Original Article

Factors Involved in Megakaryocytosis and Platelet Origin

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Abstract

Background: Developments in the field of platelet biology led to attention given to their origins and constituents. Objectives: we aimed to highlight the important factors involved in megakaryocytosis and platelet origin. **Methods:** We searched websites including PupMed, Medline, Google scholars, and Cochrane library for megakaryocytosis. **Results:** Platelets are a blood component. Indeed, they are not true cells but the cytoplasmic fragmentation of mature megakaryocytes. Their production process (megakaryocytopoiesis) occurs in bone marrow under the regulation of thrombopoietin, starting with the commitment and differentiation of HSCs and ending with the formation of polyploid megakaryocytes and the release of platelets in the blood stream as proplatelets. Recent research has focused on the implications of platelets not only in their primary role in hemostasis but also in other physiological, pathophysiological, and regenerative processes. The biological importance of platelets originates from their bioactive contents in the three intracellular storage granules, particularly alpha granules, as they have a wide range of growth factors. **Conclusion:** this resulted in the use of platelets at the target site in concentrations above the baseline, named platelet concentrates (PRP, PRF, and CGF), which are rich in platelets and growth factors.

Keywords: Platelets, Platelet Granules, Megakaryocytopoiesis, Thrombopoietin.

Introduction

Platelets are the smallest cellular blood components.[1] The principle function of these cell fragments is maintaining the hemostasis and clot formation at the site of vessel damage. They have important roles other than hemostasis including immunity, inflammation, repair and regeneration. Platelets express immune receptors and adhesion molecules on their membrane, additionally, upon activation, numerous stored mediators such as chemokines and cytokines are exocytosed, in these ways, platelets targeting neutrophils, monocytes and lymphocytes to the site of tissue injury or infection. Moreover, platelets capture and engulf microbes.[2,3]

Due to the unique biological activity of platelets, which comes from their contents, they have been the subject of recent scientific research and technological advancements, and the biological rationale for using them in high concentrations under the concept of "platelet concentrates", including "platelet-rich plasma (PRP)", "platelet-rich fibrin (PRF)", and concentrated growth factor (CGF).[4] These autologous platelet-based biomaterials are obtained from the centrifugation of whole blood and contain an abundance of platelets and "growth factors" that enhance tissue repair and regeneration.[5]

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Platelets

Platelets were firstly introduced by a pathologist Giulio Bizzozero in 1882.[6] Platelets, or thrombocytes, are small anucleated cell fragments with a diameter of around 2-4 µm and a mean lifespan of 8-10 days. They travel in the circulation as resting discoid fragments. Megakaryocytes that reside in the "bone marrow" are the precursor cells of platelets that produce and discharge platelets into the blood circulation. Without interacting with the blood vessel walls, inactivated platelets flow in the bloodstream in an isolated, resting, discoid form. Nevertheless, they are constantly sensing their surroundings through a variety of receptors and adhesion molecules on their surfaces, and at the end of their lives, they are eventually removed from the blood. As such, to maintain normal platelet counts, ongoing platelet synthesis is necessary.[7]

The lungs also involved in the biogenesis of platelets, the lung interstetium containing platelet pregeniters

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(megakaryocytes) which are then differentiate into platelets under the action of thrombopoietin.[8]

About two-thirds of platelets are in circulation in the blood stream, and the remaining one third is stored in the spleen. In a healthy human adult, the normal range of platelets count per microliter of blood (150 to 400×103). Each megakaryocyte can produce 5000–10000 platelets, with normal daily production of ($1x10^{11}$) platelets in healthy subjects, and the older ones are undergo destruction and clearance by the phagocytosis process in liver (by Kupffer cells) and spleen organs.[9]

The absence of a nucleus in mammalian platelets is partially offset by the presence of RNAs in the cytoplasm, in addition to the cellular organelles like mitochondria for energy production and ribosomes for protein translation.[10] However, it was suggested that the presence of a nucleus in a platelet may impede the platelet from performing its role; the presence of nucleus increases its size, reducing its ability to spread optimally and to travel through small vessels; additionally, platelets, in order to undergo morphological changes require flexibility, and are able to modulate their internal space.[11]

Recently, scientific research has given a new insight on platelets and their functions, as they have a vital role in various biological events thanks to their bioactive contents that are contained in their granules, specifically alpha granules, including growth and angiogenic factors, chemokines, cytokines, and other biomodulators that can respond to various signals and regulate many biological processes involving angiogenesis, inflammation, chemoattraction, stem cell engraftment, multiplication and differentiation, and tissue healing and regeneration.[7,12]

Platelet Formation

The formation of platelets is a fascinating and intricately coordinated series of cellular processes that can be divided into two phases, termed "megakaryocytopoiesis and thrombopoiesis". This involves the "commitment of hematopoietic stem cells" proliferation and ultimate proliferation of "megakaryocytic progenitors", and "maturation of megakaryocytes" to produce "functional platelets". This process take place in bone marrow in the highly specialized endosteal and vascular niches, where megakaryocytes extend proplatelet projections—long, cytoplasmic processes—to release platelets into the bloodstream.[13] Megakaryocytes are one of the biggest (50-100 μm) and rarest, as it constituent (0.05% to 0.1%) of cell population in the bone marrow, they are originated from hematopoietic stem cells and specialized in platelet formation.[14]

Megakaryopoiesis is a unique sequential cellular process through which the pluripotent "hematopoietic stem cells" (HSCs) undergo differentiation into the "myeloid lineage" to ultimately produce "mature megakaryocytes". MKs within bone marrow are highly specialized precursor cells for generating platelets and are derived from haematopoietic stem cells (HSCs), which develop from the "multipotential haemangioblast". The HSC gives rise to "multipotential progenitors" (MPPs), which further give rise to two main lineages, which are: the "common lymphoid progenitors" (CLPs), which advance to "lymphocyte progenitors" (T, B, and NK cells); and the "common myeloid progenitors" (CMPs), which then give rise to "bipotent granulocyte/macrophage progenitors" (GMPs); and the "megakaryocyte/erythroid progenitors" (MEPs), which subsequently give rise to erythroid progenitor and unipotent megakarcytic progenitors (MKPs), which eventually mature into mature megakaryocytes.[15-20]

Nevertheless, there is evidence suggesting that the MEP may develop directly from HSC, bypassing the CMP intermediate, to give rise to either an megakaryocyte or erythroid lineage.[21] The differentiation might be related to the low oxygen level in the deep dense environment of the bone marrow synchronized by released cytokine profile; these action has been confirmed in earlier in vitro cell culture studies.[22-24]

After the completion of terminal differentiation, megakaryocytes undergo a maturation phase, which is necessary for platelet production. Megakaryocytes undergo endomitosis as they mature, producing a polyploid nucleus that is typically 16 N but can occasionally reach 128 N.[25] Additionally, mature MKs have an enlarged size and characteristic structure named the demarcation membrane system (DMS) that provides membranes needed for successful extension of "proplatelet shafts", that fragments proplatelet from their apexes.[26] These proplatelets extend into the "bone marrow" sinusoids' lumen and are discharged into circulation under the action of shear and turbulent flow, then they reorganize into platelets.[20]

Megakaryopoiesis and thrombopoiesis processes are chiefly regulated by Thrombopoietin (TPO) in conjunction with other cytokines (including "interleukin-11, interleukin-6, interleukin-3, granulocyte– macrophage colony-stimulating factor and, the steel factor").[18,27,28]

Thrombopoietin, or c-Mpl ligand, is a glycoprotein that is synthesized primarily by the liver while the kidneys contribute to a lesser extent.[29,30] It is the chief physiological regulator of megakaryocytopoiesis and thrombopoiesis. Thrombopoietin is the primary cytokine regulator of steady-state "megakaryopoiesis and thrombopoiesis". It is implicated in HSC self-renewal, the proliferation of MKPs, the maturation of MK, and the production of platelets.[29,31]

TPO's biological action is achieved via its interaction with thrombopoietin receptors. TPO receptor, also referred to as c-MPL (cellular-myeloproliferative leukaemia) is expressed on hemangioblasts, "hematopoietic stem cells", megakaryocytes at all differentiation stages, and platelets. In its unliganded state, c-Mpl on the cell surface presents as an inactive monomer or homodimer. Following TPO binding, c- Mpl dimers undergo conformational changes and become active, resulting in transphosphorylation and activation of related "Janus Kinase 2 (JAK2)" proteins and consequently, phosphorylation of intracellular receptor tyrosine residues, there by stimulating multiple downstream biochemical cascades, including the "signal transducers and activators of transcription 3 and 5 (STAT3, STAT5)", "phosphoinositol 3- kinase (PI3K)", and the "mitogen-activated protein kinase

(MAPK) pathways", so this c-MPL/TPO singling pathway regulates and promotes MK and platelet production,[19,32,33] thereby activation the subcellular cascade STATs, PI3K, the "mitogen-activated protein kinases (MAPKs)", and "extracellular signal regulated kinases-1 and -2".

Platelet count regulation is dependent on the "negative feedback mechanism" of TPO, which is synthesized at a constant rate, but it binds to its receptor and is then degraded by megakaryocytes and platelets. Thus, when systemic platelet counts are high, plasma-free TPO levels are low, thus thrombopoiesis is depressed. When systemic platelet counts are low, plasma-free TPO levels are high, and thrombopoiesis proceeds rapidly.[34-36]

Structure of Platelets

Structurally, four major zones have been identified for platelets: i) peripheral zone, ii) a sol-gel zone, iii) an organelle zone, and iv) membrane systems.[37,38] The peripheral zone is composed of the membranes and related structures. The platelets possess an open canalicular system (OCS), which is a surface-connected system of channels. These channel system walls are contained in this zone. This zone consists of the glycocalyx, unit membrane, and submembrane area. A glycocalyx, or exterior coat, consists of glycoproteins, makes the outermost layer of the peripheral zone; these glycoproteins are in charge of platelet adhesion and signal transduction.[37] The platelet unit membrane consists of the same lipid bilayer as other cell types. It has an abundance of phospholipids that are distributed asymmetrically, which gives the coagulant the necessary surface to interact on. The third constituent of the peripheral zone is the region lying just below the unit membrane. It is intimately connected to the unit membrane and functions to translate external signals into chemical motifs and physical transformation needed for the activation of platelets.[37]

The sol-gel zone represents the cytoplasmic matrix of the platelets. The submembrane area of the peripheral zone and the sol-gel zone are continuous. It contains fiber systems in various states of polymerization that are responsible for maintaining the discoid outline of naive platelets and provide a contractile system engaged in platelet outline change, pseudopod expansion, contraction, and component release.[39] This zone comprises circumferential coils of microtubules, microfilaments, smooth and coated vesicles, and glycogen.[40]

The organelle zone is made up of the three fundamental kinds of secretory organelles: alpha (α) granules, dense (δ) granules, and lysosomes, in addition to mitochondria and glycogen granules.[40-42] The α-granules and δ-granules are unique to platelet structure and necessary for their biological function. Immediately, once the platelets are activated, degranulation process takes place, resulting in the release of numerous bioactive substances from these granules, including growth and angiogenic factors, cytokines, and chemokines that are able to respond to a multitude of signals and regulate a broad range of important biological processes, including inflammation, chemotaxis, cellular proliferation and differentiation, and angiogenesis/ new blood vessel formation. All these processes are of prime importance in the wound resolution and tissue repair.[12]

The contents of platelet granules[7] (Figure 1).

Alpha (α) granules are the majority granules in platelets; they constitute around 10% of the total platelet volume, there are about 40-80 α granules per platelet—tenfold more than dense granules. These granules ranging in size from 200 to 500 nm and have a round to oval shape.[43-46] α-granules store proteins in resting, non-activated platelets and release them only upon activation, which causes degranulation. The plethora of proteins and biomolecules in the α-granules is an attractive approach to delivering therapeutic growth factors and other bioactive molecules into the target site. More than 300 different proteins are stored in α- granules.[47]

They contain the greatest abundance of factors, including "adhesion molecules", angiogenic factors, "growth factors", chemokines, cytokines, fibrinolytic, antifibrinolytic, coagulation, and anticoagulation factors (Figure 1). Additionally, microbicidal proteins and immunologic molecules are also contained within α-granules, in addition to matrix metalloproteinases such as MMP-1, MMP-2, and MMP9 and necrotic factors such as TNFα and TNFβ.[7,42,43,48-50]

Dense (δ) granules are the second most prevalent platelet granules and are smaller than α-granules; roughly there are 3-8 dense "granules per platelet" and around 150 nm in size. The contents of δ-granules are fewer than α-granules and are composed mainly of cations, polyphosphates, serotonin, histamine, and adenine nucleotides, including "adenosine diphosphate (ADP)" and "adenosine triphosphate (ATP)".[46,51] A vesicular H+-ATPase proton pump keeps the luminal pH of dense granules at approximately 5.4.[52,53]

The least abundant granules are lysosomes. Typically, a platelet has 1-3 lysosomes, which are 0.1-0.5 μm in diameter. Enzymes are released from lysosomes, which degrade biological macromolecules like proteins, carbohydrates, lipids, and nucleic acids.[51] Despite the nucleus being lacking, platelets are metabolically active cells, as they include organelles such as "endoplasmic reticulum", mitochondria, and "Golgi apparatus", and they produce a variety of proteins from mRNA.[12]

In spite of lacking a nucleus, the platelets are equipped with functional mitochondria; normally, each platelet has five to eight mitochondria. The mitochondria are largely responsible for determining the lifespan of platelets. In addition to their involvement in energy metabolism and ATP synthesis, platelets' mitochondria are also essential for platelet activation and apoptosis, both of which are vital for platelet function and lifespan. For these reasons, platelets' mitochondria are significantly more important than nucleated cell mitochondria.[11]

Different secretion mechanisms are employed by alpha and dense granules upon platelet initiation. As alpha granule membranes merge with the nearby surface-connected canalicular system (SCCS), allowing their contents to pass through SCCS, dense granules move to the platelet periphery and fuse with cell membrane directly, where their contents are released.[54-56]

P-selectin, a cell adhesion molecule, is a type 1 transmembrane protein found in alpha granules. It mediates platelet-leukocyte interaction and is referred to as a platelet stimulation

biomarkers. Upon activation of the platelet, the p-selectin translocated and tethered to the outside of the plasma membrane of the platelet, and bind with leukocyte cells (monocyte and neutrophil cells) via its "ligand P-selectin glycoprotein-1 (PSGL-1)", this in turn contributed to the enrollment of these cells.[57-59]

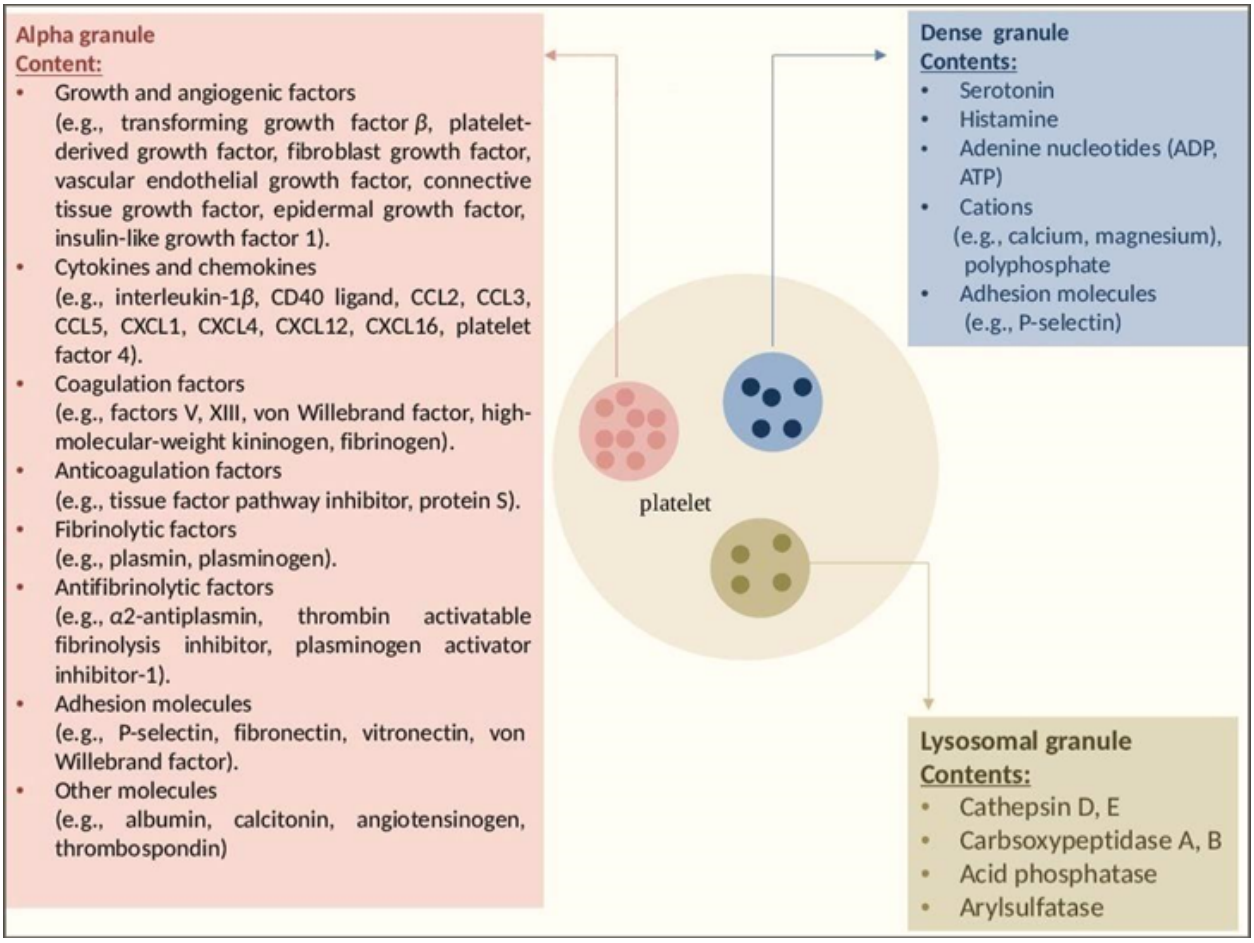

Figure 1: Platelet Granules and their Contents.

Conclusion

Platelets are derived from huge progenitor cells called megakaryocytes. Through a series of precisely orchestrated cellular processes, one mature megakaryocyte can give rise of thousands of platelets. Platelets perform their principle function in hemostasis and other biological processes such as inflammation and immunity, as well as wound healing and regeneration processes, thanks to their structure, receptors, and biomolecule contents which are saved in their granules and discharged upon activation.

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