Review Article

Platelets’ Functionality in Hemostasis, Inflammation, andImmune Response to Infections

ABSTRACT

Platelets play a central role in hemostasis and are increasingly recognized for their critical functions in immune responses and inflammation. This review explores the mechanisms by which platelets contribute to these processes, from their involvement in clot formation and wound healing to their emerging role in modulating immune cell activity during infections. The interaction between platelets and the inflammatory cascade creates a complex inflammation-hemostasis loop, with implications for both acute and chronic disease states. Platelets aggregate at the site of tissue damage, and adhere to the white blood cells, with subsequent release of cytokines and chemokines which are required for targeting lymphocytes, monocytes, and neutrophils to promote inflammation. Similarly, platelets engulf microbes and affect the prognosis of bacterial and viral infections. Recent advances in understanding platelet function during bacterial and viral infections are discussed, with a focus on the therapeutic potential of targeting platelet-mediated pathways in various pathological conditions.

Keywords:Inflammation, Clotting, Immune response, infections

1. INTRODUCTION

The blood consists of the plasma, the cells, and cell fragments called plateletswith each having its distinct functionality [1]. The blood platelets (also known as thrombocyte**s)** are products of fragmented large cells known as megakaryocytes [2], which are produced during haematopoiesis in a sub-process called thrombopoiesis [3].

The cellular processes of thrombopoiesis involve; the commitment of haematopoietic stem cells, proliferation and terminal differentiation of megakaryocytic progenitors, and maturation of megakaryocytes to produce functional platelets [4]. During thrombopoiesis, the myeloid progenitor cells in the bone marrow differentiate to form promegakaryocytes and then into megakaryocytes. The formed megakaryocytes generate and release proplatelets into the cytoplasmic extension upon stimulation by cytokines. The released proplatelets in turn disintegrate into several (in hundreds) platelets that circulate into the blood streams as the remnant of the megakaryocytes is engulfed by macrophages [3].

The production of megakaryocytes and platelets is regulated by the hormone thrombopoietin (produced by the hepatic and renal cells), which stimulates the differentiation of myeloid progenitor cells into megakaryocytes and the eventual release of platelets. The action of thrombopoietin is regulated by a negative feedback mechanism; high blood levels of platelets reduce the synthesis and activity of thrombopoietin, and vice versa [5]. Thrombopoietin is constantly produced in the hepatic cells and the level of circulation is affected by the formation and clearance of circulating platelets, and possibly by the bone marrow megakaryocytes (Kuter, 2020). A range of 5,000 – 10,000 platelets are produced by each megakaryocyte before final cellular depletion, and about 10^{11} platelets are synthesized daily in a healthy adult [6]. Platelets have a lifespan of 5 – 10 days, after which the old platelets are destroyed in the spleen and the liver via macrophages engulfment and Kupffer cells, respectively. About 40% of platelets are reserved in the spleen and are released in severe injury by splenic muscle contraction [7,8].

Platelets are not classified as cells but as fragments of bone marrow cells. They play important roles in the pathological and physiological processes of hemostasis, immune response to infections, inflammation, wound healing, and tumor metastasis[4,9]. This review hereby provides an overview of the structure and roles of platelets in hemostasis, inflammation, and infections.

2. Structure of platelets

Platelets are irregular in shape; they have no nucleus, and they have a diameter ranging from 2-4μm. They are not considered true cells but instead are regarded as cell fragments resulting from the disintegration of giant cells called Megakaryocytes [10]. Platelets are anucleated, and thus lack nuclear DNA but contain mitochondria and mitochondrial DNA and fragments of endoplasmic reticulum inherited from the megakaryocyte parent cell [11,12]. Platelets contain adhesive proteins that allow them to adhere to fibrin mesh and the vascular endothelium, and microtubule and microfilament skeleton that extends into filaments during their activation. When a platelet has not been activated (resting platelet), the components can be broadly divided into three parts namely internal structure, surface receptors, and the organelles[12].

The internal structure of the platelet is enveloped by the plasma membrane (containing the platelet's membrane skeleton) which is separated from the general intracellular space by a thin rim of clear peripheral cytoplasm as viewed under an electron microscope [11]. The cytoplasm contains granules, organelles, and specialized membrane systems [11,12]. The granules are secretory vesicles serving storage functions. They release their contents to the platelet surface or intracellular fluid by endocytosis. The three types of secretory granules found in platelets are *alpha, dense (dense bodies), and lysosomal* granules - which all derive their cargo from megakaryocytes [4]. The alpha granules are the largest and most abundant (50–80 per platelet), forming roughly 10% of the platelets' volume. They store a vast array of proteins important for primary hemostasis such as integrin (αIIbβ3) immunoglobulin family receptors [e.g., glycoprotein VI (GPVI), platelet endothelial cell adhesion molecule (PECAM)], leucine-rich repeat family receptors, tetraspanins, and other clotting proteins, e.g., von Willebrand Factor (vWF), fibrinogen, and Factors V, and X involved in secondary hemostasis [4].

The dense granules store high concentrations of non-protein molecules that stimulate platelet activation such as adenosine diphosphate (ADP), adenosine triphosphate (ATP), calcium, histamine, polyphosphate, and serotonin [4]. Their sizes are smaller with fewer numbers (3–8 per platelet). The Lysosomal granules are sparse and contain enzymes such as acid hydrolases and proteases vital for the digestion of cytosolic components. The lysosomal contents are involved in extracellular functions such as receptor cleavage, fibrinolysis, and degradation of the extracellular matrix [4]. The features of the 3 platelets granules are compared in Table 1.

Table 1: Comparison of Platelet granules

Alpha granules	**Dense granules**	**Lysosomal granules**
Theare most abundant platelet granules, numbering approximately 50–80 per cell	Are much less in comparison with alpha granules	represent the third category of platelet granules. Contain proteolytic enzymes
are relatively large with 200–500 nm in diameter and constitute approximately 10% of the platelet volume	Normally, each human platelet contains only three to eight DGs with 200–300 nm in diameter	The size is intermediate between α- and dense granules (200–250 nm)
contain hundreds of proteins including typically membrane-associated receptors P-selectin, soluble fibrinogen (FGN), and secretory von Willebrand factor (vWF).	unlike AGs with hundreds of proteins, DGs contain non-protein compounds such as serotonin, calcium, pyrophosphate, and a non-metabolic adenine nucleotide pool of ADP and ATP that play a pivotal role in platelets' activation.	contain acid hydrolases (cathepsins, hexosaminidase, β-galactosidase, arylsulfatase, β-glucuronidase, and acid phosphatase) as their most important cargo, and similarly to dense granules they express CD63 and LAMP-1/2.
	They are acidic and accumulate acidophilic dyes such as acridine orange and mepacrine.	[13-14]

The major platelets receptors include integrin, C-type lectin receptors (P-Selectin, CLEC-2), leucine-rich repeat receptors (Glycoprotein GPIb-IX-V, Toll-like receptors), tyrosine kinase receptors (Ephrins and Ephrin kinases), proteins belonging to the immunoglobulin superfamily (GPVI, FcγRIIA) and other receptors shared with vascular cells (Tumor Necrosis Factor (TNF) receptor type, CD63, CD36, P selectin Glycoprotein Ligand (PSGL-1)) [4]. These receptors are expressed on the platelets membrane and are essential for platelet functions and signaling.

Integrins are type I transmembrane cell adhesion receptors that consist of a short intracellular and larger extracellular domain, as well as α and β subunits, which enables them for bi-directional signaling [4]. Integrins transmit information concerning the chemical and mechanical status of the extracellular matrix (ECM) to the cell during signal transduction. The five integrin receptors expressed by the platelets are αIIbβ3 (fibrinogen), α2β1 (collagen), α5β1 (fibronectin), αVβ3 (vitronectin), and α6β1 (laminin). These receptors have an affinity for specific ligands and are involved in related transduction processes [4,15]. Furthermore, platelets express several G-protein coupled receptors (GPCRs); a large family of receptors that can identify molecules outside the cell and initiate signal transduction pathways, resulting in cell function [16]. Major GPCRs present on platelets include thrombin receptor, also called protease-activated receptors (PARs) - PAR1 and PAR4; ADP receptors (P2Y1, P2Y12,), of which approximately 150 P2Y1 receptors are present on the platelet; thromboxane receptors (TPα and TPβ); and glycoprotein receptors [4,16].

Platelets contain few mitochondria that serve as the energy source during their approximately 7 days life span of circulation in the bloodstream of humans [17]. Also present in the cytoplasm of platelets are lysosomes and peroxisomes. Peroxisomes are oxidative organelles that sequester diverse oxidative reactions and detoxify reactive oxygen species. They contain the antioxidant enzyme catalase that metabolizes and converts hydrogen peroxide to water [18]. Lysosomes are tiny organelles that contain several degradative enzymes, including β-galactosidase, cathepsin, arylsulfatase, β-glucuronidase, and acid phosphatases. They function primarily in the breakdown of material ingested by phagocytosis or pinocytosis. The main acid hydrolase contained in lysosomes is β-hexosaminidase [17]. Figure 1 depicts the release of platelets from megakaryocyte and the structure of a mature platelet.

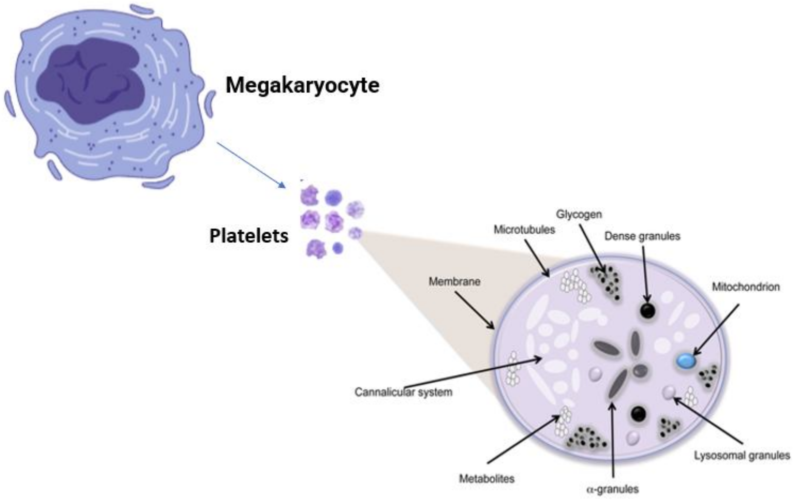

Figure 1: Platelets structure and release

Adapted from Zapata et al.[19] and modified

3. Role of platelets in hemostasis

Hemostasis is a process that combines biological and biochemical events to keep blood in the liquid state and prevent excessive loss of blood via the formation of blood clots at the site of injury [20]. Hemostasis results in sealing off the damaged blood vessels, retaining blood in a fluid state, and dissolving blood clots after the restoration of vascular integrity. The process of hemostasis is controlled by three basic components (the vascular wall, the platelets, and the coagulation cascade) that are required for normal hemostasis to maintain blood in a liquid, clot-free state, and to induce a swift and localized blood clot at the site of vesicular injury [21]. The blood clotting process involves a series of protein reactions that converge at proteolytic cleavage of soluble plasma fibrinogen by the enzyme thrombin to form an insoluble fibrin clot. Tight regulation of this process is required to maintain the fluid nature of blood [22].

Hemostasis thus involves the interactions of platelets, plasma coagulation cascades, fibrinolytic proteins, blood vasculatures, and cytokine mediators [23]. The systems are simultaneously activated and function together upon the disruption of the endothelial lining of the blood vessels (by either chemical, physical, or mechanical injury) to produce blood clots that staunch the bleeding. The formed blood clots are later dissolved by the fibrinolytic system, which is a control mechanism that prevents excessive blood clots. Maintaining the delicate balance between clot formation and breakdown is crucial during hemostasis, as any disruption can lead to thrombosis (from hypercoagulation) or hemorrhage (from hypocoagulation)[20].

Normal hemostatic responses occur in three phases namely primary, and secondary. and tertiary hemostasis.Primary hemostasis involves the response of the vascular system and platelets to vessel injury. The platelets stick together to create a clot plug at the site of injury to the blood vessel. This process is the beginning of the formation of blood clots. The initial stage of clot formation is vasoconstriction, after which the exposed collagen from the compromised tissue surface will promote platelets to adhere, activate, and aggregate to form a platelet plug thereby sealing off the injured area [23]. Platelets are activated upon cellular injury, and this induces a conformational change in the shape of platelets. During injury to the endothelial cells, the thrombogenic, subendothelial ECM becomes exposed to facilitate platelet adherence and activation. The released secretory granules upon platelet activation stimulate the release and further activation of additional platelets to form a plug at the site of injury. The platelet adhesion mechanism is promoted by specific interactions between the membrane receptors and absorbed proteins. Damage and removal of normal endothelial cells result in the exposure of the subendothelial collagen from the ECM immediately under the endothelial cells, and the eventual release of von Willebrand factor (vWF). The released vWF causes platelets to change form, thus promoting the adhesion of the subendothelial collagen to the endothelial wall. This is followed by the binding of the subendothelial collagen to the receptors on the platelet, initiating platelet activation [24].

During platelet activation, platelets release biochemical substances, such as cytokines and chemical mediators, through a process called degranulation. Some of these substances, including ADP, facilitate the activation and aggregation of neighboring platelets. Additionally, von Willebrand Factor (vWF), which is primarily secreted by endothelial cells and megakaryocytes, plays a key role in platelet adhesion[23,25]. The final step of platelet plug formation is the aggregation of the platelets into a barrier-like plug. Receptors on the surface of platelets bind to VWF and fibrinogen molecules, platelets also bind to subendothelial VWF to hold them to the damaged endothelium. The formed plug will then block the damaged components of the endothelium which will prevent blood flow out of it. If the wound is large enough, coagulation of blood will not occur until the fibrin mesh from the coagulation cascade is produced which further strengthens the platelet plug. For a minor wound, the platelet plug may be sufficient to stop the bleeding [26].

The secondary hemostasis is the coagulation cascade that produces a fibrin network to strengthen the platelet plug. This phase occurs consecutively with primary hemostasis and consists of two main pathways; intrinsic and extrinsic pathways that converge in the common pathway to form fibrin clots [27]. The intrinsic pathway is also known as the contact activation pathway. This takes place on exposure to negatively charged molecules, such molecules are found in bacteria and some lipids on the production of thrombin, factor XI becomes activated, and the active factor XIa combines with factor VIIa and tissue factor to activate factor IX. Factor IXa in complex with factor VIIIa activates factor X (factor Xa) that binds to factor Va in conjunction with calcium to form a prothrombinase complex that cleaves prothrombin to thrombin (factor IIa). Thrombin serves as a cofactor and catalyzes the bioactivity of many proteolytic pathways. The extrinsic pathway generates a “thrombin burst” (i.e., production of large amounts of thrombin) that cleaves fibrinogen to fibrin [10].On the formation of the fibrin mesh, the activated platelets will be well arranged and take a position to contract their intracellular actin or myosin cytoskeleton. This occurs at the tertiary hemostasis phase (Figure 2).

The intracellular actin network will directly link to a glycoprotein (integrin GpIIbIIIa) and the fibrinogen receptor internally. Subsequently, the external component of the glycoprotein will adhere to the fibrin mesh of the clot, making the clot compact and slowly decreasing the clot volume. This process is called clot retraction, which is the beginning of wound healing [28]. The fibrinolytic process is activated by the plasminogen activator, a serine protease that converts plasminogen to plasmin thus resulting in the degradation of the fibrin networks. Plasmin resolves the fibrin meshes formed around the site of injury and promotes the clearance of other circulating platelets by proteases in the liver or kidney. The clot resolution mechanism clears the compromised and obstructed vessels and regenerates the normal blood flow. Integrin (GpIIbIIIa) disrupts the binding of fibrin to platelets, thus completing the clot resolution process [28].

The first step in the process of wound healing is epithelial cell migration, stimulated by platelet-derived growth factor (PDGF) which results in clot retraction. After clot retraction, tissue development, and renewal begin. The collagen from the extracellular matrix becomes deposited in the wound while granulation tissue forms and angiogenesis (formation of new blood vessels) is stimulated by vascular endothelial growth factor (VEGF). These result in the growth of new epithelial cells to cover the wound[26].

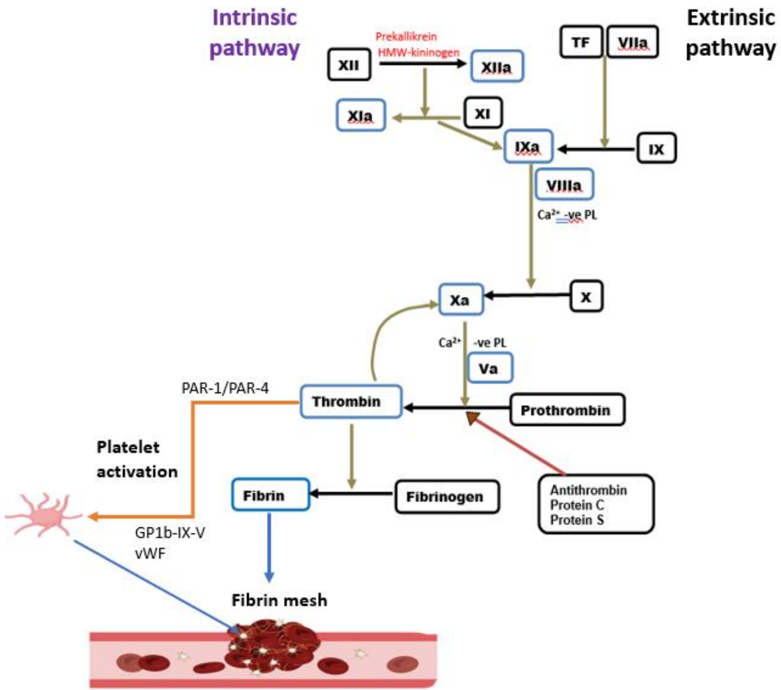

Figure 2: The hemostasis cascade and platelets activation.

4. Role of Platelets and Inflammation

Inflammation is a complex biological response that protects the body from threats like pathogens, injuries, and toxins. Involving blood vessels, immune cells, and molecular mediators, it plays a crucial role in the body's defense and tissue healing processes[29]. The innate immune system responds to pathological stimuli such as microbes and pathogens via inflammation. The symptoms of local inflammation include pain, heat, redness, swelling, and loss of function; while systemic inflammation occurs during chronic disease conditions, massive trauma, or infections clinical responses during systemic inflammation include altered body temperature, elevated pulse rate, and other symptoms. The process of inflammatory response involves the recruitment of immune cells, such as neutrophils and monocytes by the vessel wall, followed by their migration to the tissues.

Inflammation can be either acute or chronic. Acute inflammation is short-lived; it clears off within hours or days, while chronic inflammation lasts longer (up to months or years) even after the initial trigger is withdrawn or removed [29]. Platelets have been shown to directly recognize, take in and kill pathogens, activate and mobilize leukocytes to sites of infection and inflammation, modulate leukocyte behavior by enhancing their ability to ingest and kill pathogens, and induce some effector functions such as the production of Neutrophil Extracellular Traps (NETs). The multifaceted responses of platelets to infection and inflammation are due, in part, to the several soluble mediators and cell surface molecules they produce [30].

Platelets contain several inflammatory peptides and protein mediators, some of which retain the capability of synthesizing *de novo*, whereas others are stored and secreted from granules [30].The activation and release of these cytokines and chemokines, as well as eicosanoids enable platelets' recruitment of leukocytes to the site of inflammation or injury [31]. Platelet-derived inflammatory mediators include IL-1β, PF4/CXCL4, RANTES (CCL5), polyphosphates, and serotonin amongst others. The α-granules of platelets contain large proteins that are involved in the regulation of the inflammatory responses, among which the Platelet factor 4 (PF4) is the most abundant, making up to approximately 25% of the α-granule content.

PF4 accelerates atherogenesis by promoting vascular inflammation and retention of lipoproteins in the vascular wall, which contributes to atherosclerosis. It also prevents the full interaction of Low-density lipoprotein (LDL) with its receptor, thus sustaining the deposit of lipoproteins on the cell surface instead of their degradation [32]**.** Platelet-originating thromboxane A2 (TxA2), synthesized *de novo* from arachidonic acid upon activation, induces platelet activation and aggregation, thus facilitating the further release of pro-inflammatory cytokines which may mediate several inflammation-related diseases. Platelets are thus regarded as important players in inflammation.

The Platelet-activating factor (PAF) has been reported to be a viable mediator of inflammation, immunologic and allergic responses [30]. It is an effective phospholipid mediator, initially recognized to be able to cause platelet aggregation and dilation of blood vessels. It causes inflammation of the air passage, thus resulting in symptoms relating to asthma. PAF production can be induced by toxins released from engulfed and degraded bacteria, causing vasodilation, and reduced blood pressure, leading to a reduction in cardiac output and shock [33]. PAF is continuously produced at low concentrations by platelets, endothelial cells, macrophages, monocytes, and neutrophils. PAF and PAF-like phospholipids are hydrolyzed by Lipoprotein-associated phospholipase A2 (Lp-PLA2), also known as PAF acetylhydrolase, thus controlling their activities [34]. Lp-PLA2 is a biomarker for cardiovascular risk assessment and is associated with unstable atherosclerosis plaques. The activity of PAF increases when specific stimuli activate inflammatory cells, and this is indicated in various medical conditions such as asthma, myocardial infarction, stroke, certain tumors and cancers, and various other inflammatory conditions [35].

PAF can be synthesized via two different pathways: remodeling and de-novo synthesis. The remodeling pathway starts with phosphatidylcholine by substituting an acetyl residue for the long-chain fatty acyl residue, the sn-2 of phosphatidylcholine. The plasma membrane of normal cells contains a very low level of phosphatidylcholine, however, that of PAF-producing cells such as endothelial and neutrophils contain 10-40% phosphatidylcholine[35]. Biosynthesis through the remodeling pathway majorly contributes to PAF production during inflammation. It consists of two steps; in the first step, phospholipase A2 acts on phosphatidylcholine producing eicosanoid (arachidonic acid) and lysophosphatidylcholine, while acetyl residue is transferred to lysophosphatidylcholine by an acetyltransferase to produce PAF in the second step. The *de novo pathway* for PAF synthesis is mainly for the production of physiological levels of PAF for normal cellular functions[35]. At normal physiologic conditions, the synthesis of PAF is maintained at a very low concentration by de novo synthesis. The synthesis increases during inflammatory responses via the remodeling pathway. PAF synthesis can be stimulated by antigen-antibody interactions, collagen, thrombin, and other inflammatory mediators involved in inflammation[35].

4.1 Platelets in Tumor Metastasis Promotion

The activation of platelets and the coagulation system play a critical role in cancer progression. Within the circulatory system, platelets protect tumor cells from immune elimination and support their arrest at the endothelium, thus promoting the establishment of secondary lesions [36]. Cells that contribute to metastasis within the bloodstream include endothelial cells, lymphocytes, platelets, macrophages, mast cells, fibroblasts, and bone marrow-derived progenitor cells [37]. It is fully validated that in cancer patients, tumor growth is usually accompanied by the development of an increased tendency towards a hypercoagulable state, platelets activation and abnormalities, and an increased risk of thromboembolic disease [38].

Platelets contribute to tumor metastasis through various mechanisms, including aiding in tumour cell survival, facilitating immune evasion, promoting extravasation, and assisting in the establishment of secondary tumor sites [39].Platelets form aggregates around circulating tumour cells (CTCs) in the bloodstream, shielding them from shear stress and immune surveillance [39]. This interaction with CTCs provides a protective cloak, reducing the likelihood of detection and elimination by natural killer (NK) cells [40] and also promotes tumor cell survival by enhancing their resistance to apoptosis, which is crucial for successful metastasis [41]. The interaction also triggers the release of various cytokines and growth factors from platelets, which modulate immune responses and create an environment conducive to immune evasion [42].

Platelets play a critical role in tumour cell extravasation, a process by which CTCs exit the bloodstream and invade new tissues. The platelet-tumour cell aggregates secrete matrix metalloproteinases (MMPs), which degrade the extracellular matrix, enabling CTCs to penetrate the endothelial lining and invade distant organs [43]. The release of vascular endothelial growth factor (VEGF) and other angiogenic factors, which increase vascular permeability, further facilitates CTC extravasation [40]. Platelet-derived factors, such as transforming growth factor-beta (TGF-β), VEGF, and platelet-derived growth factor (PDGF), have been implicated in altering the tissue microenvironment to make it more conducive for metastatic growth [41]. These factors promote inflammation, angiogenesis, and matrix remodeling, all of which are essential for establishing and maintaining secondary tumours[43].

Disseminated intravascular coagulation (DIC), a complex condition characterized by systemic activation of blood coagulation frequently occurs in cancer patients due to the pro-coagulant and inflammatory environment created by tumours[44]. In the tumour environment, cancer cells release

Tissue factors and cancer procoagulants, which activate platelets and promote systemic coagulation [45]. This activation leads to the formation of platelet-rich microthrombi that can obstruct blood vessels, resulting in ischemia and organ dysfunction. Patients with DIC associated with cancer may suffer severe thrombocytopenia, resulting in a paradoxical risk of both thrombosis and bleeding. The fibrin clots formed in DIC consume large quantities of platelets and coagulation factors, and the body's inability to sustain these levels results in hemorrhage, particularly in cases of advanced tumours [46]. Thus, the intricate interplay between platelets, tumour cells, and the coagulation system amplifies the risk of DIC in cancer, underscoring the need for balanced therapeutic approaches.

5. Platelets in hemostasis and inflammation

Inflammation and hemostasis are closely interconnected pathophysiological processes that significantly influence one another. In this bidirectional relationship, the inflammatory response activates the hemostatic system, which in turn has a profound effect on the inflammatory response itself. This creates an “inflammation-hemostasis loop,” where the hemostatic and inflammatory pathways act synergistically [47,48]. Platelets play a crucial role in this cycle, as they are integral to the function of the hemostatic system. Components such as vascular endothelial cells, platelets, the plasma coagulation cascade, physiological anticoagulants, and fibrinolytic activity illustrate the broad interaction between the immune and hemostatic systems.

Inflammatory mediators, particularly proinflammatory cytokines, influence the hemostatic system through several mechanisms. These include endothelial cell dysfunction, increased platelet activation, activation of the plasma clotting cascade, impaired function of physiological anticoagulants, and reduced fibrinolytic activity [48].

This close interplay between inflammation and hemostasis contributes to the development and progression of conditions such as systemic inflammatory responses in sepsis or infection and acute arterial thrombosis triggered by ruptured atherosclerotic plaques [47]. While inflammation aims to repair tissues damaged by trauma or infection, hemostasis, a natural defense mechanism, serves to prevent bleeding following vascular injury. During infections, platelets are pivotal in fostering inflammation and orchestrating immune responses. When platelets aggregate and bind to white blood cells at sites of tissue injury, they release cytokines and chemokines that attract lymphocytes, monocytes, and neutrophils to the injury site, thereby promoting inflammation.The role of platelets in modulating hemostasis and inflammation is illustrated in Figure 3.

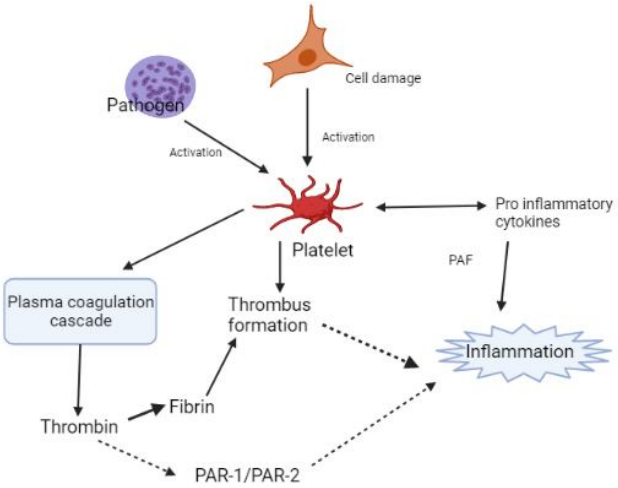

Figure 3: Platelets in hemostasis, immune response, and inflammation.

Damage to the endothelial cell and pathogen infection results in the activation of platelets. Activation of platelets leads to activation of the plasma coagulation cascade to form fibrin clots at the site of injury, thus promoting thrombus formation. Furthermore, platelet activation promotes inflammation via the release of proinflammatory cytokines and platelet activation factor (PAF). Activation of the blood coagulation proteases also increases the expression of inflammatory peptides by the release of protease-activated receptors (PA-1 and PA-2).

6. Platelets function in immune responses to infectious pathogens

Beyond the dynamic role, platelets play in hemostasis and inflammation, emerging pieces of evidence have shown that they are also key modulators of immune responses to different pathogens [38]. Platelets directly recognize pathogens, activate, and recruit leukocytes to sites of inflammation and infection; to modulate leukocyte behavior enhancing their ability to carry out phagocytosis and kill pathogens. They also induce unique effector functions such as the production of Neutrophil Extracellular Traps (NETs) [50]. Upon detection of a pathogen, platelets quickly activate and continue to drive the ensuing inflammatory response. Due to their diverse array of adhesion molecules, platelets can adhere to leukocytes and facilitate their recruitment to the site of damaged tissue or infection. Platelet-neutrophil interactions are known to induce the release of neutrophil extracellular traps. Platelets have been shown to participate in the host immune response by directly killing the infected cells[51]. The receptors and proteins secreted by the platelets enable them to interact with leukocytes and endothelial cells through contact-dependent mechanisms and secreted immune mediators. Likewise, the expression of these surface receptors known as toll-like receptors (TLRs) on platelets enables the recognition, binding, and entry of infectious pathogens particularly viruses [52].

Blood platelets are active players in antimicrobial host defense and in the induction of inflammation [53]. In bacterial infection, bacterial peptidoglycans (TLR2) and LPS (TLR4) in Gram-positive and Gram-negative bacteria are recognized by the TLRs on the surfaces of platelets [54,55]. Platelet interaction with bacterial pathogens such as *Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli, and Clostridium perfringens* has been shown to involve the formation of platelet-leukocyte complexes, expression of P-selectin and release of platelet granules [56,57]. Although the number of clinical trials on *Streptococcus pneumoniae* is limited, there have been reports of elevated platelet count in patients with the infection [58,59]. Hence, some biomarkers such as platelet CXC chemokines, platelet factor-4 (PF4) and -thromboglobulin, miR-126, a microRNA have been shown to correlate with platelet activation [60-64]. Likewise, pulmonary bacterial infection with *Staphylococcus aureus* and *Klebsiella pneumonia* was associated with thrombocytopenia [65,66]. Associated markers were the elevated expression of surface P-selectin, granular secretion, and increased circulation of platelet-monocyte and platelet-neutrophil complexes [67]. More so, interactions of these platelets with bacterial pathogens may result in the engulfment of the bacteria [68] or the prevention of bacterial infection in the lungs [69].

Quite a few studies have evaluated the role of platelets in immune responses to viral infections [18,70–74]. Platelets can internalize HIV and lentivirus through the receptors C-type lectin-like receptor (CLEC)-2 and DC-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin (DC-SIGN) expressed on their membrane [68,75,76]. Viral particles of HIV, dengue virus and hepatitis C virus have been reported to be endocytosed in circulating platelets [77,78]. When platelets are activated, they interact with different types of leukocytes by the binding of the platelet P-selectin to leukocyte P-selectin glycoprotein ligand 1 (PSGL-1) [79,80]. This aggregation of platelets with monocytes or lymphocytes has been reportedly found to increase in numbers among HIV- infected individuals. In HIV-infected patients and AIDS subjects, an increase in markers of platelet activation had a corresponding increase in the viral load of the patients. Likewise, P-selectin surface expression on platelets increased in patients yet to commence Antiretroviral Therapy (ART). This decreased subsequently after the commencement of antiretroviral treatment [81,82]. In dengue virus infection, an increase in activation of the platelets corresponds to the severity of the disease [71,72,83]. Aggregation of platelets with leukocytes also occurs in dengue virus infection and this has been attributed to thrombocytopenia [72,84]. Besides platelet activation and intravascular thrombosis, increased platelet apoptosis may contribute to thrombocytopenia [49]. Thrombocytopenia, platelet secretion of stored and newly synthesized factors, and complex interactions with leukocytes comprise platelet features that may have both injurious and protective immune consequences in viral infections [49].

Furthermore, host defense against the respiratory syncytial virus (RSV), a leading cause of lower respiratory tract infections in young children involves the interaction of platelets–leukocytes and the subsequent alteration in cytokine production [85]. It was postulated that platelet-mediated reduction of monocyte activation during RSV infection may be important for preventing lung inflammation. Platelets could also induce the formation of platelet-monocyte aggregates as reported in influenza infection [86]. Increased platelet activation and increased formation of platelet–monocyte aggregates have been reported in the blood of critically ill H1N1 influenza patients presenting ALI/ARDS relative to those with bacterial pneumonia in ICU [86]. Similarly, activated platelets and platelet–monocyte aggregates have been also shown in influenza-vaccinated subjects [87,88].

Various reports have also shown the occurrence of thrombocytopenia in cases of COVID-19 disease and the incidence is related to disease severity [89–91]. The platelet count of those with severe cases of COVID-19 was lower than those with non-severe disease [92–94]. However, mild thrombocytopenia has been reported in several cases and it is postulated that this could be due to a compensatory regulatory mechanism in COVID-19 patients [95].

The function of these platelets is controlled by their receptors and the molecules stored in their granules [18]. Their interactions with immune cells aid in ameliorating the impacts of infection [30] but this may lead to excessive stimulation of the immune responses which may be detrimental [30].

Conclusion

Platelets circulate in the blood plasma and are central players in hemostasis and thrombosis. However, they also contribute to the physiological processes of inflammation, tumor metastasis, wound healing, and host defense [84].The primary physiological function of platelets is to stop and reduce the loss of blood. They are activated by vessel wall injury and work with the fibrinolytic system and coagulation cascade to perform their hemostatic function. Not only do they function in the process of hemostasis, but they also play a pivotal role in the defense mechanism and inflammation.

Platelets are important in the development of inflammation and have a pivotal role in hemostasis. They store inflammatory responses that upon release, they stimulate immune cells' leukocytes to elicit immune responses. The hemostatic system acts in conjunction with the inflammatory cascade, thereby creating an inflammation-hemostasis cycle in which Platelets participation is involved via the action of PAF/receptors. These molecules play roles in several overlapping and inseparable processes linking hemostasis and inflammation. Further investigations are required to provide more insight and unravel new molecules involved in the mechanisms of platelets-mediated hemostasis, inflammation, and immune response during infection to provide a broader understanding of these loop reactions, and also discover molecular and therapeutic targets in controlling platelets over activation and accompanied biochemical and physiological conditions.

List of Abbreviations

ADP: Adenosine diphosphate
ATP: Adenosine triphosphate
ART: Antiretroviral Therapy
(CLEC)-2: C-type lectin-like receptor
DC-SIGN: DC-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin
ECM: Extracellular matrix
GPVI: Glycoprotein VI
GPCRs: G-protein coupled receptors
LDL: Low-density lipoprotein
NETs: Neutrophil Extracellular Traps
PAF: Platelet-activating factor
PDGF: Platelet-derived growth factor

PECAM: Platelet endothelial cell adhesion molecule
PARs: Protease-activated receptors
PSGL-1: P selectin Glycoprotein Ligand
TLRs: Toll-like receptors
TNF: Tumor Necrosis Factor
VEGF: Vascular endothelial growth factor
vWF: von Willebrand Factor

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Data availability
All relevant data can be found within the manuscript.