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Review Article

The Biological Structure of Platelet and their Role with Subpopulations in Haemostasis

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ABSTRACT

Platelets are the smallest blood cells which circulated in the blood in inactive status. It is activated during the blood vessel injury to stop the bleeding through formation of platelet plug. It is also enhance the coagulation pathway by expose of Phosphatidylserine (PS) to increase the generation of thrombin and thereby increase the activation of other platelets. The unique structure of platelets supports them to do multifunction in different aspects. There are a different platelet populations based on their functions and their ages. In this review we aim to write overview of platelets including the structure, receptors, functions in adhesion and aggregation and identify the platelet subtypes and their role in haemostasis and thrombosis.

Keywords: Platelet; Haemostasis; Procoagulant; Thrombosis

INTRODUCTION

Platelets were first discovered in 1874 by Osler and have since been a significant focus of research [1]. Platelets are anucleated and the smallest of the blood cells, with a diameter of approximately 2-4 μm, and they circulate at a concentration of 140-450 × 10^9/L in their inactive state [2]. Megakaryocytes are the precursor cells for platelets in bone marrow, and each can produce 5-10 × 10^3 platelets. In a normal platelet count, two-thirds are circulated in the blood and one-third is stored in the spleen. Dead platelets are cleared from the blood circulation to the liver and spleen *via* phagocytosis [2].

Platelets become activated when a blood vessel is damaged, and they play a crucial role in haemostasis [3]. In blood circulation, platelets have a shorted life-span (approximately seven to twelve days) and their production and clearance are tightly regulated [4]. Additional to their role in haemostasis, platelets have a different function in pathological processes such as inflammation and cancer metastasis [5]. They can recognize vascular damage through their receptors, which bind to subendothelial collagen and von Willebrand Factor (vWF) produced by endothelial cells [6]. Activated platelets induce signalling pathways including integrin activation, cytoskeletal rearrangements, and granular secretion [7].

LITERATURE REVIEW

In this review we will explain the biological structure of platelets and how this unique structure assists platelets to do their functions in haemostasis. Also we will focus on the role of platelet subpopulations in primary haemostasis.

Platelet structure

Platelets are non-nucleated, although they have unique structures and distinct mitochondria. Their structure contains several features which help them perform their function of forming a platelet plug and reducing blood loss during vascular injury [8]. These features include a cell membrane, cytoskeleton, and a variety of granules and receptors (Figure 1) [9]. The platelet cell membrane is composed of a phospholipid bilayer integrated with glycoproteins, glycolipids, and cholesterol. These catalytic phospholipids are located in the inner leaflet of inactive platelets, known as phosphatidylserine [10], which is the site of different platelet surface receptors and lipid rafts. The platelet

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surface receptors are associated with most intracellular and extracellular signaling pathways, which include the following markers: CD36, CD63, CD9, GPCR, IIbIIIa, and GLUT-3 [2]. G-Protein-Coupled Receptors (GPCR) plays a key role in secretion of α granules and Adenosine diphosphate (ADP) from dense granules [11]. The Open Canalicular System (OCS) is like a tunnel between the cell and plasma membrane which enhances the entry and release of external and internal elements and promotes the formation of filopodia during platelet activation [12]. In addition, the dense tubular system is an internal network of endoplasmic reticulum which contains prostaglandin, thromboxane synthesis, and calcium. In activated platelets, prostaglandin is used to carry the calcium from the dense tubular system into the cytoplasm in order to enhance the activation process [13]. The cytoskeleton proteins such as actin and spectrin play a critical role in maintaining the normal discoid platelet shape in resting platelets and also change platelets to irregular shapes upon activation [14].

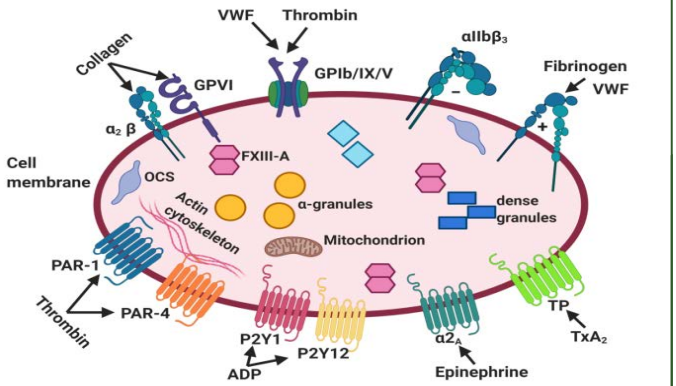

Figure 1: The basic platelet structure. This basic schematic of platelet structure include the cell membrane receptors and ligands, mitochondrion, actin cytoskeleton, α and dense granules, cellular FXIII-A and Open Canalicular System (OCS).

Platelets contain two major storage granules: α and dense granules, which contain most of the biologically active molecules required to trigger the coagulation pathways [15].The platelet α-granules contain numerous proteins such as fibrinogen, plasminogen, plasminogen activator inhibitor 1 (PAI-1), GPIIbIIIa, vWF, factor V, factor XI, factor XIII, and protein S, which are important for coagulation cascade [16]. The dense granules contain several activated molecules such as Adenosine 5'-diphosphate (ADP), Adenosine 5'-triphosphate (ATP), calcium, and serotonin, which are secreted during platelet activation [17].

Platelet receptors

Most of the recent advances in platelet research have focused on platelet receptors, with the purpose of enhancing understanding of platelet molecular functions and downstream signalling pathways. The platelet membrane is covered by several types of these receptors, such as integrins ($\alpha_{IIb}\beta_3$, $\alpha_2\beta_1$, $\alpha_5\beta_1$), G protein-coupled transmembrane receptors (PAR-1, PAR-4 thrombin receptors; P2Y1, P2Y12 ADP receptors; TxA2 receptor), C-type lectin receptors (P-selectin), and tyrosine kinase receptors (Figure 2) [18]. The membrane surface Glycoproteins GPVI and $\alpha_2\beta_1$ mediate platelet adhesion to subendothelial collagen, and GPIb–IX–V mediates adhesion to vWF. Additionally, the conformational change in integrin $\alpha_{IIb}\beta_3$ leading to platelet aggregation and activated integrin $\alpha_{IIb}\beta_3$ binds to fibrinogen, vWF, and fibronectin to form a bridge and stabilize the initial platelet plug [19].

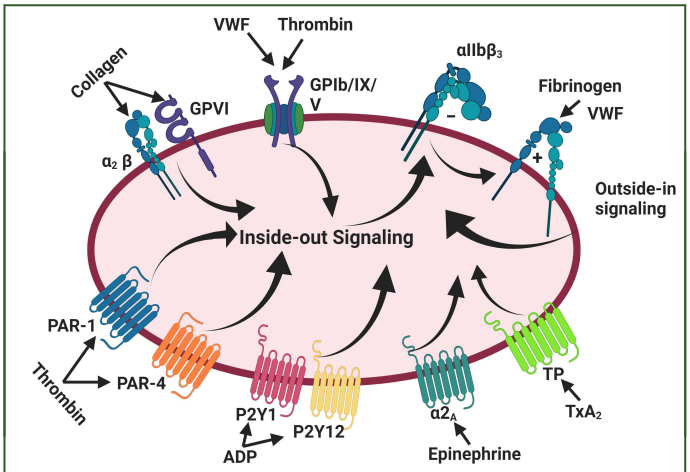

Figure 2: Major platelet receptors and ligands. Platelet is covered by different types of receptors which play important roles in platelet functions.

Platelets from formation until clearance

Platelets are the smallest blood cells, with a diameter of approximately 1-3 μm. Platelets were first discovered in 1874 by Osler, and in 1881 Bizzozero identified the role of platelets in haemostasis and thrombosis [20]. Today, most cellular and molecular platelet pathways are known, and number of therapeutic agents has been identified for the treatment and prevention of thrombotic disorders [21]. Haemostasis is mediated by thrombocytes in non-mammalian vertebrates; however, non-nucleated cells (platelets) mediate haemostasis in mammals and generate thrombi more effectively than thrombocytes [22]. Platelets are produced from megakaryocytes in the bone marrow after maturation and still live in the circulation for approximately eight to ten days [23]. After this, platelets release more PS, which may trigger macrophages to clear them *via* phagocytosis [24].

Platelet adhesion

Platelet adhesion can occur either at low shear rates in the venous system or at high shear rates in the arterial system [25]. When the blood vessel is injured, the subendothelial collagen exposed to the flowing blood and the plasma von Willebrand Factor (vWF) binds to collagen [26]. The platelet receptor Glycoprotein Ibα (GP Ibα) can interact with immobilized plasma vWF and trigger the platelet adhesion by gathering platelets at the site of injury [27]. Moreover, platelet Glycoprotein VI (GPVI) and integrin $\alpha_2\beta_1$ receptors can bind to collagen and carry the active signals to the platelets [28]. The binding of several platelet integrins to their ligands on the vessel wall-such as $\alpha_{IIb}\beta_3$ to fibrinogen, $\alpha_5\beta_1$ to fibronectin, and $\alpha_2\beta_1$ to collagen-enhances the stability of the platelet adhesion phase (Figure 3) [29].

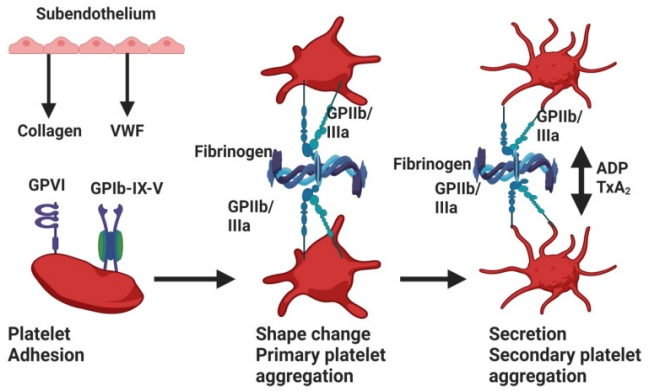

Figure 3: Platelet adhesion and aggregation. After vessel injury, the platelet activation need start and involves to adhere platelets to sub-endothelium surface to form the platelet adhesion. Interaction between platelet receptors GPIb-V-IX, GPIa-IIa, and subendothelial compounds triggers the release of platelet granule contents which accelerate the platelet aggregation.

Platelet activation

As previously mentioned, the initial binding between platelet surface receptors and their ligands can activate platelets [30]. Additionally, when blood vessel injury occurs, the coagulation cascade is activated and generates small amount of the potent platelet agonist thrombin, which is able to activate more platelets *via* the cleavage of Protease-Activated Receptors (PARs) and link to GPIbα [31]. Moreover, activated platelets express PS on their surface membrane, which facilitates the generation of thrombin and thus the activation of further platelets [32]. As a result of these activation cascades, platelets secrete the content of their α granules, including P-selectin, fibrinogen, vWF, fibronectin, vitronectin, and other adhesion molecules and proteins because they contain around 300 types of proteins [33-36]. In addition, Adenosine di-phosphate (ADP) secreted from the dense granules enhances further platelet aggregation through the activation of integrins [37]. Ca^{2+} is secreted from endoplasmic reticulum and dense granules and is essential for platelet activation [38]. The release of combined ADP and thromboxane A2 (Tx) also amplifies platelet activation by inducing inside-out signalling mechanisms and supporting platelet aggregation (Figure 3) [39].

Platelet aggregation

Platelet aggregation occurs after platelet activation and when integrin $\alpha_{IIb}\beta_3$ binds to fibrinogen in a fibrinogen-dependent pathway and other ligands bind to other elements in independent-fibrinogen pathways (Figure 3) [40]. As a result, outside-in signal mechanisms are delivered to enhance further platelet activation, cytoskeleton rearrangement, and secretion of platelet granules, which promotes the stability of the primary platelet plug [20].

In fibrinogen-dependent pathways, fibrinogen γ chain and vWF molecules bind to integrin $\alpha_{IIb}\beta_3$ and make a bridge to neighbouring activated platelets [41]. However, in fibrinogen knockout mice, the thrombus formation still occurs, which indicates the presence of mechanisms other than fibrinogen-dependent pathways [27]. In a study conducted by Xu et al., platelet fibronectin was increased 3-5 fold in fibrinogenemic patients and in fibronectin knockout mice, and the thrombus formation was impaired, which proved the role of fibronectin in platelet aggregation [40]. Indeed, fibronectin and vitronectin play a role in platelet aggregation, particularly in fibrinogen-independent pathways [35].

Platelet subtypes

Platelets have different subtypes based on function (procoagulant, aggregatory) or their age (mature or immuature) platelets (Figure 4) [42]. The first platelets which adhere to collagen and spread to form a monolayer called vanguard platelet. The platelet which adhere over vanguard platelets and onto collagen known as follower platelets and both are described as a subpopulation of platelets [43]. These subpopulations are essential for platelet adhesion and, thereby, platelet aggregation [43].

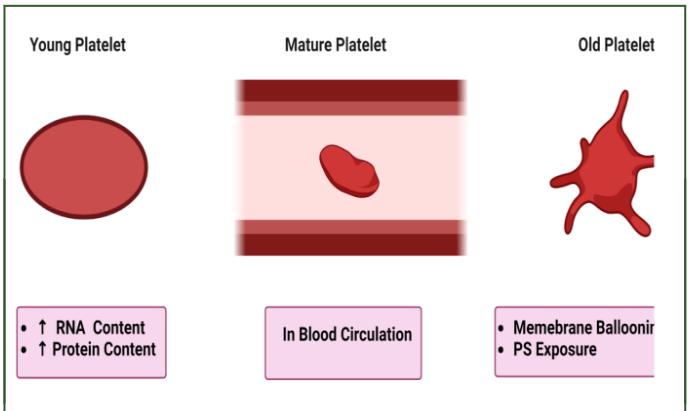

Figure 4: The structural changes of platelets during lifetime in the blood circulation. The immature platelets are characterize by increasing of RNA and protein contents. However, the membrane ballooning and PS exposure are marker for old platelets.

Pro-coagulant and aggregatory platelets

Platelets in normal conditions circulate in resting discoid shape [44]. As a result of haemostatic response, platelets are activated and change their shape to irregular blebbing structures with different names, including procoagulant, coated, or balloon platelets. These platelets are characterized by the absence of Glycoprotein IIb/IIIa (GPIIb/IIIa) engagement, and they only enhance coagulation cascade by exposing PS on their surface [45]. By phase-contrast live-cell microscopy, adhesion platelets form balloon platelets when extracellular Ca^{2+} is exposed, and this is associated with procoagulant activity and PS exposure [46]. Defective procoagulant platelet activity causes a clinical disorder called Scott syndrome [47]. Scott syndrome is a rare inherited bleeding disorder caused by impaired transfer of PS from the inner leaflet to the outer leaflet of the membrane of both erythrocytes and platelets [48]. As a result of this impairment, the activity of the procoagulant platelets is low and thrombin generation is reduced, leading to deficient fibrin formation. Due

to the rearrangement of the platelet microtubule cytoskeleton, the Na^+, Cl^-, and water-dependent fluids enter and form the balloon shape, which leads to the spreading of procoagulant, expression of microparticles, enhanced PS exposure, and ultimately, increased thrombin generation [43]. However, the inhibition of the influx of these fluids leads to impaired balloon platelet formation and reduced thrombin generation [43]. Understanding of the role of procoagulant platelets is important in terms of targeting therapy to regulate haemostasis, because using platelet-based therapies to reduce risk of thrombosis is not enough to stop the recruitment of platelets [49].

There are a significant differences between procoagulant and aggregatory platelets. As we mentioned before, procoagulant platelets characterize by PS externalization. However, the main characteristic of aggregatory platelets is having active αIIbβ3 integrins on their surfaces [50]. This activity enabling them to consolidate the platelet plug and decrease the distance between platelets to allow contact-dependent signalling mechanisms [51].

Immature and mature platelets

The age of platelets is crucial for their protein composition and, thereby, their structure and functions [52]. The immature platelets are representing the youngest platelets which released from megakaryocytes (MKs) and found in the circulation (Figure 4). It is also known as reticulated platelets due to increasing RNA contents similar to reticulocytes in erythropoiesis [53]. During activation, It is contain high level of surface activation markers and more dense granules than mature platelets [54]. Immature platelets counts are increased in the bone marrow around 2 times than in peripheral blood [55]. In contrast, the old platelets have low cytoskeletal protein, mitochondria number, calcium dynamics and granule secretions (Figure 4). Recently, they found around 50% of total platelet proteins are lower in old compared to young platelets [56].

DISCUSSION AND CONCLUSION

For many decades after the discovery of platelets, it is remain an exciting field for research. It is the smallest anucleated blood cell, and its unique structures enhance it to do multifunctions in different aspects. In hemostasis, it initiates blood clotting formation; however, this crucial role is not the sole role of platelets. It plays a fundamental role in monitoring the homeostasis of the body. Platelets are susceptible cells; thereby, they are one of the most accessible markers of several diseases and conditions. Despite the interaction between platelets and leukocytes, endothelial cells adapt their behavior and act as inflammatory markers. It is circulate in an inactive form and are activated during the blood vessel injury. It has a different subtypes based on their function or maturation to enhance platelet adhesion and aggregation.

AUTHOR CONTRIBUTIONS

F.S.M.A Supervised the research, create the figures and wrote the manuscript; S.S.S.A wrote the manuscript; A.M.S.A wrote the manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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