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Review Article

The roles of platelets in inflammation, immunity, wound healing and malignancy

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Abstract: The roles of platelets as essential effector cells in hemostasis have been known for over a century. Platelets also have many other functions, which are facilitated by their complex morphological structures and their ability to synthesize and store a variety of biochemical substances. These substances are released via the platelet release reaction in response to tissue/cell damage. The aim of the current study was to review the reported functions of platelets in inflammation, immunity, wound healing and malignancy. For this purpose, we used relevant data from the latest numerous scientific studies, including review articles, and original research articles. Platelets physiologically respond to inflammation by recruiting inflammatory cells to repair and resolve injuries. This response is facilitated by the ability of platelets to promote vascular permeability under inflammatory conditions. Platelets have critical roles in innate and adaptive immune responses and extensively interact with endothelial cells, various pathogens, and almost all known immune cell types, including neutrophils, monocytes, macrophages and lymphocytes. Additionally, platelets affect wound healing by integrating complex cascades between their mediators, which include multiple cytokines, transforming growth factors, platelet growth factors, and vascular endothelial growth factors, among others. In addition, recent evidence suggests that platelets play a significant role in the pathogenesis of malignancy by forming complex, bidirectional interactions with tumor cells. In the future, platelet functions, including their actions in vivo, will become further clarified, especially their clinical implications.

Keywords: Inflammation, innate and adaptive immunity, interactions, metastasis, platelets, wound healing

Introduction

Platelets, also known as thrombocytes, are small anucleate cells that circulate in the bloodstream. They are essential for normal hemostasis and play major roles in inflammation, immunity and wound healing [1]. Like other blood cells, platelets originate from pluripotent stem cells (CFU-S); they derive from megakaryocytes via a unique proliferation process termed endomitosis [2]. William Osler was likely the first physician to identify that platelets in the blood existing as individual units. Based on earlier observations by Schultze, who noted abundant, irregular masses of colorless globules in normal blood in 1865, Osler found they were almost certainly platelets [3]. Platelets were established as hemostatic mediators by Guilo Bizzozero in 1982 [4]. In 1906, James Wright demonstrated that platelets originate from giant bone marrow cells, now recognized as megakaryocytes [5].

Platelets are highly specialized for hemostasis and the chief effector cells in this process. Conversely, they have extremely general roles as effectors of inflammation and immune activity and specialized roles in host defense responses and adaptations to injury [6]. Platelets exert these functions by physiologically responding to tissue/cell damage, which facilitates injury repair and resolution via the recruitment of inflammatory cells [7]. The role of platelets in inflammation is related to their ability to promote vascular permeability under inflammatory conditions [8]. According to Herter et al., platelets have key roles in innate and adaptive immune responses and form extensive interactions with immune cells [9]. During microbial invasion, platelets have important recognition and surveillance activities, providing host protection. They also possess signaling functions that promote the responses of leucocytes and lymphocytes, which are primary immune effector cells [10]. Additionally, plate-

Table 1. Multifunctional biologically active substances (synthesized and/or stored in platelets granules or in their plasma membranes), which participate in inflammation, immunity, wound healing and malignancy

	Substances	Type of mediators	Stored or Synthesized	Biological activity
Inflamation	Histamine	Mediator of inflammation	Stored (δ-granules)	Regulation of vascular permeability
	Serotonin (5-HT)	Potent modulatotor of inflammation	Stored (δ-granules)	Platelet aggregation, and vasoconstriction
	PF4 (CXCL4)	Chemokines	α-granules	Pro-and anti-inflammatory effects
	RANTES (CCL5)	Chemokines	α-granules	
	β-thromboglobulins	Chemokines	α-granules	Activate and recruit cells to sites of inflammation
	IL-1α and IL-1β	Proinflammatory cytokines	Synthesized	Strongly proinflammatory effect
	TXA_2	Proinflammatory	Synthesized-PM	Vasoconstriction
	P-selectin, fibrinogen, VWF	Adhesive glycoproteins	α-granules	Promote interaction between platelets, leukocytes, plasma proteins, and vessels walls
	PAF			Platelet activation, chemotaxis
Immunity	TRLs	Pathogen recognition receptors	PM	Chemotaxis, phagocytosis, cytotoxicity and activation of adaptive immune responses
	Fc	Platelet immunoreceptors	PM	to recognize immunoglobulin's
	GPCRs	Signaling receptors	PM	inflammatory and immunomodulatory
	PARs	G-protein-coupled receptors	PM	Potent signaling paradigms associated with platelet biology
	LPS	Signaling receptor	PM	Stimulates platelet secretion of dense bodies and α granules
	FcγRIIA	Plateled-related immunoreceptors	PM	Key component in the recognition of Staphylococcus
	GPVI and CLEC-2	Reladet plateled immunoreceptors	PM	Tyrosine phosphorylation
	$\alpha_{II}\beta_3$ (GP IIb/IIIa)	Integrins	PM	Connection of platelets to pathogens through vWF and fibrinogen
Wound Healing	CCL7 (MCP3), Defensins	Soluble mediators (chemokines)	α-granules	Elimination of engulfed pathogens
	CD40, CD40L	Adhesion molecules	α-granules and PM	Inflammatory and immune response
	PDGF	Mitogenic factors	α-granules	Wound healing and angiogenesis
	TGF-β	Mitogenic factors	α-granules	Wound healing and angiogenesis
	EGF	Mitogenic factors	α-granules	Wound healing and angiogenesis
	VEGF	Mitogenic factors	α-granules	Wound healing and angiogenesis
Malignancy	GP1b/IX/V	Platelets receptors	PM	Interaction between tumor cells and platelets
	GPIIb/IIIa ($\alpha_{II}\beta_3$)	Platelets receptors	PM	Interaction between tumor cells and platelets
	GPVI	Platelets receptors	PM	Interaction between tumor cells and platelets

Abbreviations: PF4, platelet factor 4; RANTES, regulated upon activation normal T cell expressed and secreted; IL-1α and IL-1β, interleukin 1α and 1β; TXA_2, thromboxane A_2; P-selectin, platelets selectin; VWF, von Willebrand factor; PAF, platelets activating factor; PM, plasma membrane; TRLs, toll-like receptors; Fc, crystallizable fragment; GPCRs, G-protein-coupled receptors; PARs, protease-activated receptors; LPS, lipopolysaccharide; FcγRIIA, Fc-gamma receptors (bind immunoglobulin A); GPVI, glycoprotein VI; CLEC-2, C-type lectin-like receptor 2; GP IIb/IIIa, glycoprotein IIb/IIIa ($\alpha_{II}\beta_3$); CCL7, chemokine (C-C motif) ligand 7; CD40, cluster of differentiation 40; CD40L, cluster of differentiation 40 Ligand; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor β; EGF, epidermal growth factor; VEGF, vascular endothelial growth factor.

lets trigger endothelial cells, which play important roles in inflammation by directing innate and adaptive immune responses [11]. According to Jenne et al., after detecting a pathogen, platelets are quickly activated and begin to drive inflammatory responses. They also participate in the host immune response by directly killing infected cells [12]. Additionally, activated platelets release many substances that promote tissue repair. Accordingly, the ability of platelets to form fibrin clots has been clinically utilized to promote healing [13]. In addition to their aforementioned functions, platelets also play a significant role in the pathogenesis of malignancy by bidirectionally interacting with tumor cells [14]. The aim of this paper was to summarize the current literature on the alternative functions (i.e., other than hemostasis) of platelets, especially their roles in inflammation, immunity, wound healing and malignancy. Platelets perform these functions via several multifunctional, biologically active substances, some of which are synthesized and stored in platelet granules. Other substances utilized by

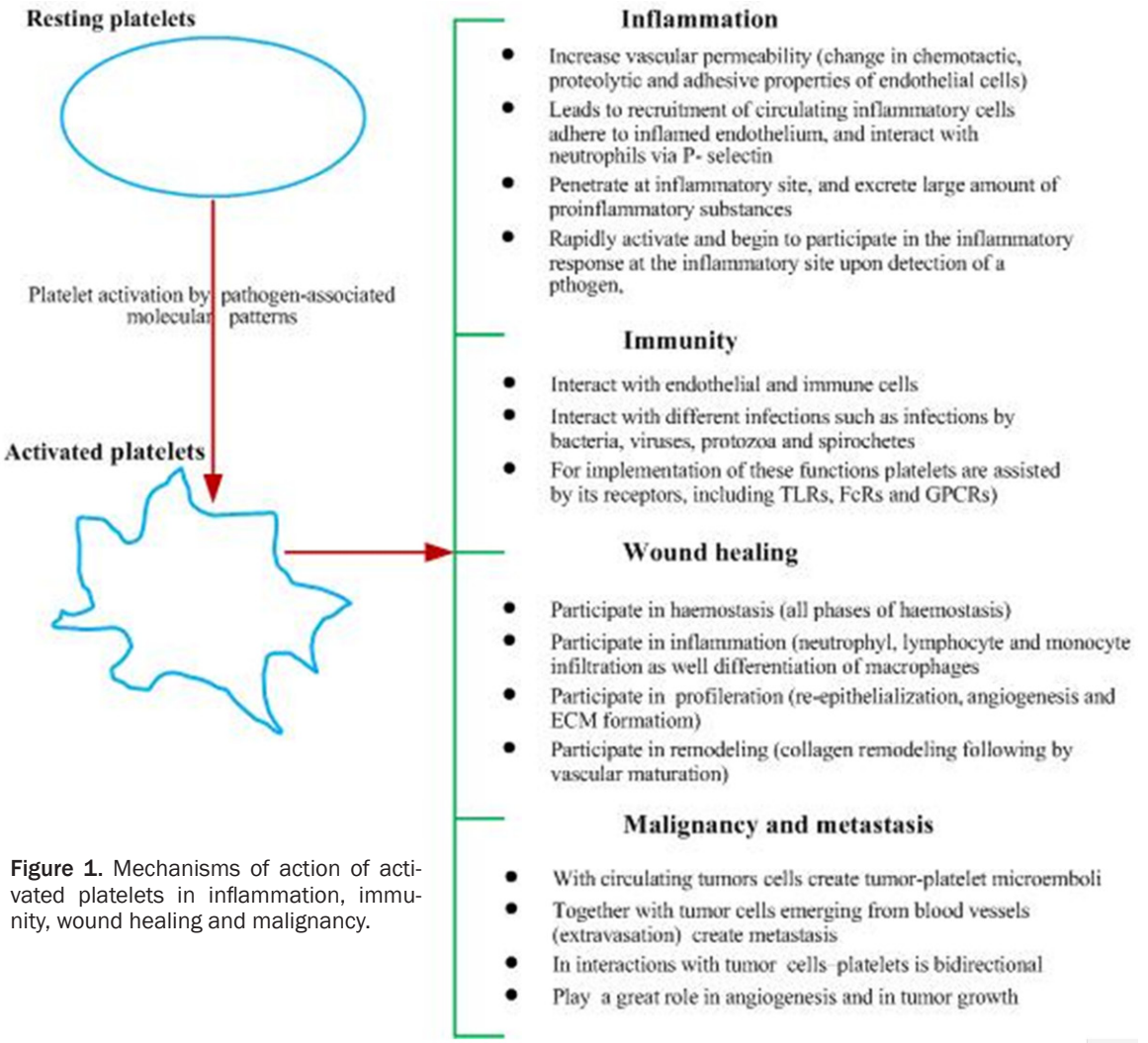

Figure 1. Mechanisms of action of activated platelets in inflammation, immunity, wound healing and malignancy.

platelets are not synthesized in the platelets themselves; rather, they enter these cells from the plasma (**Table 1**). The various functions of platelets in inflammation, immunity, wound healing and malignancy is detailed in **Figure 1**.

The role of platelets in inflammation

Platelets play a central role in inflammatory reactions and are involved in responses to a variety of inflammatory diseases. In various inflammatory conditions, platelets can increase vascular permeability, resulting in edema, defined as "a swelling tumor", which is one of the first signs of inflammation [8]. In addition to swelling, the other four cardinal signs of inflammation are rubor (redness), calor (heat), dolor (pain), and functio laesa (loss of function). These signs were first described by Celcus and Gallen [15]. The cardinal signs of inflammation are caused by the release of inflammatory mediators, such as immunomodulatory cytokines, chemokines, and other mediators, from platelets [12]. Platelets contain three types of granules: α-granules, dense bodies and lysosomes. These granules store many important platelet-derived inflammatory and immune mediators that are rapidly released following platelet activation. Notably, platelets can synthesize additional mediators, such as interleukin-1α (IL-1α) and interleukin-1β (IL-1β) [16, 17]. Recently, platelets were shown to contain an assembly of inflammasomes that mediate IL-1β secretion [18].

Platelet activation during inflammation leads to changes in the chemotactic, proteolytic and adhesive properties of endothelial cells [19]. Blood vessel inflammation is caused by interactions between platelets, leukocytes and endo-

thelial cells that result in autocrine and paracrine activation. This activation is followed by leukocyte recruitment into the vascular wall and induces an inflammatory reaction via the release of proinflammatory compounds [19, 20]. Additionally, platelet activation by pathogen-associated molecular patterns (via Toll-like receptors, TLRs) leads to the release of other cytokines, such as platelet factor 4 (PF-4), and CCL5 or RANTES (Regulated upon Activation Normal T cell Expressed and Secreted), that leads to recruitment of circulating inflammatory cells [21]. Herter et al. used a model of platelet function during acute lung injury to explain the role of platelets in inflammation [8]. According to this model, activated platelets roll along and adhere to inflamed endothelium and interact with neutrophils [22]. These transient interactions with neutrophils and endothelial cells are mediated by P-selectin, which is an integral membrane glycoprotein (GP) expressed by platelets, endothelial cells, macrophages and atherosclerotic plaques [23, 24]. P-selectin is expressed on the surfaces of activated platelets and activated endothelial cells [14].

Thromboxane A_2 (TxA_2), a product of activated platelets, can bind to its receptors on endothelial cells to up-regulate the expression of intracellular adhesive molecule-1 (ICAM-1) on the cell surface and regulate neutrophil recruitment [22]. Platelets can also independently promote neutrophil recruitment by forming aggregates via E-selectin (ESL-1), which is located on leukocyte cell surfaces [25]. Alterations in endothelial cells via potent platelet-derived proinflammatory substances accelerate and strengthen monocyte chemotaxis, adhesion and transmigration to locations of inflammation [26]. Following activation, platelets increase in size, penetrate sites of inflammation, and excrete large quantities of proinflammatory substances from their intracellular granules [27]. More than 300 types of proteins accumulate in the granules of activated platelets [28]. Some of the more abundant of these proteins include β-thromboglobulin, fibrinogen, von Willebrand factor (VWF), fibrinolytic inhibitors, coagulation V and XI factors, angiogenic and mitogenic factors, immunoglobulins, membrane ligand proteins, ADP, and serotonin, among others [27].

In addition to the aforementioned substances, platelets contain several chemokines, which play significant roles in inflammation by signaling leukocyte migration, infiltration and differentiation [29]. PF4, which is currently known as CXCL4, was the first chemokine to be identified and is secreted in large quantities by alpha granules [30]. Approximately 20 years ago, Power et al. discovered the first chemokine receptors on platelets [31]. Upon detecting a pathogen at an inflammatory site, platelets rapidly activate and begin to participate in inflammatory responses by directly modulating the activity of neutrophils, endothelial cells and lymphocytes as well as by capturing and sequestering pathogens within the vasculature [12].

The role of platelets in immunity

In addition to their pivotal roles in hemostasis and inflammation, platelets are key components of innate and adaptive immune responses [32]. Many studies have demonstrated that platelets can interact with and respond to a variety of microbes and pathogens; platelets are considered to be “first responders” in the defense of the host [33, 34]. Platelets have also been shown to defend against bacterial, viral, protozoan and spirochetal infections [35]. In response to contact with these microbes and other pathogens, platelets undergo a characteristic pattern of changes that depends on a variety of stimuli [9]. To implement these functions, platelets utilize a variety of receptors, including Toll-like receptors (TLRs), crystallizable fragment receptors (FcR), and G protein-coupled receptors (GPCRs). Platelets express several TLRs, which belong to a family of evolutionary conserved pathogen recognition receptors [9]. The primary function of innate immunity is to recognize pathogen-associated molecular patterns (PAMPs) via pattern recognition receptors [11].

Toll-like receptors

TLRs are surface molecules that trigger signals (signaling platelet function) that result in proinflammatory gene expression, which leads to additional leukocyte functions, such as chemotaxis, phagocytosis, cytotoxicity, and the activation of adaptive immune responses [6, 36]. Shiraki et al. were the first to discover TLRs in platelets (TLR1 and TLR6) using mRNA, Western blotting, and flow cytometry [37]. Cognasse et al. reported the existence of several

other TLRs (TLR2, TLR4 and TLR9) on platelets one year later [38]. The expression patterns of these TLRs are controversial: they may exist extracellularly (TLR1, TLR2, and TLR6) or intracellularly (TLR3, TLR7, TLR8, and TLR9). TLR4 and lipopolysaccharide (LPS) may also be intracellular or extracellular [38] and are up-regulated in response to interferon-γ (INF-γ). The expression levels of TLR4 and LPS generally double upon platelet activation [30]. Several authors have also identified TLRs on endothelial cells (ECs) [39]. Various types of TLRs can be expressed on ECs via different mechanisms. Atherosclerotic ECs have been shown to express TLR1 [40], although this finding has been debated [41]. TLR2 expression is induced by VWF in atherosclerotic endothelium [40], whereas TLR3 is spontaneously expressed on human umbilical vein endothelial cells (HUVECs). TLR3 ligation with polyinosinic-polycytidylic acid (Poly [I:C]) leads to up-regulated TLR3 expression together with up-regulated IFN-β, IL-28 and IL-29 expression [42]. Additionally, TLR4 is expressed on various ECs, but its expression significantly increases under inflammatory conditions. Moreover, TLR4 is expressed in coronary ECs, especially in coronary atherosclerotic plaques, suggesting its activation at these sites [42].

Fc receptors

Platelet surfaces are decorated with immunoreceptors, such as FcR, which can recognize immunoglobulin (Ig) G, IgE and IgA molecules [43, 44]. Other platelet immunoreceptors and related receptors, such as Fc-gamma receptors, bind IgA (FcγRIIA), glycoprotein VI (GPVI), and C-type lectin-like receptor 2 [CLEC-2]). These functions depend on immunoreceptor tyrosine-based activation motifs (ITAMs), which are located in the intracellular domains of the receptor or in associated FcRγ subunits [43]. Accordingly, the expression of human FcγRIIA in tumors increases with human megakaryocyte maturation [45]. FcγRIIA and integrin $\alpha_{II}\beta_3$ are key components in Staphylococcus aureus recognition, which involves the binding of IgG directed against the bacteria to FcγRIIA and the analogous binding of fibrinogen to $\alpha_{II}\beta_3$ to cause platelet activation [46]. Additionally, glycoprotein VI (GPVI) and C-type lectin-like receptor 2 (CLEC-2) cause tyrosine phosphorylation, activate $\alpha_{II}\beta_3$ and result in protein secretion from platelet granules [47].

G protein-coupled receptors

GPCRs are important signaling receptors in hemostasis. They also have inflammatory and immunomodulatory functions and may induce inflammatory and immune responses [6, 47]. G protein-coupled protease-activated receptors (PARs), which are expressed by human and mouse platelets, are notable GPCRs. Couglin showed that the activation of platelets via PARs is one of the most potent signaling paradigms in the biology of these cells [48]. The $P2Y_1$ and $P2Y_{12}$ purinergic receptors are other GPCRs on platelets. $P2Y_{12}$ is a major target for clopidogrel, which is an important antagonist for $P2Y_{12}$ and used to prevent or treat thrombotic disorders [49, 50].

Cluster of differentiation 40 (CD40) and CD40 Ligand (CD40L)

Like other platelet receptors, such as GPIb/IX/V, P-selectin, P-selectin glycoprotein ligand, and $\alpha_{II}\beta_3$ integrin, all of which have crucial roles in hemostasis, CD40 has been implicated in some inflammatory conditions and in immune responses to bacterial challenge [14]. The CD40L receptor is CD40, which is an integral membrane protein expressed in B cells, monocytes, endothelial cells, fibroblast, platelets and several other cell types [14]. However, soluble CD40L (sCD40L) is mainly produced by platelets. CD40L is a member of the TNF family and is expressed on platelet surfaces under basal conditions. After platelet activation, sCD40L translocates to the plasma membrane [6]. CD40L interactions have important roles in immune-mediated activation of inflammation and thrombosis [51]. CD40L can bind to CD40 molecules on the surfaces of most cells, including immune, endothelial, and mesenchymal cells. This leads to the induction of tissue factor (TF) in endothelial cells and monocytes [52]. In addition to human platelets, murine platelets also basally express CD40L, which is also known as CD154 and gp39 [53]. CD40L signaling integrates acute inflammation, the adaptive immune response, and hemostasis. Additionally, platelet-derived CD40L has been associated with febrile responses to transfusion and other adverse effects in humans [54]. Duffau et al. demonstrated that platelets are activated by immune complexes and FcγRIIA signaling in patients with systemic lupus erythematosus. This activation results in sCD40L-

dependent stimulation of plasmacytoid dendritic cells and interferon-α secretion [55].

Mechanisms underlying platelet actions in immunity

Platelets can actively and passively participate in immunity [56] by binding to pathogens via different membrane receptors and interacting with endothelial and immune cells [9, 11].

The details of platelet interactions with pathogens depend on the type of pathogen, but the interactions usually occur via a connection between platelet-derived GPIIb-IIIa and pathogens via plasma bridge proteins, such as VWF and fibrinogen [57]. In response to contact with pathogens, platelets release microbiocidal proteins, including several of the aforementioned chemokines and β-defensin, and contribute to the elimination of engulfed pathogens [58]. The innate antibacterial effector response resulting from interactions of platelets with pathogens following bacterial invasion has been compared to the functions of other myeloid leukocytes [59]. The granules of activated platelets are mobilized by a microtubule assembly and subsequently secreted, similar to neutrophils and macrophages. This characteristic strongly supports the concept that platelets are ancient granulocytes that recognize signals of different infectious agents and react against them [57]. In addition to the above-mentioned mechanisms by which platelets can destroy different microorganisms, platelets and Kupffer cells (KCs) are known to collaborate in eradicating blood-borne bacterial infections [60]. Platelets are early responders and effector cells in malaria infections [61]. McMorran et al. identified a unique mechanism whereby platelets can directly kill Plasmodium falciparum after binding to parasitized cells. Previously activated platelets bound to infected erythrocytes release PF4 or CXCL4, which together with erythrocyte Duffy-antigen receptor (Fy) enables the platelet-mediated killing of Plasmodium falciparum parasites [62].

Interactions of platelets with endothelial cells

Under normal conditions, platelets do not adhere to endothelial cells. Instead, platelets circulate in blood vessels without attaching to vessel walls [63]. Intact endothelial cells release mediators that inhibit platelet-endothelial interaction via different mechanisms. The most important of these endothelial cell mediators are diphosphohydrolases (a potent platelet activator to degrade ADP), aminooxidases (that deactivate local vasoconstrictors), nitric oxide (NO, a local vasodilator) and prostacyclin (PgI_2), which plays an important role in the inhibition of platelet adhesion and aggregation [9]. However, under inflammatory conditions, platelets can bind to endothelium partly because the physiological inhibitory mechanisms of endothelium are impaired and partly due to the expression of several adhesion molecules on the surfaces of activated platelets and endothelial cells [64]. Activated platelets can activate various other types of cells by releasing proinflammatory mediators. Platelets can be activated by EC-derived proinflammatory substances that bind to receptors on their surfaces [65]. Additionally, during the sequential steps of platelet-endothelial cell interactions, platelets become activated by rolling over activated endothelium or subendothelium [63]. According to Etulain et al. and Rondina et al., platelet-secreted mediators alter the chemotactic, adhesive, and photolytic properties of the endothelium. This prompts endothelial cells to switch from an angiogenic inflammatory to a thrombotic phenotype [66, 67].

Interactions of platelets with immune cells

Platelets can interact with different types of immune cells, including neutrophils, monocytes, macrophages and lymphocytes. Platelet interactions with neutrophils play an important role in inflammation and thrombosis [68]. Circulating leukocytes and platelets play important roles in both normal physiological and pathological conditions, including in inflammatory processes, thrombosis, the clearance of foreign bodies, and responding to various systemic biological signals in the bloodstream [69].

The interaction between platelets and leukocytes is manifested by the formation of circulating platelet-neutrophil complexes (PNC), which occur in a range of inflammatory disorders and infections in numerous organs of the body [66]. Platelets can adhere to leukocytes because they express many different types of adhesion molecules and chemokines. Therefore, they facilitate leukocyte recruitment to sites of tissue damage or infection [12]. Pliyek et al. found

that the adhesion molecule CD99 is a very important mediator for neutrophil migration across the endothelium [68]. Additionally, the release of other soluble factors by platelets can modulate endothelial permeability and leukocyte infiltration [70]. Caudrillier et al. reported that activated platelets induce the creation of neutrophil extracellular traps (NETs) in transfusion-related acute lung injury (TRIALI); in an experimental mouse model of TRIALI, these authors observed that the formation of NETs in the lung microvasculature depends on neutrophils and platelets [71].

Platelets can also interact with monocytes, and their binding is mediated predominantly by Ca^{2+}-dependent interactions between platelet-derived P-selectin and monocyte-derived P-selectin glycoprotein ligand-1 (PSGL-1) [72]. However, activated platelets induce a proinflammatory monocyte phenotype, which is characterized by the nuclear translocation of the transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and the secretion of inflammatory cytokines and chemokines, such as TNF-α, IL-β, IL-8 and MC [73]. As a consequence of this proinflammatory signaling in monocytes, monocyte-platelet interactions may be uncoupled [74]. Platelets opsonized with IgG have been shown to convert peripheral monocytes to IL-10-producing regulatory monocytes in vitro and in vivo in a murine model [75]. Thus, both monocytes in the bloodstream and tissue macrophages play important roles in immunity [76]. Additionally, under basal conditions, transient 'touch-and-go' interactions occur between platelets and KCs via platelet-adhesion receptor (GPIb) and VWF, which is expressed on KCs [60]. Nevertheless, data on the interactions between platelets and lymphocytes are limited. Gerdes N et al. found that platelets regulate $CD4^+$ T-cell activation and differentiation [77].

The role of platelets in wound healing

As evidenced by the above findings, platelets are not only involved in initial aggregation and plug formation but also in a complex cascade of events that ultimately leads to blood vessel repair. Platelets play crucial roles in all stages of this cascade, including in coagulation, immune cell recruitment, inflammation, angiogenesis, remodeling and wound healing [78]. Would healing depends on different types of cells, including inflammatory cells, endothelial cells, fibroblasts and keratinocytes, which ultimately restore skin integrity by promoting cell recruitment, tissue regeneration and matrix remodeling [79, 80]. Platelets play a very important role in wound healing because they express many mediators that can affect this process. These mediators integrate cascades governed by multiple cytokines, such as platelet-derived growth factor (PDGF), transforming growth factor (TGF) and vascular endothelial growth factor (VEGF) [81]. These growth factors are released after activated platelets become entrapped within the fibrin matrix and can stimulate mitogenic responses in the periosteum to induce bone repair and wound healing. Various platelet-derived products or platelet concentrates can accelerate and enhance the body's natural wound-healing mechanisms [82]. Growth factors and cytokines are known to be essential regulators of basic cell functions [83]. Autologous platelet concentrates and platelet rich fibrin (PRF) are very important healing biomaterials. They have been applied in oral and maxillofacial surgery and in other disciplines of dentistry to promote healing [84, 85]. According to Froum et al. and Arora et al., platelet-rich plasma (PRP) can be utilized during various maxillofacial procedures, including in sinus lift procedures, ridge augmentation, socket preservation, intrabody or osseous defect repair, jaw reconstruction and soft tissue procedures, such as gingival grafts and subepithelial grafts [86, 87]. Guerid et al. demonstrated the positive effect of autologous platelets combined with keratinocytes in enhancing wound healing and reducing pain [88]. Notably, activated platelets in PRF have been used as a local therapeutic for various clinical applications, including in the treatment of both soft and hard tissue injuries, such as diabetic foot ulcers [89, 90]. PRP supports all three key mechanisms of wound healing, namely, angiogenesis, immunity and epithelial proliferation. Therefore, it is used to protect wounds and accelerate healing [91]. According to recent studies, interactions between platelet gel (PG) and peripheral blood mononuclear cells (PBMCs) lead to the production of several cytokines by PBMCs, which play important roles in wound healing and tissue repair [92].

The role of platelets in malignancy

Many recent findings have indicated that platelets play a significant role in the pathogenesis

of malignancy. Animal models have demonstrated the contribution of platelets to tumor cell proliferation, metastasis, and tumor angiogenesis in different types of tumors, such as carcinomas of the breast, colon, lung, and ovary, as well as in melanoma [14, 93]. The role of platelets in tumor angiogenesis and growth suggests their potential effects on malignancies [94]. The relevance of platelets in cancer is evidenced by their influence on the multistep development of tumors [95]. Interactions between platelets and tumor cells are known to be complex and bidirectional and involve numerous other components in the tumor microenvironment, such as immune cells, endothelial cells, and extracellular matrix [93]. Therefore, interactions between tumor cells and platelets play a crucial role in cancer growth and dissemination. This evidence supports a role for the clinical use of physiologic platelet receptors (GP1b/IX/V, GPIIb/IIIa and GPVI) and platelet agonists in metastasis and angiogenesis; blockade of the above-described platelet receptors has been shown to decrease metastasis [96]. After platelets adhere to activated tumors or injured endothelium, they release many biologically active molecules into the local microenvironment. These molecules are responsible for platelet-mediated effects on blood vessel tone, repair, and neo-angiogenesis [97]. Reciprocal interplay between breast cancer and the hemostatic system has been described based on the important roles of platelets, coagulation and fibrinolysis components, all of which affect each step of tumor growth and metastasis in breast cancer patients [98].

Platelets play a similar role in ovarian cancer. Cooke at al. demonstrated that platelet adhesion to ovarian cancer cells transforms these cells into an epithelial-mesenchymal transition (EMT) phenotype, which is essential for cancer progression [99]. These authors also demonstrated that inhibiting platelet function by aspirin and inhibiting $P2Y_{12}$ by clopidogrel attenuated platelet-induced ovarian cancer cell invasion [99]. Platelets have also been postulated to perform a critical function in the pathogenesis of prostate cancer, although the precise mechanisms driving this interaction are not well established [100]. Previously, platelets were found to contain androgens, and blocking the production of androgens or androgen receptors has been proven to inhibit prostate cancer growth. However, patients eventually become resistant to androgen blockers and develop castration-resistant prostate cancer (CRPC), which over-expresses the androgen receptor (AR) to reactivate AR signaling [101]. Therefore, functional AR is a key regulator of CRPC because some of its functional domains play a crucial role in CRPC pathology [102]. Targeting the critical events and complex signaling cascades involved in CRPC progression is essential for the development of effective drugs [103]. One study reported the powerful adhesion of platelet aggregates to tumor cells inside intestinal tumors via platelet P-selectin (CD62P). However, the ability of cancer cells to recruit platelets within intestinal tumors and how they signal adherent platelets to penetrate intestinal tumor tissues are poorly understood processes [104]. Platelets, leukocytes, and other soluble components can directly interact with tumor cells and consequently contribute to cancer cell adhesion, extravasation, and the establishment of metastatic lesions [105]. The formation of platelet-tumor cell aggregates in the circulation assists immune evasion and inhibits the formation of microvasculature to stop the spread of tumor cells to distant sites [106]. Dovizio et al. showed that platelet-induced COX-2 in cancer cells affects the expression of proteins involved in malignancy and of EMT marker genes [107].

Conclusion

As evidenced in the literature discussed above, the platelets are characterized by a morphologically and biochemically integrated structure. The presence of different receptors and adhesive molecules in their membranes enables platelets to interact with endothelial cells, pathogens, immune cells and tumor cells. These interactions are assisted by platelet-released mediators (via the platelet release reaction), including immunomodulatory cytokines, chemokines, and other mediators. Together, these mediators facilitate the many functions of platelets, which undoubtedly are of clinical significance. Currently, the multiple functions possessed by platelets are poorly understood. Future studies will be needed to further elucidate these functions.

Disclosure of conflict of interest

None.

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