platelet

During the pathology of sepsis, platelets are the first to respond to injury and can be rapidly activated by pathogens.[31] Studies have shown that pathogens and their products directly or indirectly activate platelets through various mechanisms, thereby exacerbating the systemic inflammatory response and coagulation dysfunction.[32] Bacteria are the most common pathogens that interact with platelets. Many receptors on platelets can bind to bacteria in different ways. Studies

Table 1 Receptors on the Platelet Surface

Receptors on the Platelet Surface	Characteristic	Function	Reference
GPIIb/IIIa	The platelet-specific fibrinogen receptor, a member of the integrin family of cell adhesion molecules	Mediates fibrinogen binding to platelets, leading to thrombosis and contributing to platelet activation.	[13,14]
GPIb	Von Willebrand factor (vWF) Present in a complex with both GPIX and GPV	Mediates platelet adhesion to matrix-associated vWF under high shear force conditions, which induces platelet aggregation and activation.	[15–17]
GPVI	A glycoprotein receptor on the surface of platelets	Mainly binds to collagen, promoting platelet activation and coagulation, and involved in thrombosis. Diminished platelet function in response to GPVI may be an early event in the development of sepsis and disease progression.	[18–20]
P2Y1 and P2Y12 receptors	G protein-coupled receptors are expressed on platelet membranes	P2Y1 is linked to the Gq protein, which, upon activation, induces platelet shape alterations and a mild, temporary aggregation. P2Y12 is associated with the Gi protein, whose activation triggers platelet aggregation and enhances granule release, thereby regulating inflammation in sepsis.	[21,22]
PARs	G protein-coupled receptor family, of which family member PAR1 is the primary cell surface receptor responsible for thrombin-mediated aggregation of human platelets	Involved in platelet activation, aggregation, and thrombus formation, it plays a crucial role in the coagulation-inflammation crosstalk in sepsis and is a key target for antithrombotic drugs.	[23,24]
Fcγ R IIa	Superfamily receptors that bind the FC antibody fraction Unique FcR on the platelets	Combined with the pathogen-bound IgG, inducing platelet activation and involved in the immune thrombocytopenia	[25–27]
TLRs	Major TLR 2 and TLR 4	Involved in pathogen-platelet interactions and inducing platelet activation. In sepsis, platelets may be activated by TLR, causing microvascular thrombosis.	[28,29]
CLEC 2	Pathogen recognition receptor	Drives platelet aggregation and coagulation, while regulating immune cell trafficking and inflammation in sepsis	[30]

have shown that the *Staphylococcus epidermidis* fibrinogen-binding protein serine aspartate repeat protein G directly binds to GPIIb/IIIa.[33]

Meanwhile, Lipopolysaccharide (LPS) from *Escherichia coli (E. coli)* can bind TLR4 to induce platelet activation.[34] More commonly, bacteria bind to platelet receptors indirectly via plasma proteins. For example, *Staphylococcus aureus* (*S. aureus*) expresses proteins that bind fibrinogen, which in turn binds to GPIIb/IIIa, triggering the platelet activation cascade.[35] Additionally, products such as toxins secreted by bacteria can activate platelets, and the alpha toxin released by *S.* aureus leads to systemic platelet aggregation, a key causative factor in *S. aureus* sepsis.[36]

Biological Behavior of Platelets After Activation

The activation of platelets in sepsis is a complex and dynamic process (Figure 1). Platelets rapidly change shape and release bioactive molecules containing platelet particles (α-granules, dense granules, and lysosomes) when activated by pathogens in sepsis.[37] Dense granules, abundant in Adenosine diphosphate (ADP), play a crucial role in intensifying platelet activation and fostering platelet aggregation through activating P2Y1/P2Y12 receptors. Meanwhile, α-granules release P-selectin, which binds to the P-selectin glycoprotein ligand (PSGL-1) on leukocytes, triggering the activation of immune cells and the formation of platelet-leukocyte aggregates (PLAs). These interactions span the coagulation and immune systems, contributing to microvascular thrombosis and systemic inflammatory in sepsis.[38]

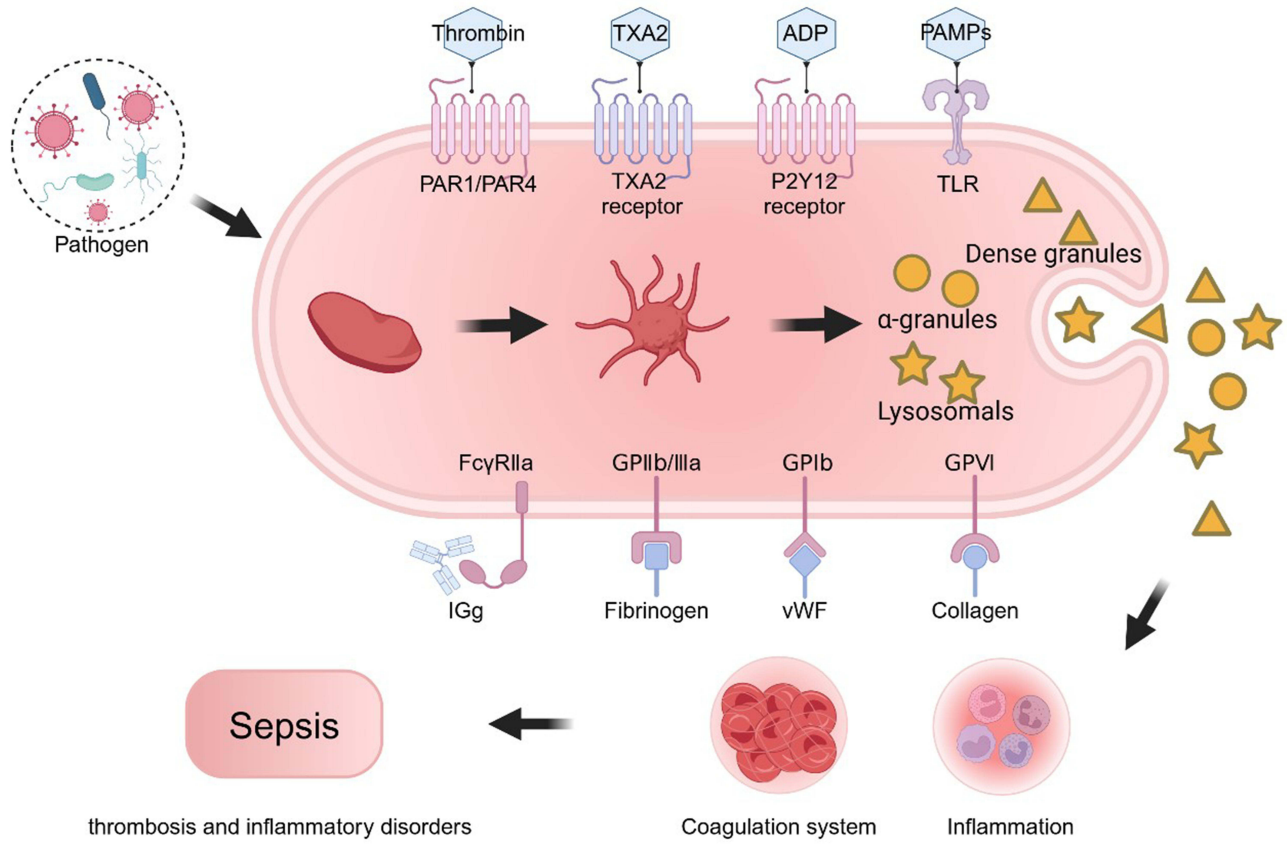


Figure 1 The activation of platelets in sepsis When pathogens (such as bacteria or viruses) invade, various receptors on the surface of platelets (such as TLR, PAR, FcγRIIa, etc.) are activated, recognizing and responding to these pathogens. Then platelets change from a resting state to an activated state and lead to the release of many bioactive molecules encapsulated in platelet granules (α-granules, dense granules and lysosomes), including coagulation regulators, growth factors and adhesion molecules. These have a wide range of interactions with both the coagulation and immune systems and are implicated in sepsis-induced coagulation disorders and inflammatory dysfunction during sepsis. Created in BioRender. tiantian, l. (2025) https://BioRender.com/gyjso0r.

The Dynamic Network of Platelet-Immune Cell Interactions

Platelets and Monocytes

In the context of sepsis, platelets can bind to monocytes, leading to the formation of platelet-monocyte aggregates (PMAs).[39] PMAs are sensitive markers of platelet activation.[40] They are clinically significant in sepsis. In the clinical setting of sepsis, the amount of PMAs is significantly greater than that in age- and sex-matched non-septic systemic inflammatory response syndrome patients. Increased circulating PMAs are associated not only with increased morbidity and mortality but also with thromboembolic complications in septic patients.[41] Moreover, increased PMAs formation and the synthesis of proinflammatory cytokines like Interleukin-6 (IL-6) and Interleukin-18 (IL-18) can predict mortality in older septic patients.[42] PMAs in serum play a crucial role in mediating the relationship between platelet activation and inflammatory responses. Huang et al[43] demonstrated that serum PMAs levels were significantly higher in sepsis patients with acute respiratory distress syndrome (ARDS) compared to those without ARDS, confirming the utility of PMAs as a valuable indicator for diagnosing sepsis with ARDS. Therefore, providing insights into the mechanistic and physiological implications of platelet-monocyte interactions can lead to new targets for treating sepsis.

Platelets and monocytes can engage in interactions via the P-selectin-PSGL-1, leading to monocyte extravasation and macrophage differentiation.[44] Additionally, P-selectin on activated platelets rapidly triggers the exposure of tissue factor (TF) on monocytes, promoting intravascular coagulation.[45] (Figure 2A) Additionally, monocytes exert a significant influence on platelets through the podoplanin–CLEC2 axis. Studies have shown that the podoplanin–CLEC2 axis plays

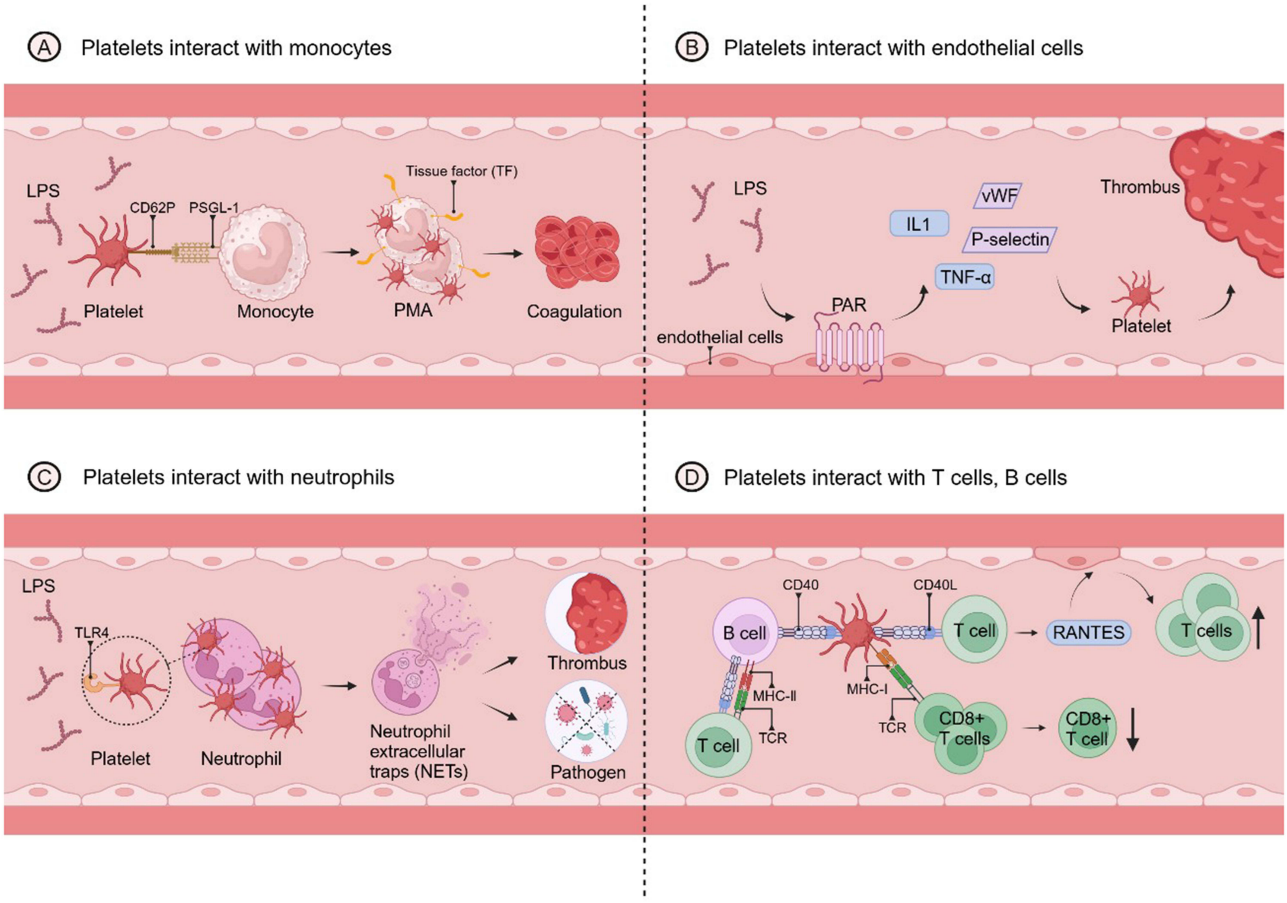


Figure 2 The dynamic network of platelet-immune cell interactions. (**A**) Platelets interact with monocytes: Platelets bind to monocytes via CD62P and PSGL-1, leading to monocyte activation and the expression of tissue factor, which plays a role in coagulation. (**B**) Platelets interact with endothelial cells: LPS activates PARs on the surface of endothelial cells, promoting platelet activation and releasing vWF, TNF-α, and IL-1, which act together to form thrombi. (**C**) Platelets interact with neutrophils: Platelets bind to neutrophils via TLR4, causing the formation of neutrophil extracellular traps, which can trap pathogens and contribute to thrombus formation. (**D**) Platelets interact with B cells through CD40 and CD40L and with T cells through MHC-I and TCR. This interaction leads to the activation of CD8+ T cells and the release of RANTES, influencing T cell activity. Created in BioRender. tiantian, l. (2025) https://BioRender.com/sg5v1qn.

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a beneficial role in a mouse sepsis model, and inhibiting the activation of this pathway can suppress the progression of inflammation.[46]

Additionally, platelet activation releases a variety of chemokines that attract monocytes to migrate to the site of inflammation. For example, platelets release platelet factor 4 (PF4), which binds to C-C Chemokine Receptor Type 1 (CCR1) and participates in monocyte migration.[47] The large amounts of PF4 released by platelets can also enhance monocyte phagocytosis by activating phosphoinositide-3-kinase, Spleen Tyrosine Kinase, and p38 Mitogen-Activated Protein Kinase (MAPK). Research has also shown that PF4 synergistically interacts with Interleukin-4 to differentiate monocytes into a unique class of antigen-presenting cells (APCs) with distinct phenotypic and functional characteristics. These cells promote pathogen clearance through antigen presentation while inducing only moderate cytokine responses.[48] Platelets can also release high mobility group box 1 protein (HMGB1), which active monocytes. Moreover, studies have demonstrated that platelet-neutrophil interactions can recruit inflammatory monocytes to the site of injury. For example, heterodimers of platelet-derived C-C Motif Chemokine Ligand 5 (CCL5) and neutrophil-secreted human neutrophil peptide 1 (HNP1) promote monocyte recruitment, and these heterodimers mediate monocyte adhesion via C-C Chemokine Receptor Type 5 (CCR5).[49] In summary, activated platelets regulate the phenotype and immune function of monocytes through the release of soluble mediators and surface receptor interactions, thereby influencing the inflammatory response in patients with sepsis.

Platelets and Endothelial Cells

Under physiological conditions, platelets do not adhere to undamaged endothelial cells (ECs). However, during sepsis, ECs are faced with substantial damage, and platelets adhere to the damaged endothelium, which undermines the endothelial barrier function, amplifying inflammatory and procoagulant responses, and ultimately leading to multiorgan dysfunction.[50,51] Typically, vascular endothelial cells are covered with a structure known as the glycocalyx. This structural domain contains core proteins (such as proteoglycans and glycosaminoglycans) and plasma proteins (like albumin and antithrombin), which are essential for antithrombotic and reduced endothelial-platelet interactions.[52] During sepsis, the glycocalyx dissociates, leading to increased endothelial permeability and exacerbating endothelial dysfunction, which in turn contributes to the development of sepsis complications. Meanwhile, adhesion molecules on the endothelial cell surface become exposed, such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and P-selectin. These structural changes promote the adhesion of white blood cells and platelets, thereby upregulating the interaction between inflammatory cells and the clotting process.[53] In the early stages of sepsis, inflammation triggers endothelial cells to express high levels of ICAM-1. However, as the disease progresses, thrombin-stimulated platelets release large amounts of PMP, which transfers miR-233 to endothelial cells, thereby reducing ICAM-1-dependent vascular inflammation. This complex process provides new insights into the treatment of sepsis.[54]

Endothelial cell-platelet interactions can be facilitated by cell surface receptors as well as adhesion proteins and occur through a variety of mechanisms. During sepsis, components of the bacterial cell wall activate pattern recognition receptors (PARs) on the surface of endothelial cells, leading to the production of cytokines (Interleukin-1 [IL-1] and Tumor necrosis factor-α [TNF-α]), increasing the expression of adhesion factors (vWF and P-selectin), and affecting platelet activation and aggregation[55] (Figure 2B). vWF plays a key role in hemostasis and thrombosis, bridges activated platelets and endothelial cells, and serves as a marker of endothelial injury and thrombosis risk in sepsis.[56] Activated platelets and endothelial damage during sepsis lead to elevated levels of vWF, which can bind to glycoprotein Ib-IX-V and exacerbate endothelial permeability.[57] Additionally, P-selectin expressed on activated endothelial cells and platelets binds to PSGL-1 on leukocytes, driving their recruitment to sites of infection and inflammation. In addition, platelets interact with endothelial cells via CD62P/CD40L, synergizing with the pathogen DNA-activated cyclic GMP-AMP Synthase and stimulator of interferon genes (cGAS-STING) pathway to jointly drive endothelial inflammation, leukocyte infiltration, and microthrombus formation. Targeting these key links may break the vicious cycle of imbalance between inflammation, coagulation, and immunosuppression, providing new directions for clinical intervention.[58] Banka et al[59] found that targeting micrometer-sized polymer particles successfully reduced platelet adhesion to inflammatory endothelial cells in a mouse model of in vitro blood stream and in vivo LPS-induced systemic inflammation, which in turn

attenuated thrombotic inflammation. Therefore, the results of this study may lead to the identification of a therapeutic target for treating sepsis-induced thrombosis.

Platelet-Neutrophil Collaboration

As the most abundant leukocyte population in the human body, neutrophils play a crucial role in the innate immune response to infections.[60] The interaction between platelets and neutrophils is orchestrated by their surface and secretory molecules. When sepsis occurs, activated platelets express CD62P, which binds to PSGL-1, mediating neutrophil tethering and rolling and participating in the inflammatory response. Moreover, GPIb can bind directly to the integrin αMβ2 (also known as Mac-1 or CD11b/CD18) on neutrophils, activating TF release from these cells and promoting thrombin generation. GPIb can interact with fibrinogen to stabilize intercellular adhesion.[61] Additionally, activated platelets release various chemokines that activate neutrophils, including PF4, neutrophil-activating peptide-2 (NAP-2), platelet-activating factor (PAF), and RANTES (regulated upon activation, normally expressed, and possibly secreted by T cells). PF4 and NAP-2 both stimulate neutrophil adhesion, chemotaxis, degranulation, and ROS production.[62] These receptors and chemokines are involved in the formation of neutrophil extracellular traps and the activation of platelets.

Neutrophil extracellular traps (NETs) are extracellular reticular chromatin structures of neutrophil origin consisting of extracellular DNA networks modified by histones, myeloperoxidase and elastase. Platelets can drive NETs in various ways, playing a crucial role in the progression of sepsis. At the earliest, Clark et al[63] found that plasma from patients with severe sepsis induced TLR4-dependent platelet-neutrophil interactions that led to NETs. Nets can capture and kill pathogens, and to some extent, can also affect thrombin production. Excessive nets lead to microthrombosis and organ damage.[64,65] (Figure 2C) The latest research found that sepsis-derived calcineurin (S100A8/A9) plays a crucial role in triggering platelet pyroptosis through the TLR4 pathway. This process releases oxidative mitochondrial DNA and promotes the formation of NETs. NETs then release more S100A8/A9, creating a positive feedback loop that amplifies pro-inflammatory cytokine production.[66] Additionally, other pathways are involved in triggering the release of NETs. Platelets initiate extracellular signaling in neutrophils through GPIb and Mac-1 binding, inducing the release of NETs.[67] Additionally, platelets may promote NETs formation through exosomes and the formation of platelet-neutrophil complexes (PNCs) in sepsis. Exosomes act as carriers of nucleic acids, proteins, and signaling molecules under both physiological and pathological conditions, promoting inflammation and organ damage by mediating intercellular communication.[68] Recent studies have shown that HMGB1 and/or miRNAs derived from platelets induce the activation of the Akt (Protein kinase B) /mTOR (The mechanistic target of rapamycin) -related autophagy pathway in neutrophils by binding to TLR4 on these cells and activating PKG-dependent ROS production, thereby triggering the formation of NETs.[69] Monitoring HMGB1 levels in platelets may provide new insights into the treatment of sepsis. PNCs act as a bridge between inflammation and coagulation, recruiting platelets and neutrophils to the site of injury, further promoting their activation, promoting neutrophil release of NETs, and providing a scaffold for platelet adhesion. This positive feedback pathway promotes systemic inflammation and coagulation.[70] It is worth noting that platelet STING, an endoplasmic reticulum-associated sensor protein, plays a crucial role in the inflammatory response to PAMPs during infection. It is involved in platelet activation and the formation of NETs, exacerbating sepsis-induced thrombosis. Yang et al[71] found that the activation of platelet STING is a key factor in sepsis-induced pathology, and the absence of STING in platelets prevents the formation of NETs during sepsis. Targeting the interaction between STING and STXBP2 may be a potential therapeutic intervention for sepsis-induced thrombosis. In addition to this, it has been demonstrated that increased production of NETs is associated with mortality and severity of septic shock.[72] Therefore, a deeper understanding of the role of NETs in the disease can be more effective in stopping the progression of the disease.

Platelets and Adaptive Immunity

T cells are lymphocytes that enable the host to fight against pathogens. In sepsis, the numbers of CD8+ T cells are reduced. The functional response of these patients is also impaired, increasing the risk of secondary infections and adverse outcomes.[73] Platelets express molecules like CD40L and major histocompatibility complex (MHC-I), which can interact with CD40 and T cell receptors (TCRs) on T cells. This interaction can lead to the activation of T cells, influencing their function and response during sepsis (Figure 2D). CD40L on platelets binds to CD40 on T cells, leading

to the release of RANTES. RANTES binds to endothelial cells, facilitating the recruitment of T cells and further amplifying the immune response. Additionally, the expression of MHC-I on platelets and their ability to cross-present antigens are significantly increased during sepsis. This interaction is crucial for modulating the immune response. Li et al[74] identified a novel mechanism by which platelets interact with antigen-specific CD8+ T cells via MHC-I, thereby reducing the numbers and functions of CD8+ T cells in vivo, which affects the immune response (Figure 2D).

As a bridge to the adaptive immune system, B cells are another key player in adaptive immunity and differentiate into antibody-producing plasma cells during secondary immune responses. They are also crucial in antigen presentation and participate in immune regulation by secreting cytokines. Platelet CD40L can induce isoform switching in B cells and enhance CD8+ T-cell responses. The interaction between platelets and B cells is also closely associated with CD40/CD40L.[75] Additionally, platelets can induce B cell differentiation through interactions with monocytes. They can directly bind to B cells, promoting their activation and differentiation, and subsequently secreting a large number of cellular molecules involved in immune responses. In the early stages of sepsis, the number of monocytes and B cells increases, enabling them to recognize and phagocytose various invading pathogens, thereby reducing the risk of sepsis.[76] Research has found a negative correlation between platelets, monocytes, and B cells. Therefore, thrombocytopenia may increase the number of monocytes and B cells, alleviating the immune suppression caused by sepsis. They primarily interact with platelets through the CLEC signaling axis, thereby regulating the genetic association between platelets and sepsis.[77] Unlike previous studies, this research confirmed the protective effect of platelets against sepsis. However, the observational data were only obtained from European populations, and further studies are needed to closely monitor the dynamic changes in platelets, monocytes, and B cells in the early stages of sepsis to identify potential targets for prevention and treatment.

Platelet-Mediated Organ Damage in Sepsis

Sepsis can cause damage to many organs, which are closely related to platelets (Figure 3). There is increasing evidence that the platelet count is closely associated with the severity and prognosis of sepsis, suggesting that it plays a crucial role in the pathophysiology of this condition. Platelet count is also one of the components of the Sepsis-related Organ Failure Assessment score, which evaluates the severity of organ dysfunction in critically ill patients.[78]

Thrombocytopenia

Thrombocytopenia (TCP) is a prevalent condition among patients diagnosed with severe sepsis in intensive care units, with an incidence of up to 55%. TCP is defined as a decreased platelet count.[79] Sepsis-associated thrombocytopenia (SAT) is an essential indicator of disease severity.[80] Recent studies have suggested that thrombocytopenia during sepsis may be due to changes in thrombopoiesis and endothelial dysfunction.[81] Pathogens associated with sepsis and their secretions damage the vascular endothelium, triggering the activation of platelets. Platelets adhere to the damaged endothelium, affecting the coagulation system and leading to massive platelet depletion.[82] In addition, elevated platelet reactivity is noted in the initial phases of sepsis, where activated platelets aggregate with leukocytes to form PLAs. PLAs facilitate the release of platelets, which then activate neutrophil NETs. The activation of NETs contributes to TCP by consuming platelets in the process.[83] Furthermore, TCP is associated with the presence of antiplatelet autoantibodies, suggesting that platelets may be phagocytosed during sepsis, resulting in increased consumption.[10] Moreover, interleukin-18 and interleukin-35 are inversely associated with decreased platelet levels in sepsis and may play essential roles in the pathogenesis of TCP in sepsis patients.[84] Therapeutic strategies aimed at modulating these cytokines may help manage TCP and reduce the severity of sepsis.

Acute Lung Injury

Sepsis is the most common cause of ARDS, which occurs in 40% of patients with sepsis or septic shock.[85] ARDS is characterized by an increased alveolar capillary permeability, pulmonary edema and severe hypoxemia.[86] Experimental and clinical observations have revealed that platelets are effector cells in ARDS. Multiple studies have demonstrated that interactions between platelets and white blood cells result in increased alveolar capillary permeability and the accumulation of protein-rich alveolar edema fluid in sepsis.[87] For example, increased platelet-neutrophil polymers lead to

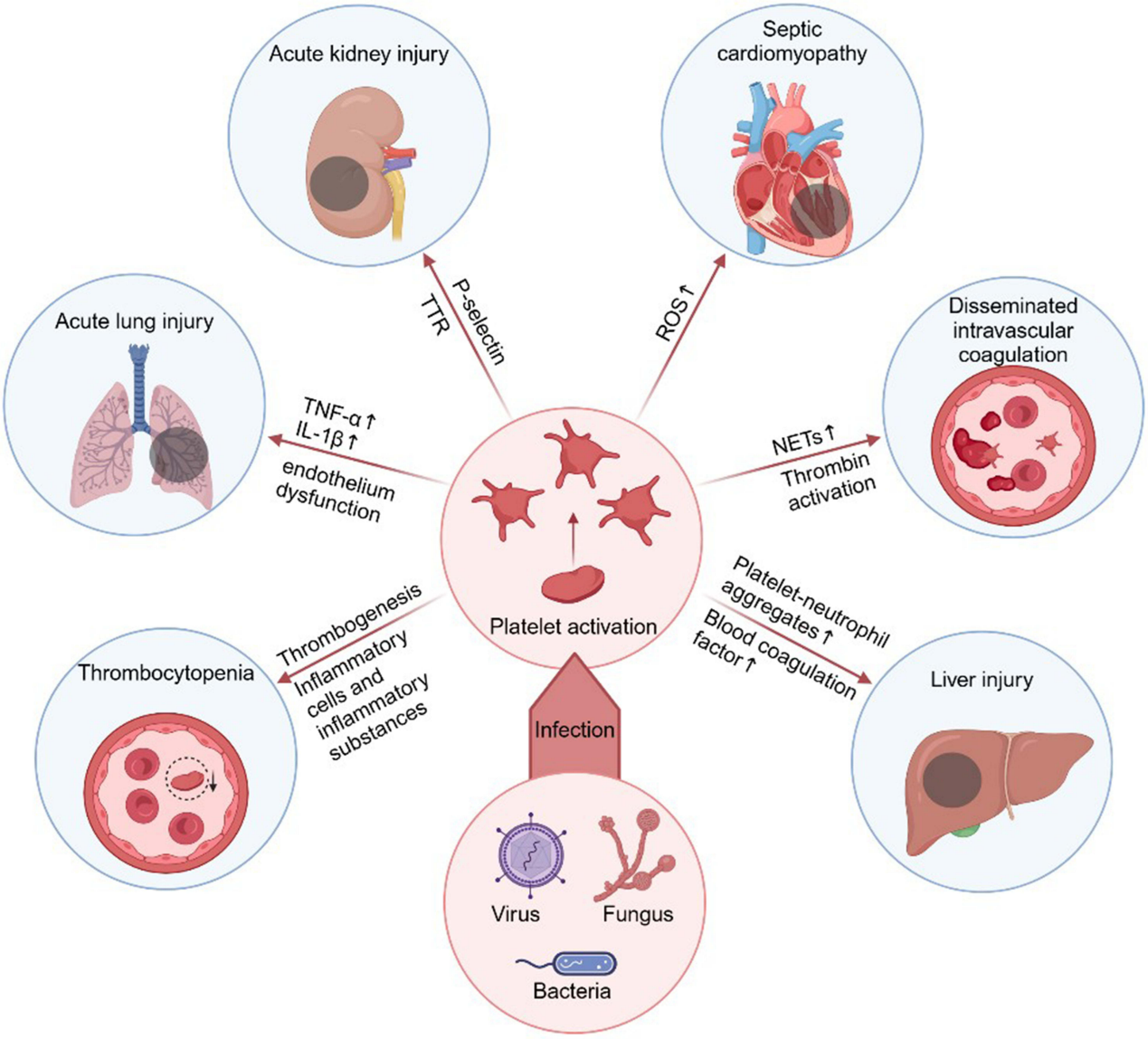

Figure 3 Platelet-mediated organ damage in sepsis During sepsis, platelets can be activated by pathogens. Activated platelets interact with immune cells, releasing inflammatory and coagulation factors that mediate organ damage. Acute kidney injury is associated with P-selectin and transport proteins. Septic myocarditis is related to ROS. Disseminated intravascular coagulation is associated with thrombin activation and increased neutrophil extracellular traps. Liver injury is associated with platelet-neutrophil aggregation and increased coagulation factors. Thrombocytopenia is related to thrombosis and inflammatory cells and substances. Acute lung injury is associated with endothelial dysfunction and increased levels of TNF-α and IL-1β. These mechanisms of organ damage interact through various inflammatory and coagulation pathways, leading to complex. Created in BioRender. tiantian, l. (2025) https://BioRender.com/ c2uncmd.

increased pulmonary vascular permeability, and circulating leukocytes and platelets also cause endothelial damage by producing barrier destabilizing factors and proinflammatory signaling factors such as TNF-α and platelet-activating factor, which lead to pulmonary edema and hypoxemia.[88] Hong et al[89] found that endothelial PPARδ knockdown activated STAT1 (signal transducer and activator of transcription 1), which significantly increased C-X-C Motif Chemokine Ligand 10 (CXCL10) expression in ECs. Targeting CXCL10 signaling can reduce vascular injury and lung inflammation in acute lung injury. Middleton et al[90] demonstrated an elevated concentration of platelet-specific α-granulin in alveolar lavage fluid from patients. The elevated levels of PF4 released from α-granulin were particularly pronoun. Reducing PF4 levels in systemic circulation and lung tissue protects lung function.

Acute Kidney Injury

Acute kidney injury (AKI) is a common complication in patients with sepsis.[91] Sepsis accounts for 45–70% of all AKI cases in critically ill patients.[92] Activated platelet aggregation may lead to thrombosis in the renal microcirculation, resulting in renal damage.[93] Sepsis-induced platelet activation drives AKI by inducing P-selectin-mediated recruitment of neutrophils to the kidney. This recruitment is crucial for neutrophil-mediated renal failure following acute ischemia. It has been shown that kidney morphology is protected by inhibiting neutrophil infiltration.[94] Recently, several researchers have proposed a new model suggesting that sepsis-associated kidney injury (SA-AKI) results from inflammatory damage and adaptive responses of renal tubular cells to pathogen-related molecular patterns.[95] Additionally, Lv et al[96] reported that platelet-derived thyroxine transporter protein (TTR), which further induces apoptosis in renal cells, plays a crucial role in SA-AKI.

Liver Injury

Sepsis-associated liver injury (SALI) is a common disease in critically ill patients. Mortality rates of 54–68% are greater in sepsis patients with hepatic insufficiency or failure than in those with pulmonary insufficiency or failure.[97] The liver plays a crucial role in immune and metabolic responses to sepsis.[98] Platelet activation is closely related to liver injury in sepsis. During fatal sepsis, *S. aureus* α-toxin concomitantly alters platelet activation and promotes neutrophil inflammatory signaling by interacting with its cellular receptor A Disintegrin And Metalloproteinase 10 (ADAM10). Platelet toxicity hinders endothelial barrier repair and encourages the formation of harmful platelet-neutrophil aggregates, leading to liver injury.[36] Additionally, it has been found that Gaucocalyxin A (GLA) prevents acute liver dysfunction caused by *E. coli b*y inhibiting platelet activation, which is achieved by decreasing the surface expression of the complement component 3a receptor (C3aR), thereby protecting the liver from damage caused by excessive complement activation.[99] This is a novel therapeutic agent for the control of sepsis-associated hepatic dysfunction.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is a common life-threatening complication of sepsis, which is closely associated with platelet activation and is a key factor contributing to high mortality in sepsis patients.[100] During sepsis, activated platelets promote the formation of NETs, leading to intravascular coagulation. Neutralization of histone H4 in NETs significantly attenuated intravascular coagulation and microvascular dysfunction.[101] In addition, activated platelets release procoagulant factors such as vWF and PF4, which can facilitate platelet aggregation and promote microthrombosis.[102]

Certain specific markers of platelet activation (soluble trem-like transcript-1 [sTLT-1] and nerve injury-inducible protein 1 [NINJ1]) are closely associated with DIC. sTLT-1 is a receptor expressed only by platelets and megakaryocyte lineages. It moves to the platelet surface upon activation by thrombin, collagen, or lipopolysaccharide.[103] Blood levels of sTLT-1 are significantly elevated in patients with sepsis and are thought to correlate with the clinical manifestations of disseminated intravascular coagulation. Additionally, upon platelet death or activation, damage-associated molecular patterns are released from plasma membrane rupture into the circulation, promoting a procoagulant phenotype and thereby facilitating immunothrombosis.[104] This suggests that platelet plasma membrane rupture is strongly associated with the worsening of septic DIC. Zhou et al[105] found that NINJ1, a typical marker of cell death, is expressed in human and mouse platelets. It is closely related to plasma membrane disruption in platelets. Inhibition of NINJ1 can inhibit platelet PANoptosis and delay the progression of DIC in sepsis. PANoptosis is a novel form of cell death triggered by a storm of cytokines. It is present in septic platelets and is closely associated with the onset and progression of DIC.[106]

Not only is DIC associated with hypercoagulability, but due to clotting factor and platelet depletion, DIC also frequently leads to severe bleeding events, further complicating treatment.[100] Therefore, effective treatment should address both the inhibition of excessive coagulation system activation and the preservation of proper coagulation function to prevent severe bleeding complications.

Sepsis Cardiomyopathy

Septic cardiomyopathy (SCM) is a serious complication and one of the main causes of death in sepsis, which directly affects the prognosis of septic patients.[107] Platelet-derived exosomes contain phagocyte-like NADPH oxidase subunits that favor the generation of oxygen free radicals that cause myocardial injury.[108] A study finds that Recombinant Human Thrombopoietin (rhTPO) ameliorates myocardial damage and improves inflammatory markers in patients with sepsis.[109] rhTPO has been found to improve inflammatory markers and reduce myocardial injury, offering a potential therapeutic approach for SCM.[110]

Antiplatelet Drugs and Sepsis

Numerous bacterial components and inflammatory mediators abnormally activate platelets in sepsis. As mentioned above, platelet activation can lead to thrombocytopenia, DIC, liver injury, and lung injury in sepsis patients. Antiplatelet therapy can reduce the inflammatory response in patients with sepsis, improve microcirculatory dysfunction, and some drugs can reduce mortality. However, it may increase the risk of bleeding, and its clinical efficacy remains unclear. Individualized treatment and higher-quality randomized controlled trials are needed (Table 2).

Table 2 Antiplatelet Drugs and Sepsis

Antiplatelet Therapy	Representative Drug	Mechanism	Potential Benefits	Risk	Clinical Stage	References
Cyclooxygenase inhibitors	Aspirin	Inhibit COX, reduce platelet aggregation, and the inflammatory response	Improve microcirculation and organ function	High risk of bleeding and controversial clinical use	Observational study, partial RCT	[111–117]
P2Y12 receptor inhibitors	Clopidogrel	Inhibit P2Y12 receptor and block platelet aggregation	Improve the microcirculation	Unclear risk of bleeding	Small-scale RCT	[118,119]
	Tegretol	Increase the systemic bactericidal action of platelets	Improve blood flow and tissue perfusion	Increased bleeding risk and possible cardiovascular events	Small-scale RCT	[120,121]
GPIIb/IIIa Antagonists	Eptifiatide	Inhibit platelet aggregation by blocking fibrinogen binding to GPIIb/IIIa receptors on activated platelets.	Dual therapy with iloprost and eptifibatide for 48h in patients with septic shock is safe and may even be beneficial	Unclear risk of bleeding	Small-scale RCT	[122]
Chinese herbal medicines	Xuebijing Injection	Increase platelet counts and lower prothrombin time	Multiple synergistic effects, relatively inexpensive, and offer new methods for individualized treatment	Variability in herbal content, contamination risks, and difficulty identifying active ingredients.	Large-scale multicenter RCT	[123]
PAR-4 inhibitors	BMS-986120	Inhibit platelet activation	Reduce the risk of bleeding	Unclear mechanism	Small-scale RCT	[124,125]
TLR4 inhibitors	TAK242	Reduce platelet activation	Alleviate mouse lung and kidney injury	Lack of randomized controlled trials	Preclinical	[126]
Tyrosine kinase inhibitors	Fostamatinib	Regulate downstream signals of GPVI and CLEC-2 to mediate platelet activation	Inhibit the formation of NETs and reduce the lung injury and mortality in septic mice	Clinical trials have not been conducted in sepsis	Preclinical	[127,128]
Leukotriene receptor antagonists	Montelukast	Inhibit excessive platelet activation	Prevention of oxidative pancreatic injury induced by LPS	Lack of randomized controlled trials	Preclinical	[129]
Vasodilator	Prostacyclin	Inhibit platelet aggregation	Improve microcirculation	Hypotension	Small-scale RCT	[130]
FcRIIA signaling inhibitors	IVIg	Mediate pathogen-induced platelet activation	Reduce the mortality of adult sepsis	Low affinity	Small-scale RCT	[131]

Cyclooxygenase Inhibitors

As a representative cyclooxygenase inhibitor, aspirin (ASA) has anti-inflammatory and antiplatelet activities. ASA irreversibly inhibits COXI and COXII enzymes, and this inhibition prevents the conversion of membrane phospholipid-derived arachidonic acid into thromboxane and prostaglandins. In a national cohort study, researchers discovered that ASA has a fascinating dual mechanism of action depending on the dosage used. At the lower 75 mg dose, especially at lower doses, it inhibits COXI more strongly than COXII, thereby preventing platelet activation and aggregation.[132] Additionally, ASA induces the production of a specific lipoxin analog, aspirin-triggered 15-epi-lipoxin A4 (ATL), via COX-2. This lipoxin analog promotes the release of nitrogen monoxide (NO), inhibits the production of IL-8 and Myeloperoxidase (MPO), thereby facilitating inflammation resolution and reducing leukocyte migration.[133] However, excessive inhibition of ATL may lead to the formation of microthrombi. Surprisingly, it can also increase NO production without affecting COX enzymes. NO acts as an anti-adhesive agent, inhibiting leukocyte migration and infiltration through the endothelium, while regulating vascular tone and microthrombosis formation under septic conditions. At the high 200mg dose, which exceeds the serum therapeutic concentration, ASA primarily affects the COX-2 and NF-κB pathways, inhibiting the production of pro-inflammatory factors and chemokines. It also increases ATL production, thereby raising the risk of bleeding.[133] Based on the analysis of the MIMIC-IV database, researchers found that ASA reduced the risk of death in sepsis-associated encephalopathy (SAE),[114] SA-SKI,[115] and SALI,[116] improved sepsis-induced myocardial injury,[117] and did not increase the risk of gastrointestinal bleeding. However, in a Phase 2 randomized controlled trial (RCT), it was found that in critically ill patients diagnosed with sepsis for no more than 48 h and with high severity of illness, ASA did not reduce organ dysfunction and may increase severe bleeding compared to placebo.[134] For SAE patients, those receiving high-dose aspirin (>300 mg/day) exhibited a higher mortality rate compared to the low-dose group (≤300 mg/day). For SA-AKI patients, high-dose aspirin (>300 mg/day) may be superior to traditional low-dose aspirin (≤300 mg/day). For SA-AKI patients, there was no difference in efficacy between high-dose (>81 mg/day) and low-dose (≤81 mg/day) aspirin. However, these results may be due to significant individual differences between the two groups rather than the direct effect of aspirin dosage on specific physiological pathways. Further exploration of the mechanisms of action of aspirin in these conditions is needed. A randomized controlled trial from Australia showed that daily low-dose aspirin (100 mg/day) treatment did not reduce sepsis-related mortality in community-dwelling older adults. The study restricted participation to individuals aged 70 years or older and those without primary medical conditions.[111] Therefore, the potential benefits of ASA in sepsis may vary among patient subgroups, and the risks associated with different doses may also differ. Randomized clinical trials have failed to replicate these results, indicating that baseline patient characteristics and the severity of sepsis strongly influence treatment response. In addition to these observations, Carestia et al[135] reported that ASA could help prevent intravascular coagulation and hepatic dysfunction in *S. aureus*-induced sepsis by limiting neutrophil-mediated microthrombosis. This study offers new insights into how ASA protects against sepsis.

P2Y12 Receptor Inhibitors

P2Y12 receptor is the primary receptor for ADP-induced platelet aggregation. The binding of ADP to the P2Y12 receptor stimulates the release of additional ADP from dense granules. This process enhances platelet aggregation and thrombus formation, further exacerbating microcirculatory disturbances.[21] Clopidogrel and ticagrelor are two representatives of antagonistic platelet agents. In clinical practice, P2Y12 inhibitors are rarely administered alone and are more commonly used in combination with aspirin. A retrospective study found that combined treatment with aspirin and ticagrelor reduced the risk of multiple Staphylococcus-related infections compared with aspirin and clopidogrel or prasugrel.[136] Ulloa et al[121] found that ticagrelor is used as an adjunctive therapy for methicillin-resistant Staphylococcus aureus bacteremia by protecting platelets so that they can perform their role in clearing the infection. This therapeutic effect is not due to direct bactericidal action, but rather to an increase in the systemic bactericidal activity of platelets. However, another study found that P2Y12 inhibitors did not improve the 30-day mortality rate in sepsis-3 patients and increased gastrointestinal bleeding.[137] Therefore, P2Y12 inhibitors are only beneficial for specific sepsis subgroups (*S. aureus* infections). In addition, in a mouse model of intra-abdominal sepsis, clopidogrel inhibits platelet activation, reduces

platelet-leukocyte interactions, and attenuates lung injury.[138] Albayati et al[139] found that clopidogrel targets platelets to control the proliferation and activity of regulatory T cells, leading to altered platelet-regulatory T cell interactions during sepsis, which ameliorated sepsis-induced splenomegaly and splenic injury, and reduced mortality in the Cecal Ligation and Puncture (CLP) model of sepsis. Interestingly, people also get inconsistent results in their studies. In a human model of sepsis caused by intraperitoneal injection of LPS, Thomas et al[140] demonstrated that clopidogrel and ticagrelor inhibited a variety of promoters of inflammation and thrombosis, including IL-6, TNF-α and D-dimer generation. Compared with clopidogrel, ticagrelor also inhibited the prethrombotic changes in the ultrastructure of the fibrin clot. In a model of sepsis induced by LPS or CLP, some groups have observed that clopidogrel and tegretol ameliorated lung injury,[118] renal injury[141] and TCP.[142] In another study, a mouse model of sepsis induced by intraperitoneal LPS injection showed that P2Y12 knockout mice had increased circulating leukocyte counts and plasma cytokine levels, as well as more severe lung injury, compared to wild-type mice.[143] Therefore, sepsis is a complex process with high heterogeneity. Different modeling methods, severity, and stages of sepsis may lead to varying treatment outcomes, suggesting that the application of P2Y12 antagonists should be selective. In addition, although P2Y12 receptor inhibitors have shown promising results in preclinical studies to improve the pathogenesis of sepsis, their bleeding risks are unknown, and a large number of clinical trials will be needed to confirm whether the findings in animals can be applied to humans.

GPIIb/IIIa Antagonists

GPIIb/IIIa (α1b/β3) receptor is a key mediator of platelet aggregation. Its exposure is the final common pathway leading to platelet activation and aggregate formation.[144] GPIIb/IIIa antagonists can exert potent antiplatelet effects by inhibiting the final common pathway of platelet aggregation. AZ-1 is an anti-glycoprotein IIb/IIIa antibody used to inhibit platelet aggregation. In a sepsis model, AZ-1 has been shown to effectively inhibit platelet function, thereby reducing coagulation activation and preventing endothelial cell dysfunction and tissue damage.[145] However, this study was only published in 2001, and no further experimental or clinical studies have been conducted. Additionally, eptifibatide is also a GPIIb/IIIa antibody antagonist used to inhibit platelet activation and aggregation. It has shown promise in the treatment of sepsis, particularly septic shock. In a study, the co-administration of Eptifibatide and iloprost was investigated for its effects on patients with septic shock. The results indicated that this combination therapy could reduce endothelial injury, platelet consumption, and fibrinolytic biomarkers, leading to an improved Sequential Organ Failure Assessment (SOFA) score.[122]

Chinese Herbal Medicines

Chinese herbal medicines (CHMs) can inhibit platelet aggregation, regulate inflammation and the immune response, and improve microcirculation, thereby preventing the progression of sepsis and improving the prognosis of sepsis patients.[146] Currently, CHMs is gradually being accepted in the treatment of sepsis, and the mechanism of traditional Chinese medicine injections in the treatment of sepsis is also being analyzed. For example, Xuebijing Injection reduces inflammatory markers (eg, TNF-α, IL-6) by inhibiting NF-κB and MAPK signaling.[147] Clinical studies have shown that Xuebijing injection reduces the incidence of DIC by increasing platelet counts and lowering prothrombin time, thereby decreasing endothelial damage and improving the short-term prognosis of patients with severe sepsis complicated by DIC.[123] In addition to injections, other CHMs have potential for treating sepsis. Zixue Powder (ZXP) is a traditional Chinese herbal formula with the potential to treat microvascular and infectious diseases. Zhang et al[148] found that ZXP effectively mitigates platelet granule secretion primarily through modulation of the stimulator of interferon genes pathway, consequently impeding NET-associated thrombosis in sepsis. Moreover, it is reported that myristic ethanol extract (MF) has an essential effect on sepsis and SAT. Jeong et al[149] demonstrated that MF treatment significantly reduced the expression of the platelet activation marker P-selectin, inhibited sialidase-mediated platelet desialylation, and alleviated thrombocytopenia and tissue damage. In addition, Curdione is a bioactive sesquiterpenoid compound derived from *Curcuma zedoary*, which is an effective constituent that enhances anti-inflammatory properties and inhibits platelet aggregation, as well as eliminates blood stasis.[150] Yang et al[151] found that it ameliorates sepsis-induced lung injury by inhibiting platelet-mediated neutrophil extracellular trap formation. Although Xuebijing injection has demonstrated benefits in reducing mortality in Chinese RCTs, broader validation in multicenter, international trials is crucial to confirm its role in the treatment of sepsis. Additionally, other CHMs have demonstrated some efficacy in

laboratory and animal models; however, their clinical application remains highly challenging. The active components of CHMs are complex, making it challenging to identify specific active components and their corresponding targets. Furthermore, existing mechanism studies are limited to observable effects (such as reduced inflammatory factors and improved tissue damage), with insufficient research on deeper mechanisms such as immune cell subset regulation and epigenetic modifications. Most studies are still confined to the animal level, and converting promising CHMs into clinical applications remains a significant challenge.

Challenges in the Clinical Translation of Targeted Therapy

Heterogeneity Among Patients with Sepsis

Sepsis is a highly heterogeneous clinical syndrome, primarily manifested in the diversity of etiologies, variations in host immune responses, clinical presentations, and treatment responses. Studies have shown that increased expression of TLR4 on platelets is associated with bacterial models and disease severity in sepsis patients. In Gram-negative bacterial subjects, TLR4 was positively correlated with P-selectin, TNF-α, and LPS, but this phenomenon was not observed in Gram-positive bacterial subjects.[152] Additionally, a retrospective study found that Gram-negative bacteria caused lower platelet count levels and more severe sepsis outcomes compared to Gram-positive bacteria. Therefore, platelet indices may have potential diagnostic and prognostic value in bacterial sepsis.[153] Future studies should consider including a larger number of patients, encompassing those with various pathogens, treatment methods, and outcomes, to gain a deeper understanding of platelet dysfunction in sepsis. Additionally, compared to non-elderly patients, elderly patients exhibit milder coagulation responses and reduced inflammatory responses.[154] These differences, caused by varying pathogens and age, may also impact the practical application of antiplatelet drugs in sepsis, necessitating further research to achieve personalized treatment.

Heterogeneity of Sepsis Models

Prior to hospitalization, the progression of sepsis in patients remains unclear. Therefore, animal models of sepsis are needed to understand the complex pathophysiological processes of sepsis and provide solutions for clinical practice. Various animal models have been developed to study the role of platelets and their receptors in sepsis, such as LPS, bacterial infusion, and CLP. Platelets regulate the pathological processes of sepsis through receptor-dependent and pathogen-dependent mechanisms. For example, LPS from Gram-negative bacteria (such as *E. coli* or *Klebsiella*) stimulates TLR4 on platelets, promoting the recruitment of MyD88 and triggering an inflammatory response. However, platelets lacking MyD88 do not alter this effect.[155] This effect is found to be dependent on human platelets.[156] Gram-positive bacteria primarily trigger sepsis through the combination of lipoteichoic acid and peptidoglycan. The LPS model offers a better understanding of the pathophysiological mechanisms of sepsis; however, it cannot accurately reflect the dynamic process of a live bacterial infection and cannot be directly applied to humans. In contrast, the CLP model is more suitable for simulating human sepsis, reflecting the time course of sepsis in human patients. Early on, thrombocytopenia and increased activation markers can be observed, making it suitable for studying changes and mechanisms in platelet and coagulation responses.[157] However, it primarily uses young animals, while sepsis is more common in elderly patients. Additionally, factors such as age, gender, and differences between humans and mice can influence studies on platelet function in sepsis. Future research could adopt a different approach to develop animal models with greater clinical relevance.

The Dilemma of Bleeding and Clotting

Platelets play a dual role in sepsis, and current research has not yet balanced their pathological and physiological effects. For example, in the early stages of sepsis, antiplatelet drugs inhibit platelet aggregation and thrombus formation. However, in the later stages, excessive inhibition of platelets and a lack of clotting factors can increase the risk of bleeding.[158] In septic DIC patients, the risk of bleeding will increase when using antiplatelet drugs, but the potential benefits may outweigh the risks, with a more significant reduction in mortality. Therefore, mortality benefit predominates in hyperinflammatory/DIC subgroups. Therefore, there remains significant controversy surrounding the use of antiplatelet

therapy, and further research is needed to assess and validate whether antiplatelet drugs improve outcomes in patients with sepsis. These factors limit the clinical translational value of the research results. In the future, it will be necessary to develop models that more closely resemble human pathophysiology.

Future Directions: (1) Development of specific targeted biomarkers (eg single-cell sequencing of platelet subpopulations) (2) Innovative drug development (platelet membrane coated nanoparticles to improve targeting efficiency) (3) Construction of real-time monitoring platform (microfluidic chip integrated detection: platelet function, coagulation status, inflammation level) (4) Design individualized treatment plans (using artificial intelligence to integrate clinical data and dynamically optimize treatment plans).

Conclusion

In sepsis, pathogenic microorganisms bind to various receptors on the surface of platelets, activating them and leading to their interaction with immune cells, endothelial cells, and coagulation factors. This interaction releases inflammatory mediators and activates the coagulation process, ultimately resulting in organ damage. Numerous studies have demonstrated that antiplatelet therapy plays a crucial role in reducing sepsis-related inflammation and mitigating organ damage, suggesting that platelets serve as key mediators of the immune response in sepsis. However, despite the gradually clarified immune-coagulation mechanisms of platelets in sepsis and the validated potential of antiplatelet therapy in animal models, its clinical translation still faces significant challenges. In the future, single-cell multi-omics technology can be utilized to map the interaction patterns of platelets and immune cells in sepsis, and real-time imaging technology can be employed to track the dynamic changes of platelets, thereby facilitating the transition from animal experiments to clinical treatment. Then, patients can be classified based on biomarkers, ultimately achieving personalized treatment targeting platelets.

Abbreviations

GPIIb/IIIa, Glycoprotein IIb/IIIa; GPIb, Glycoprotein Ib; GPVI, Glycoprotein VI; vWF, Von Willebrand factor; TXA2, Thromboxane; PAR-1 and −4, Rrotease-activated receptors 1 and 4; CLEC 2, C-type lectin-like receptor 2; TLRs, Toll-like receptors; LPS, Lipopolysaccharide; *E. coli, Escherichia coli; S. aureus, Staphylococcus aureus*; ADP, Adenosine diphosphate; PSGL-1, P-selectin GP ligand; PLA, Platelet-leukocyte aggregates; PMA, Platelet-monocyte aggregates; IL-6, Interleukin-6; IL-8, Interleukin-18; ARDS, Acute respiratory distress syndrome; TF, Tissue factor; PF4, Platelet factor 4; HMGB1, High mobility group box 1; CCR1, C-C Chemokine Receptor Type 1; CCL5, C-C Motif Chemokine Ligand 5; HNP1, Human neutrophil peptide 1; CCR5, C-C Chemokine Receptor Type 5; ECs, Endothelial cells; ICAM-1, Intercellular adhesion molecule-1; VCAM-1, Vascular cell adhesion molecule-1; PRPs, Pattern recognition receptors; IL-1, Interleukin-1; TNF-α, Tumor necrosis factor-α; CD62P, P-selectin; CD40L, CD40 Ligand; NAP2, Neutrophil-activating peptide-2; NETs, Neutrophil extracellular traps; TLR4, Toll-like receptor 4; S100A8/A9, Sepsis-derived calcineurin; PAMPs, Pathogen-associated molecular patterns; PNCs, Platelet-neutrophil complexes PNCs; MHC-I, Major histocompatibility complex; TCRs, T cell receptors; RANTES, Regulated upon Activation, Normal T Cell Expressed and Secreted; cGAS-STING, cyclic GMP-AMP Synthase and stimulator of interferon genes; TCP, Thrombocytopenia; SAT, Sepsis-associated thrombocytopenia; STAT1, signal transducer and activator of transcription 1; CXCL10, C-X-C Motif Chemokine Ligand 10; AKI, Acute kidney injury; SA-AKI, Sepsis-associated kidney injury; TTR, Thyroxine transporter protein; SALI, Sepsis-associated liver injury; ADAM10, A Disintegrin And Metalloproteinase 10; GLA, Gaucocalyxin A; C3aR, Complement Component 3a Receptor; DIC, Disseminated intravascular coagulation; sTLT-1, soluble trem-like transcript-1; NINJ1, Nerve injury-inducible protein 1; SCM, Septic cardiomyopathy; ROS, Reactive oxygen species; rhTPO, Recombinant Human Thrombopoietin; ASA, Aspirin; COX-1, Cyclooxygenase-1; ATL, Aspirin-triggered 15-epi-lipoxin A4; NO, Nitrogen monoxide; MPO, Myeloperoxidase; SAE, Sepsis-associated encephalopathy; RCT, Randomized Controlled Trial; MF, Myristic ethanol extract; CLP, Cecal Ligation and Puncture; SAT, Sepsis-associated thrombocytopenia; TTR, Thyroxine transporter protein; IL-18, Interleukin-18; IL-35, Interleukin-35; ARDS, Acute respiratory distress syndrome; AKI, Acute kidney injury; SOFA, Sequential Organ Failure Assessment; CHMs, Chinese herbal medicines; ZXP, Zixue Powder; MyD88, Myeloid Differentiation Primary Response Protein 88.

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Author Contributions

All authors made a significant contribution to the paper reported, whether that is in the conception, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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