

Platelet Physiological Function

Platelets (thrombocytes) are small pieces of cytoplasm released from the cytoplasm of mature Megakaryocyte in bone marrow. Although Megakaryocyte are the least number of hematopoietic cells in bone marrow, accounting for only 0.05% of the total number of bone marrow nucleated cells, the platelets they produce are extremely important for the hemostatic function of the body. Each Megakaryocyte can produce 200-700 platelets.



The platelet count of a normal adult is $(150-350) \times 10^9/L$. Platelets have the function of maintaining the integrity of blood vessel walls. When the platelet count decreases to $50 \times 10^9/L$, minor trauma or only increased blood pressure can cause blood stasis spots on the skin and submucosa, and even large purpura. This is because platelets can settle on the vascular wall at any time to fill the gaps left by endothelial cell detachment, and can fuse into vascular endothelial cells, which may play an important role in maintaining endothelial cell integrity or repairing endothelial cells. When there are too few platelets, these functions are difficult to complete and there is a tendency for bleeding. The platelets in the circulating blood are generally in a "stationary" state. But when blood vessels are damaged, platelets are activated through surface contact and the action of certain coagulation factors. Activated platelets can release a series of substances necessary for the hemostatic process and exercise physiological functions such as adhesion, aggregation, release, and adsorption. Platelet producing Megakaryocyte are also derived from hematopoietic stem cells in bone marrow. Hematopoietic stem cells first differentiate into megakaryocyte progenitor cells, also known as colony forming unit megakaryocyte (CFU Meg). The chromosomes in the nucleus of the progenitor cell stage are generally 2-3 ploidy. When the progenitor cells are diploid or tetraploid, the cells have the ability to proliferate, so this is the stage when Megakaryocyte lines increase the number of cells. When the megakaryocyte progenitor

cells further differentiated into 8-32 ploidy Megakaryocyte, the cytoplasm began to differentiate and the Endomembrane system gradually completed. Finally, a membrane substance separates the cytoplasm of Megakaryocyte into many small areas. When each cell is completely separated, it becomes a platelet. One by one, platelets fall off from Megakaryocyte through the gap between the endothelial cells of the sinus wall of the vein and enter the blood stream.

Having completely different immunological properties. TPO is a glycoprotein mainly produced by the kidneys, with a molecular weight of approximately 80000-90000. When platelets in the bloodstream decrease, the concentration of TPO in the blood increases. The functions of this regulatory factor include: ① enhancing DNA synthesis in progenitor cells and increasing the number of cell polyploids; ② Stimulate Megakaryocyte to synthesize protein; ③ Increase the total number of Megakaryocyte, resulting in increased platelet production. At present, it is believed that the proliferation and differentiation of Megakaryocyte are mainly regulated by two regulatory factors on the two stages of differentiation. These two regulators are megakaryocyte Colony-stimulating factor (Meg CSF) and Thrombopoietin (TPO). Meg CSF is a regulatory factor that mainly acts on the progenitor cell stage, and its role is to regulate the proliferation of megakaryocyte progenitor cells. When the total number of Megakaryocyte in bone marrow decreases, the production of this regulatory factor increases.

After platelets enter the bloodstream, they only have physiological functions for the first two days, but their average lifespan can be 7-14 days. In physiological hemostatic activities, platelets themselves will disintegrate and release all active substances after aggregation; It may also integrate into vascular endothelial cells. In addition to aging and destruction, platelets may also be consumed during their physiological functions. Aging platelets are engulfed in the spleen, liver, and lung tissues.

1. Ultrastructure of platelets

Under normal conditions, platelets appear as slightly convex discs on both sides, with an average diameter of 2-3 μ m. The average volume is 8 μ M³. Platelets are nucleated cells with no specific structure under an optical microscope, but complex ultrastructure can be observed under an electron microscope. At present, the structure of platelets is generally divided into surrounding area, sol gel area, Organelle area and special membrane system area.

The normal platelet surface is smooth, with small concave structures visible, and is an open canalicular system (OCS). The surrounding area of the platelet surface is composed of three parts: the outer layer, the unit membrane, and the submembrane area. The coat is mainly composed of various glycoproteins (GP), such as GP Ia, GP Ib, GP IIa, GP IIb, GP IIIa, GP IV, GP V, GP IX, etc. It forms a variety of adhesion receptors and can connect to TSP, thrombin, collagen, fibrinogen, etc. It is crucial for platelets to participate in coagulation and immune regulation. The unit membrane, also known as the plasma membrane, contains protein particles embedded in the lipid bilayer. The number and distribution of these particles are related to platelet adhesion and coagulation function. The membrane contains Na⁺- K⁺- ATPase, which maintains the ion concentration difference inside and outside the membrane. The submembrane zone is located between the lower part of the unit membrane and the outer side of the microtubule. Submembrane area contains submembrane filaments and Actin, which are related to platelet adhesion and aggregation.

Microtubules, microfilaments and submembrane filaments also exist in the sol gel region of platelets. These substances constitute the skeleton and contraction system of platelets, playing an important role in platelet deformation, particle release, stretching, and clot contraction. Microtubules are composed of Tubulin, accounting for 3% of the total platelet protein. Their main function is to maintain the shape of platelets.

Microfilaments mainly contain Actin, which is the most abundant protein in platelets and accounts for 15%~20% of total platelet protein. Submembrane filaments are mainly fiber components, which can help Actin-binding protein and Actin crosslink into bundles together. On the premise of the presence of Ca²⁺, actin cooperates with prothrombin,

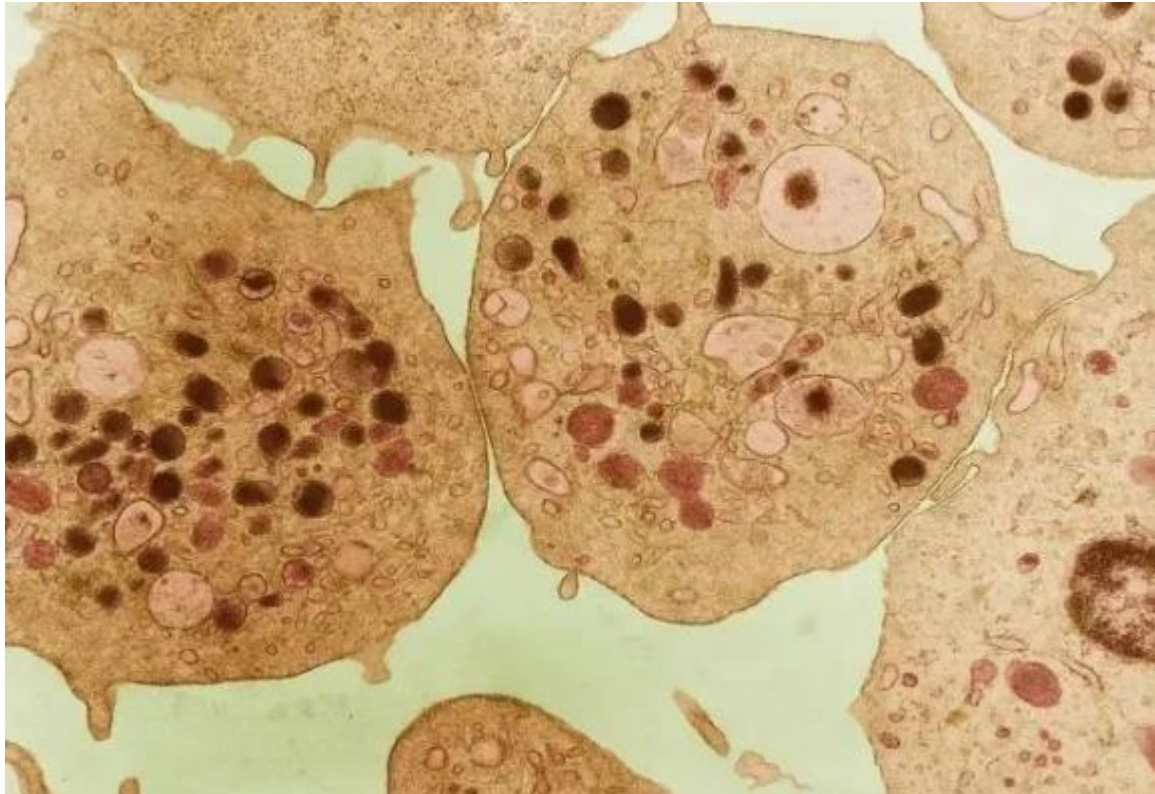
contractin, binding protein, co actin, myosin, etc. to complete platelet shape change, pseudopodium formation, cell contraction and other actions.

Table 1 Main Platelet Membrane Glycoproteins

Dense Granule	α Granule	Lysosome
ADP	PF4	Acid Hydrolase
ATP	β -TG	Cathepsin
5-serotonin (5-HT)	TSP	
Ca ²⁺	CTAP 3	
Pyrophosphate	PAI-1	
	Protein S Transforming Growth Factor (TGF)	
	Fibrin	
	Factor V Factor VIII Factor XIII	

The Organelle area is the area where there are many kinds of Organelle in platelets, which has a vital impact on the function of platelets. It is also a research hotspot in modern medicine. The most important components in the Organelle area are various particles, such as α Particles, dense particles (δ Particles) and Lysosome (λ Particles, etc., see Table 1 for details. α Granules are the storage sites in platelets that can secrete proteins. There are more than ten in each platelet α Particles. Table 1 lists only the relatively main components, and according to the author's search, it has been found that α There are over 230 levels of platelet derived factors (PDF) present in the granules. Dense particle ratio α The particles are slightly smaller, with a diameter of 250-300nm, and there are 4-8 dense particles in each platelet. At present, it has been found that 65% of ADP and ATP are stored in dense particles in platelets, and 90% of 5-HT in blood is also stored in dense particles. Therefore, dense particles are crucial for platelet aggregation. The ability to release ADP and 5-HT is also being used clinically to evaluate platelet secretion function. In addition, this region also contains mitochondria and Lysosome, which is also a research hotspot at home and abroad this year. The 2013 Nobel Prize in Physiology and Medicine was awarded to three scientists, James E. Rothman, Randy W. Schekman, and Thomas C. Südhof, for discovering the mysteries of intracellular transport mechanisms. There are also many unknown fields in the metabolism of substances and energy in platelets through intracellular bodies and Lysosome.

The special membrane system area includes OCS and dense tubular system (DTS). OCS is a tortuous pipeline system formed by the surface of platelets sinking into the interior of platelets, greatly increasing the surface area of platelets in contact with plasma. At the same time, it is an extracellular channel for various substances to enter platelets and release various particulate contents of platelets. The DTS pipeline is not connected to the outside world and is a place for the synthesis of substances within blood cells.



2. The Physiological Function of Platelets

The main physiological function of platelets is to participate in hemostasis and thrombosis. The functional activities of platelets during physiological hemostasis can be roughly divided into two stages: initial hemostasis and secondary hemostasis. Platelets play an important role in both stages of hemostasis, but the specific mechanisms by which they function still differ.

1) The initial hemostatic function of platelets

The thrombus formed during initial hemostasis is mainly white thrombus, and activation reactions such as platelet adhesion, deformation, release, and aggregation are important mechanisms in the primary hemostasis process.

I. Platelet adhesion reaction

The adhesion between platelets and non platelet surfaces is called platelet adhesion, which is the first step in participating in normal hemostatic reactions after vascular damage and an important step in pathological thrombosis. After vascular injury, platelets flowing through this vessel are activated by the surface of the tissue under the vascular endothelium and immediately adhere to the exposed collagen fibers at the injury site. At 10 minutes, the locally deposited platelets reached their maximum value, forming white blood clots.

The main factors involved in the process of platelet adhesion include platelet membrane glycoprotein I (GP I), von Willebrand factor (vW factor) and collagen in subendothelial tissue. The main types of collagen present on the vascular wall are types I, III, IV, V, VI, and VII, among which types I, III, and IV collagen are the most important for the platelet adhesion process under flowing conditions. The vW factor is a bridge that bridges the adhesion of platelets to type I, III, and IV collagen, and the glycoprotein specific receptor GP Ib on the platelet membrane is the main site for platelet collagen binding. In addition, glycoproteins GP IIb/IIIa, GP Ia/IIa, GP IV, CD36, and CD31 on the platelet membrane also participate in the adhesion to collagen.

II. Platelet aggregation reaction

The phenomenon of platelets adhering to each other is called aggregation. The aggregation reaction occurs with the adhesion reaction. In the presence of Ca^{2+} , platelet membrane glycoprotein GPIIb/IIIa and fibrinogen aggregate dispersed platelets together. Platelet aggregation can be induced by two different mechanisms, one is various

chemical inducers, and the other is caused by shear stress under flowing conditions. At the beginning of aggregation, platelets change from a disk shape to a spherical shape and protrude some pseudo feet that look like small thorns; At the same time, platelet degranulation refers to the release of active substances such as ADP and 5-HT that were originally stored in dense particles. The release of ADP, 5-HT and the production of some Prostaglandin are very important for aggregation.

ADP is the most important substance for platelet aggregation, especially the endogenous ADP released from platelets. Add a small amount of ADP (concentration at 0.9) to the platelet suspension μ Below mol/L), can quickly cause platelet aggregation, but quickly depolymerize; If moderate doses of ADP (1.0) are added μ At around mol/L, a second irreversible aggregation phase occurs shortly after the end of the first aggregation phase and the depolymerization phase, which is caused by the endogenous ADP released by platelets; If a large amount of ADP is added, it quickly causes irreversible aggregation, which directly enters the second phase of aggregation. Adding different doses of thrombin to platelet suspension can also cause platelet aggregation; And similar to ADP, as the dosage gradually increases, reversible aggregation can be observed from only the first phase to the appearance of two phases of aggregation, and then directly entering the second phase of aggregation. Because blocking the release of endogenous ADP with adenosine can inhibit platelet aggregation caused by thrombin, it suggests that the effect of thrombin may be caused by the binding of thrombin to thrombin receptors on the platelet cell membrane, leading to the release of endogenous ADP. The addition of collagen can also cause platelet aggregation in suspension, but only irreversible aggregation in the second phase is generally believed to be caused by the endogenous release of ADP caused by collagen. Substances that can generally cause platelet aggregation can reduce cAMP in platelets, while those that inhibit platelet aggregation increase cAMP. Therefore, it is currently believed that the decrease in cAMP may cause an increase in Ca^{2+} in platelets, promoting the release of endogenous ADP. ADP causes platelet aggregation, which requires the presence of Ca^{2+} and fibrinogen, as well as energy consumption.

The role of platelet Prostaglandin The phospholipid of platelet plasma membrane contains Arachidonic acid, and the platelet cell contains Phosphatidic acid A2. When platelets are activated on the surface, Phospholipase A2 is also activated. Under the catalysis of Phospholipase A2, Arachidonic acid is separated from phospholipids in the plasma membrane. Arachidonic acid can form a large amount of TXA2 under the catalysis of platelet cyclooxygenase and Thromboxane synthase. TXA2 reduces cAMP in platelets, resulting in a strong platelet aggregation and vasoconstriction effect. TXA2 is also unstable, so it quickly transforms into an inactive TXB2. In addition, normal vascular endothelial cells contain prostacyclin synthase, which can catalyze the production of prostacyclin (PGI2) from platelets. PGI2 can increase cAMP in platelets, so it has a strong inhibitory effect on platelet aggregation and Vasoconstriction.

Adrenaline can be passed through α 2. The mediation of Adrenergic receptor can cause biphasic platelet aggregation, with the concentration of (0.1~10) μ Mol/L. Thrombin at low concentrations (<0.1 μ At mol/L, the first phase aggregation of platelets is mainly caused by PAR1; At high concentrations (0.1-0.3) μ At mol/L, the second phase aggregation can be induced by PAR1 and PAR4. Strong inducers of platelet aggregation also include platelet activating factor (PAF), collagen, vW factor, 5-HT, etc. Platelet aggregation can also be induced directly by mechanical action without any inducer. This mechanism mainly works in arterial thrombosis, such as atherosclerosis.

III. Platelet release reaction

When platelets are subjected to physiological stimulation, they are stored in dense particles α The phenomenon of many substances in particles and lysosomes being expelled from cells is called a release reaction. The function of most platelets is achieved through the biological effects of substances formed or released during the release reaction. Almost all inducers that cause platelet aggregation can cause release reaction. The release reaction generally occurs after the first phase aggregation of platelets, and the substance released by the release reaction induces the second phase aggregation. The inducers that cause release reactions can be roughly divided into:

- i. Weak inducer: ADP, adrenaline, Norepinephrine, vasopressin, 5-HT.
- ii. Medium inducers: TXA₂, PAF.
- iii. Strong inducers: thrombin, pancreatic enzyme, collagen.

2) The role of platelets in blood coagulation

Platelets mainly participate in various coagulation reactions through phospholipids and membrane glycoproteins, including adsorption and activation of coagulation factors (factors IX, XI, and XII), formation of coagulation promoting complexes on the surface of phospholipid membranes, and promotion of prothrombin formation.

The plasma membrane on the surface of platelets binds to various coagulation factors, such as fibrinogen, factor V, factor XI, factor XIII, etc. α The particles also contain fibrinogen, factor XIII, and some platelet factors (PF), among which PF₂ and PF₃ are both promoting blood coagulation. PF₄ can neutralize heparin, while PF₆ inhibits fibrinolysis. When platelets are activated on the surface, they can accelerate the surface activation process of coagulation factors XII and XI. The phospholipid surface (PF₃) provided by platelets is estimated to accelerate the activation of prothrombin by 20000 times. After connecting factors Xa and V to the surface of this phospholipid, they can also be protected from the inhibitory effects of antithrombin III and heparin.

When platelets aggregate to form a hemostatic thrombus, the coagulation process has already occurred locally, and platelets have exposed a large amount of phospholipid surfaces, providing extremely favorable conditions for the activation of factor X and prothrombin. When platelets are stimulated by collagen, thrombin or kaolin, the Sphingomyelin and Phosphatidylcholine on the outside of the platelet membrane turn over with phosphatidyl Ethanolamine and phosphatidylserine on the inside, resulting in the increase of phosphatidyl Ethanolamine and phosphatidylserine on the surface of the membrane. The above phosphatidyl groups flipped over on the surface of platelets participate in the formation of vesicles on the membrane surface during platelet activation. The vesicles detach and enter the blood circulation to form microcapsules. The vesicles and microcapsules are rich in phosphatidylserine, which helps in the assembly and activation of prothrombin and participates in the process of promoting blood coagulation.

After platelet aggregation, its α The release of various platelet factors in particles promotes the formation and increase of blood fibers, and traps other blood cells to form clots. Therefore, although platelets gradually disintegrate, hemostatic emboli can still increase. The platelets left in the blood clot have pseudopodia that extend into the blood fiber network. The contractile proteins in these platelets contract, causing the blood clot to retract, squeezing out the serum and becoming a solid hemostatic plug, firmly sealing the vascular gap.

When activating platelets and the coagulation system on the surface, it also activates the fibrinolytic system. The Plasmin and its activator contained in platelets will be released. The release of serotonin from blood fibers and platelets can also cause endothelial cells to release activators. However, due to the disintegration of platelets and the release of PF₆ and other substances that inhibit proteases, they are not affected by fibrinolytic activity during the formation of blood clots.

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