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Normal platelet function

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Abstract

Platelets play an important role in the vessel. Following their formation from megakaryocytes, platelets exist in circulation for 5–7 days and primarily function as regulators of hemostasis and thrombosis. Following vascular insult or injury, platelets become activated in the blood resulting in adhesion to the exposed extracellular matrix underlying the endothelium, formation of a platelet plug, and finally formation and consolidation of a thrombus consisting of both a core and shell. In pathological conditions, platelets are essential for formation of occlusive thrombus formation and as a result are the primary target for prevention of arterial thrombus formation. In addition to regulation of hemostasis in the vessel, platelets have also been shown to play an important role in innate immunity as well as regulation of tumor growth and extravasations in the vessel. These primary functions of the platelet represent its normal function and versatility in circulation.

Keywords

Hemostasis; Thrombosis; Immunity; Signal transduction; Bleeding; Cardiovascular disease

1 Platelet formation in the blood

The platelet is a small, anucleated cell that originally derives from the hematopoietic lineage *via* the megakaryocyte. The production of platelets from megakaryocytes is a systematic and regulated process that is thought to occur either in the bone marrow or, as has been shown more recently, the lung [1]. Due in large part to the extreme shear forces, the platelet is exposed to in the vessel as well as the limitations imposed on the platelet due to the absence of a nucleus; the lifespan of the platelet is limited to between 5 to 7 days following formation and separation from the megakaryocyte. While several labs have recently demonstrated that it is possible for the platelet to split into several smaller functional platelets under certain experimental conditions by utilizing the transcription machinery within the platelet, this process has rarely been observed outside of controlled conditions in the lab, and its importance in normal physiology of the vessel remains unclear [2, 3]. During its normal life cycle, platelets decrease in size such that young platelets are measurably larger than older platelets. At the end of their life in the vessel or following full activation of

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the platelet and incorporation into a forming clot in the vessel, they are removed from the vessel by neutrophils and macrophages and transported to the spleen for removal from the body.

2 Platelet role in hemostasis and thrombosis

2.1 Platelet clot formation

It has long been thought that the primary role of the platelet in circulation is to help maintain primary hemostasis and blood flow within the vessel [4, 5]. In order to accomplish this goal, the platelet flows through the vessel in close proximity to the vessel wall due to the biophysical nature of the blood constituents and shear forces within the vessel. This close proximity to the vessel wall allows for a quick response when a vascular insult or injury occurs. This response is typically thought to occur in several stages starting with adhesion to the subendothelial extracellular matrix through initial interaction of the matrix with specific receptors on the platelet including the GP1b/V/IX complex binding to Von Willebrand factor as well as GPVI and $\alpha\text{IIb}\beta 1$ receptors on the platelet surface binding to the collagen component of the extracellular matrix. Following this initial tethering of the platelet to the vessel wall, subsequent firm adhesion results in signal transduction within the platelet and flattening of the initially round or “plate” looking platelets. Secondary to firm adhesion, which results in the initial clot or thrombus formation, the activated platelets bound within the thrombus will begin to incorporate new platelets from circulation through platelet-platelet interactions mediated by the integrin receptor $\alpha\text{IIb}\beta 3$ (Fig. 1). Additionally, circulating platelets and loosely associated platelets will become activated through positive feedback initiated through the formation of secondary signals *via* the oxygenases COX-1 and 12-LOX as well as through granule secretion of small molecules known to activate the platelet. The resulting platelet thrombus will therefore consist of a “core” of tightly packed P-selectin positive platelets surrounded by a “shell” of loosely packed platelets that require secondary feedback through various receptors [6–8].

2.2 Platelet granule secretion

Platelets are thought to contain three types of granules. The first type is known as the dense granule. There are thought to be approximately 4–6 dense granules packed into each platelet. The dense granule contains more than 200 small molecules including calcium, ATP, ADP, 5-HT, and epinephrine. Following the initial steps of platelet activation, the dense granule fuses with the plasma membrane of the platelet *via* SNARE complexes such as VAMP8 and releases its contents to the extracellular vascular space. Many of these small molecules can signal the platelet through surface receptors. One of the most highly studied receptor classes on the platelet that is known to respond to the dense granule releasate is the purinergic receptor (P2Y_x). The platelet expresses two purinergic receptors, P2Y_1 and P2Y_{12} , both of which have been shown to play an important role in platelet activation and one of which (P2Y_{12}) is the target for antiplatelet therapy. The second type of granule is known as the alpha granule, and it has been reported that each platelet contains between 60–80 alpha granules. The alpha granule contains a number of larger proteins that are released either to the surface of the platelet or into circulation following granule secretion. One of the most predictable markers of platelet activation that is released from the alpha granule is P-selectin

which becomes tethered to the outside of the plasma membrane of the platelet following alpha granule secretion and can function as tether between platelets and other cells in the vessel. The third type of granule contained in the platelet is the lysosomal granule that plays an important role in degrading protein. While many of the granule releasates play an important role in positive feedback in the platelet activation process and possibly recruitment of new platelets into a growing thrombus, other releasates are thought to signal to the surrounding blood cells and endothelium. This is likely the case following injury in the vessel and is a mechanism that likely plays a role in wound healing following initial platelet activation and clot formation.

2.3 Eicosanoid and prostaglandin formation in the platelet

Bioactive lipids formed in the platelet following initial activation play a significant role in reinforcing the primary signal initiated through thrombin and collagen [9]. The majority of the lipid products are formed by oxidation of free fatty acids to their oxidized active forms. In the platelet, the most common fatty acid in the phospholipid membrane is arachidonic acid (AA). Fatty acid oxidation primarily occurs through two enzymes, cyclooxygenase-1 (COX-1) and 12-lipoxygenase (12-LOX). COX-1, a primary target for non-steroidal anti-inflammatory drugs (NSAIDs), produces a number of series-2 prostaglandins including PGE₂ and TxA₂ following AA oxidation. Both of these prostaglandins have G protein-coupled receptors (GPCRs) on the surface of the platelet that are selectively activated by their respective metabolites and play a role in reinforcing platelet activation. 12-LOX oxidizes free fatty acids to form eicosanoids (HETEs) that are thought to have a variety of functions both in the platelet as well as other cells in circulation or cells and tissues with accessibility to the HETEs in circulation. To this end, since a number of cells have recently been shown to express the GPCR for 12-HETE (GPR31), this is an area of active investigation. While the field of bioactive metabolites is complex, it is clear that many of the metabolites formed in the platelet or formed in other blood cells or endothelium play a role in regulating normal platelet function in hemostasis and thrombosis.

3 Non-traditional function of platelets

Although the traditional role of the platelet has been thought to be limited to maintaining hemostasis in the vessel under normal conditions and causing an occlusive thrombus under pathological conditions, other potential roles for the platelet have been proposed that are independent of either hemostasis or thrombosis. These roles include a role in immunity. Platelets were recently shown to express all nine Toll-like receptors (TLRs). Further, the expression pattern of the TLRs was observed to differ by gender [10, 11]. It will be interesting to see how the potential role for platelets in immunity is delineated in future studies and if the platelets play an important role in innate immunity against bacteria, virus, or even tumors. To this end, a recent study has shown that platelets exhibit the ability to autophagy; however, its role in autophagy in circulation is still unclear [12]. Another related function of the platelet that has recently been proposed is its ability to sample the blood environment. This sampling of the environment may serve the purpose of presenting the foreign virus or bacteria to other immune cells. Finally, platelets are known to release micro-particles in a regulated manner in the blood. Since more than 95% of micro-particles are

thought to be derived from platelets, it is possible that these particles that contain genetic material (miRNA, mRNA, *etc.*), enzymes, proteins, and small molecules, can alter or modulate the function of other cells in the vessel. It will be interesting to determine for example if platelets modify tumor extravasation into the vessel through communication with the endothelium or the tumor itself *via* these micro-particles. These recent studies have significantly widened the potential role for platelets in the body beyond acting as a “bandage” at sites of injury in the endothelium to prevent blood loss. Current and future focus of the platelet will help elucidate its “normal” role in regulating these physiological and pathophysiological processes.

4 Summary

The platelet is a complex anucleated cell that is multifunctional. While the primary function of the platelet is thought to be hemostasis, thrombosis, and wound healing through a complex activation process leading to integrin activation and formation of a “core” and “shell” at the site of injury, other physiological roles for the platelet exist including immunity and communication with other cells and tissue in the vessel. Further elucidation of these non-traditional roles of the platelet will help delineate the expansive regulatory role platelets play in the body.

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Fig. 1.

Platelet activation in the vessel occurs in several steps beginning with attachment to the endothelial or sub-endothelial matrix followed by firm adhesion, flattening of the platelets, and intraplatelet signal transduction. The initial platelet plug will form a core at the region of the injury that is fibrin rich, P-selectin positive and densely packed. More loosely packed platelets in the shell of the thrombus will surround the core and are more sensitive to antiplatelet therapies such as COX-1 and P2Y₁₂ receptor inhibition