Platelet

Platelets or **thrombocytes** (from Ancient Greek θρόμβος *(thrómbos)* 'clot', and κύτος *(kútos)* 'cell') are a component of blood whose function (along with the coagulation factors) is to react to bleeding from blood vessel injury by clumping, thereby initiating a blood clot.[1] Platelets have no cell nucleus; they are fragments of cytoplasm derived from the megakaryocytes[2] of the bone marrow or lung,[3] which then enter the circulation. Platelets are found only in mammals, whereas in other vertebrates (e.g. birds, amphibians), thrombocytes circulate as intact mononuclear cells.[4]:3

One major function of platelets is to contribute to hemostasis: the process of stopping bleeding at the site of interrupted endothelium. They gather at the site and, unless the interruption is physically too large, they plug the hole. First, platelets attach to substances outside the interrupted endothelium: *adhesion*. Second, they change shape, turn on receptors and secrete chemical messengers: *activation*. Third, they connect to each other through receptor bridges: *aggregation*.[5] Formation of this platelet plug (primary hemostasis) is associated with activation of the coagulation cascade, with resultant fibrin deposition and linking (secondary hemostasis). These processes may overlap: the spectrum is from a predominantly platelet plug, or "white clot" to a predominantly fibrin, or "red clot" or the more typical mixture. Some would add the subsequent *retraction* and *platelet inhibition* as fourth and fifth steps to the completion of the process[6] and still others would add a sixth step, *wound repair*. Platelets also participate in both innate[7] and adaptive[8] intravascular immune responses.

In addition to facilitating the clotting process, platelets contain cytokines and growth factors which can promote wound healing and regeneration of damaged tissues.[9][10]

Platelets

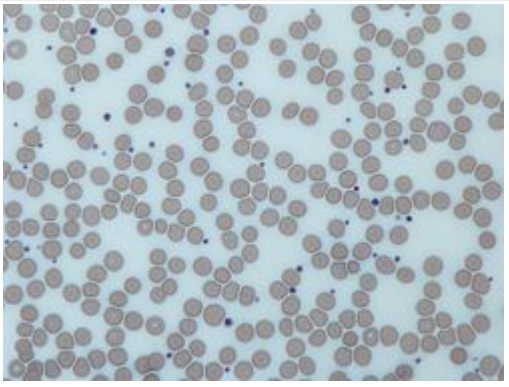


Image from a light microscope (500 ×) from a Giemsa-stained peripheral blood smear showing platelets (small purple dots) surrounded by red blood cells (large gray circular structures)

Details	
Precursor	Megakaryocytes
Function	Formation of blood clots; prevention of bleeding
Identifiers	
Latin	*thrombocytus*
MeSH	D001792 (https://meshb.nlm.nih.gov/record/ui?ui=D001792)
FMA	62851 (https://bioportal.bioontology.org/ontologies/FMA/?p=classes&conceptid=http%3A%2F%2Fpurl.org%2Fsig%2Font%2Ffma%2Ffma62851)

Anatomical terms of microanatomy

Structure

Structure

Structurally the platelet can be divided into four zones, from peripheral to innermost:

- Peripheral zone – is rich in glycoproteins required for platelet adhesion, activation and aggregation. For example, GPIb/IX/V; GPVI; GPIIb/IIIa.

- Sol-gel zone – is rich in microtubules and microfilaments, allowing the platelets to maintain their discoid shape.
- Organelle zone – is rich in platelet granules. Alpha granules contain clotting mediators such as factor V, factor VIII, fibrinogen, fibronectin, platelet-derived growth factor, and chemotactic agents. Delta granules, or dense bodies, contain ADP, calcium, and serotonin, which are platelet-activating mediators.
- Membranous zone – contains membranes derived from megakaryocyte smooth endoplasmic reticulum organized into a dense tubular system which is responsible for thromboxane A2 synthesis. This dense tubular system is connected to the surface platelet membrane to aid thromboxane A2 release.

The ligands, denoted by letter L, signal for platelets (P) to migrate towards the wound (Site A). As more platelets gather around the opening, they produce more ligands to amplify the response. The platelets congregate around the wound in order to create a cap to stop blood flow out of the tissue.

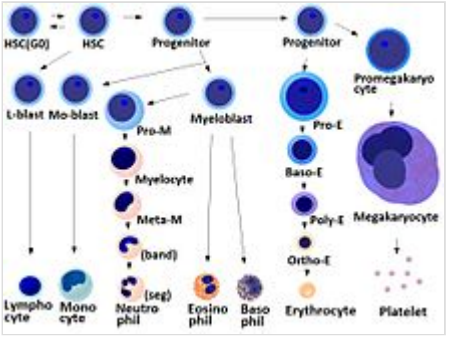
Shape

Circulating inactivated platelets are biconvex discoid (lens-shaped) structures,[11][4]:117–118 2–3 μm in greatest diameter.[12] Activated platelets have cell membrane projections covering their surface.

In a first approximation, the platelet shape can be considered similar to oblate spheroids, with a semiaxis ratio of 2 to 8.[13] This approximation is often used to model the hydrodynamic and optical properties of a platelet population, as well as to restore the geometric parameters of individual measured platelets by flow cytometry.[14] More accurate biophysical models of the platelet surface morphology, which model its shape from first principles, make it possible to obtain a more realistic platelet geometry in a calm and activated state.[15]

Development

- Megakaryocyte and platelet production is regulated by thrombopoietin, a hormone produced in the kidneys and liver.
- Each megakaryocyte produces between 1,000 and 3,000 platelets during its lifetime.
- An average of 10^{11} platelets are produced daily in a healthy adult.
- Reserve platelets are stored in the spleen and are released when needed by splenic contraction induced by the sympathetic nervous system.

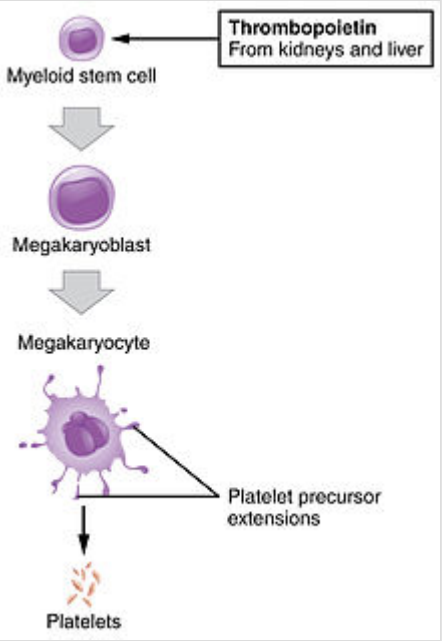


Platelets derive from multipotent marrow stem cells.

- The average life span of circulating platelets is 8 to 9 days.[16] Life span of individual platelets is controlled by the internal apoptotic regulating pathway, which has a Bcl-x_L timer.[17]
- Old platelets are destroyed by phagocytosis in the spleen and liver.

Hemostasis

The fundamental function of platelets is to clump together to stop acute bleeding. This process is complex, as more than 193 proteins and 301 interactions are known to be involved in platelet dynamics.[5] While there is much overlap, platelet function can be modeled in three steps:



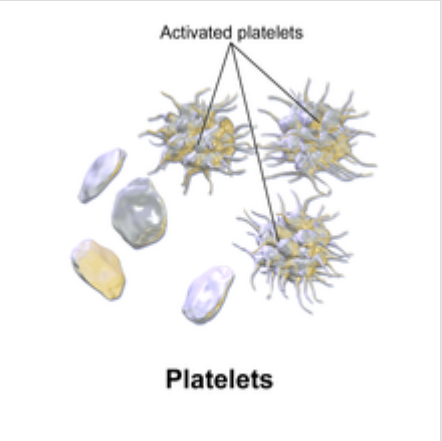
Platelets extruded from megakaryocytes

Adhesion

Thrombus formation on an intact endothelium is prevented by nitric oxide,[18] prostacyclin,[19] and CD39.[20]

Endothelial cells are attached to the subendothelial collagen by von Willebrand factor (VWF), which these cells produce. VWF is also stored in the Weibel-Palade bodies of the endothelial cells and secreted constitutively into the blood. Platelets store vWF in their alpha granules.

When the endothelial layer is disrupted, collagen and VWF anchor platelets to the subendothelium. Platelet GP1b-IX-V receptor binds with VWF; and GPVI receptor and integrin α2β1 bind with collagen.[21]



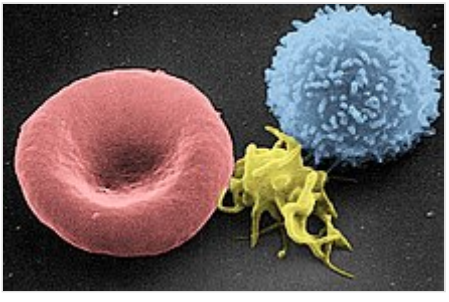
3D rendering of four inactivated and three activated platelets

Activation

Inhibition

The intact endothelial lining *inhibits* platelet activation by producing nitric oxide, endothelial-ADPase, and PGI_2 (prostacyclin). Endothelial-ADPase degrades the platelet activator ADP.

Resting platelets maintain active calcium efflux via a cyclic AMP-activated calcium pump. Intracellular calcium concentration determines platelet activation status, as it is the second messenger that drives platelet conformational change and degranulation (see below). Endothelial prostacyclin binds to prostanoid receptors on the surface of resting platelets. This event stimulates the coupled Gs protein to increase adenylate cyclase activity and increases the production of cAMP, further promoting the efflux of calcium and reducing intracellular calcium availability for platelet activation.


Scanning electron micrograph of blood cells. From left to right: human erythrocyte, activated platelet, leukocyte.

ADP on the other hand binds to purinergic receptors on the platelet surface. Since the thrombocytic purinergic receptor P2Y12 is coupled to Gi proteins, ADP reduces platelet adenylate cyclase activity and cAMP production, leading to accumulation of calcium inside the platelet by inactivating the cAMP calcium efflux pump. The other ADP-receptor P2Y1 couples to Gq that activates phospholipase C-beta 2 (PLCB2), resulting in inositol 1,4,5-trisphosphate (IP3) generation and intracellular

release of more calcium. This together induces platelet activation. Endothelial ADPase degrades ADP and prevents this from happening. Clopidogrel and related antiplatelet medications also work as purinergic receptor P2Y12 antagonists. Data suggest that ADP activates the PI3K/Akt pathway during a first wave of aggregation, leading to thrombin generation and PAR-1 activation, which evokes a second wave of aggregation.[22]

Trigger (induction)

Platelet activation begins seconds after adhesion occurs. It is triggered when *collagen* from the subendothelium binds with its receptors (GPVI receptor and integrin α2β1) on the platelet. GPVI is associated with the Fc receptor gamma chain and leads via the activation of a tyrosine kinase cascade finally to the activation of PLC-gamma2 (PLCG2) and more calcium release.

Tissue factor also binds to factor VII in the blood, which initiates the extrinsic coagulation cascade to increase thrombin production. Thrombin is a potent platelet activator, acting through Gq and G12. These are G protein-coupled receptors and they turn on calcium-mediated signaling pathways within the platelet, overcoming the baseline calcium efflux. Families of three G proteins (Gq, Gi, G12) operate together for full activation. Thrombin also promotes secondary fibrin-reinforcement of the platelet plug. Platelet activation in turn degranulates and releases factor V and fibrinogen, potentiating the coagulation cascade. So, in reality, the process of platelet plugging and coagulation are occurring simultaneously rather than sequentially, with each inducing the other to form the final fibrin-crosslinked thrombus.

Components (consequences)

GPIIb/IIIa activation

Collagen-mediated GPVI signalling increases the platelet production of thromboxane A2 (TXA2) and decreases the production of prostacyclin. This occurs by altering the metabolic flux of platelet's eicosanoid synthesis pathway, which involves enzymes phospholipase A2, cyclo-oxygenase 1, and thromboxane-A synthase. Platelets secrete thromboxane A2, which acts on the platelet's own thromboxane receptors on the platelet surface (hence the so-called "out-in" mechanism), and those of other platelets. These receptors trigger intraplatelet signaling, which converts GPIIb/IIIa receptors to their active form to initiate *aggregation*.[5]

Granule secretion

Platelets contain dense granules, lambda granules and alpha granules. Activated platelets secrete the contents of these granules through their canalicular systems to the exterior. Simplistically, bound and activated platelets degranulate to release platelet chemotactic agents to attract more platelets to the site of endothelial injury. Granule characteristics:

- α granules (alpha granules) – containing P-selectin, platelet factor 4, transforming growth factor-β1, platelet-derived growth factor, fibronectin, B-thromboglobulin, vWF, fibrinogen, and coagulation factors V and XIII

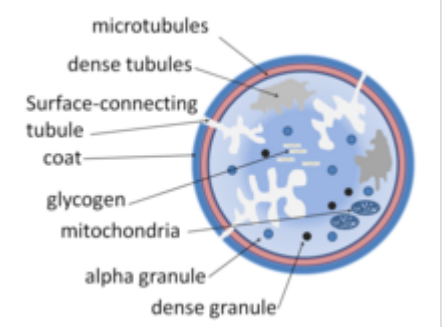


Diagram of the structure of a platelet showing the granules

- δ granules (delta or dense granules) – containing ADP or ATP, calcium, and serotonin
- γ granules (gamma granules) – similar to lysosomes and contain several hydrolytic enzymes
- λ granules (lambda granules) – contents involved in resorption during later stages of vessel repair

Morphology change

As shown by flow cytometry and electron microscopy, the most sensitive sign of activation, when exposed to platelets using ADP, are morphological changes.[23] Mitochondrial hyperpolarization is a key event in initiating changes in morphology.[24] Intraplatelet calcium concentration increases, stimulating the interplay between the microtubule/actin filament complex. The continuous changes in shape from the unactivated to the fully activated platelet is best seen on scanning electron microscopy. Three steps along this path are named *early dendritic*, *early spread* and *spread*. The surface of the unactivated platelet looks very similar to the surface of the brain, with a wrinkled appearance from numerous shallow folds to increase the surface area; *early dendritic*, an octopus with multiple arms and legs; *early spread*, an uncooked frying egg in a pan, the "yolk" being the central body; and the *spread*, a cooked fried egg with a denser central body.

These changes are all brought about by the interaction of the microtubule/actin complex with the platelet cell membrane and open canalicular system (OCS), which is an extension and invagination of that membrane. This complex runs just beneath these membranes and is the chemical motor that literally pulls the invaginated OCS out of the interior of the platelet, like turning pants pockets inside out, creating the dendrites. This process is similar to the mechanism of contraction in a muscle cell.[25] The entire OCS thus becomes indistinguishable from the initial platelet membrane as it forms the "fried egg". This dramatic increase in surface area comes about with neither stretching nor adding phospholipids to the platelet membrane.[26]

Platelet-coagulation factor interactions: coagulation facilitation

Platelet activation causes its membrane surface to become negatively charged. One of the signaling pathways turns on scramblase, which moves negatively charged phospholipids from the inner to the outer platelet membrane surface. These phospholipids then bind the tenase and prothrombinase complexes, two of the sites of interplay between platelets and the coagulation cascade. Calcium ions are essential for the binding of these coagulation factors.

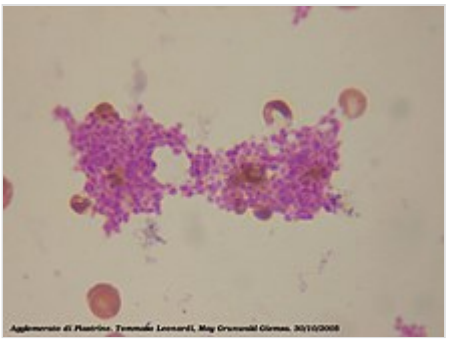
In addition to interacting with vWF and fibrin, platelets interact with thrombin, Factors X, Va, VIIa, XI, IX, and prothrombin to complete formation via the coagulation cascade.[27][28] Six studies suggested platelets express tissue factor: the definitive study shows they do not.[27] The platelets from rats were conclusively shown to express tissue factor protein and also it was proved that the rat platelets carry both the tissue factor pre-mRNA and mature mRNA.[29]

Aggregation

Aggregation of platelets begins minutes after their activation, and occurs as a result of turning on the GPIIb/IIIa receptor, allowing these receptors to bind with vWF or fibrinogen.[5] There are around 60,000 of these receptors per platelet.[30] When any one or more of at least nine different platelet surface receptors are turned on during activation, intraplatelet signaling pathways cause existing GpIIb/IIIa receptors to *change shape* – curled to straight – and thus become capable of binding.[5]

Since fibrinogen is a rod-like protein with nodules on either end capable of binding GPIIb/IIIa, activated platelets with exposed GPIIb/IIIa can bind fibrinogen to aggregate. GPIIb/IIIa may also further anchor the platelets to subendothelial vWF for additional structural stabilisation.

Classically it was thought that this was the only mechanism involved in aggregation, but three new mechanisms have been identified which can initiate aggregation, depending on the velocity of blood flow (i.e. shear range).[31]



Platelet clumps in a blood smear

Immune function

Platelets have a central role in innate immunity, initiating and participating in multiple inflammatory processes, directly binding pathogens and even destroying them. This supports clinical data which show that many with serious bacterial or viral infections have thrombocytopenia, thus reducing their contribution to inflammation. Platelet-leukocyte aggregates (PLAs) found in circulation are typical in sepsis or inflammatory bowel disease, showing the connection between thrombocytes and immune cells.[32]

The platelet cell membrane has receptors for collagen. Following the rupture of the blood vessel wall, the platelets are exposed and they adhere to the collagen in the surrounding connective tissue.

Immunothrombosis

As hemostasis is a basic function of thrombocytes in mammals, it also has its uses in possible infection confinement.[7] In case of injury, platelets, together with the coagulation cascade, form the first line of defense by forming a blood clot. Thus, hemostasis and host defense were intertwined in evolution. For example, in the Atlantic horseshoe crab (living fossil estimated to be over 400 million years old), the only blood cell type, the amebocyte, facilitates both the hemostatic function and the encapsulation and phagocytosis of pathogens by means of exocytosis of intracellular granules containing bactericidal defense molecules. Blood clotting supports immune function by trapping the pathogenic bacteria within.[33]

Although thrombosis, blood coagulation in intact blood vessels, is usually viewed as a pathological immune response, leading to obturation of lumen of blood vessel and subsequent hypoxic tissue damage, in some cases, directed thrombosis, called immunothrombosis, can locally control the spread of the infection. The thrombosis is directed in concordance of platelets, neutrophils and monocytes. The process is initiated either by immune cells by activating their pattern recognition receptors (PRRs), or by platelet-bacterial binding. Platelets can bind to bacteria either directly through thrombocytic PRRs[32] and bacterial surface proteins, or via plasma proteins that bind both to platelets and bacteria.[34] Monocytes respond to bacterial pathogen-associated molecular patterns (PAMPs), or damage-associated molecular patterns (DAMPs) by activating the extrinsic pathway of coagulation. Neutrophils facilitate the blood coagulation by NETosis. In turn, the platelets facilitate neutrophils' NETosis. NETs bind tissue factor, binding the coagulation centers to the location of infection. They also activate the intrinsic coagulation pathway by providing its negatively charged surface to the factor XII. Other neutrophil secretions, such as proteolytic enzymes which cleave coagulation inhibitors, also bolster the process.[7]

In case of imbalance throughout the regulation of immunothrombosis, this process can quickly become aberrant. Regulatory defects in immunothrombosis are suspected to be a major factor in causing pathological thrombosis in many forms, such as disseminated intravascular coagulation (DIC) or deep vein thrombosis. DIC in sepsis is a prime example of both the disregulated coagulation process as well as an undue systemic inflammatory response, resulting in a multitude of microthrombi of similar composition to that in physiological immunothrombosis – fibrin, platelets, neutrophils and NETs.[7]

Inflammation

Platelets are rapidly deployed to sites of injury or infection, and potentially modulate inflammatory processes by interacting with leukocytes and secreting cytokines, chemokines, and other inflammatory mediators.[35][36][37][38][39] Platelets also secrete platelet-derived growth factor (PDGF).

Platelets modulate neutrophils by forming platelet-leukocyte aggregates (PLAs). These formations induce upregulated production of αmβ2 (Mac-1) integrin in neutrophils. Interaction with PLAs also induce degranulation and increased phagocytosis in neutrophils. Platelets are also the largest source of soluble CD40L which induces production of reactive oxygen species (ROS) and upregulate expression of adhesion molecules, such as E-selectin, ICAM-1 and VCAM-1, in neutrophils, activates macrophages and activates cytotoxic response in T and B lymphocytes.[32]

Recently, the belief that mammalian platelets lacking nucleus are unable of autonomous locomotion was disproven.[40] In fact, the platelets are active scavengers, scaling walls of blood vessels and reorganising the thrombus. They are able to recognize and adhere to many surfaces, including bacteria, being able to fully envelop them in their open canalicular system (OCP), leading to proposed name of the process being "covercytosis", rather than phagocytosis, as OCS is merely an invagination of outer plasma membrane. These platelet-bacteria bundles are then used as an interaction platform for neutrophils which destroy the bacteria using the NETosis and phagocytosis.

Platelets also participate in chronic inflammatory disease, such as synovitis or rheumatoid arthritis.[41] Platelets are activated by collagen receptor glycoprotein IV (GPVI). Proinflammatory platelet microvesicles trigger constant cytokine secretion from neighboring fibroblast-like synoviocytes, most prominently Il-6 and Il-8. Inflammatory damage to the surrounding extracellular matrix continuously reveals more collagen, maintaining the microvesicle production.

Adaptive immunity

Activated platelets are able to participate in adaptive immunity, interacting with antibodies. They are able to specifically bind IgG through FcγRIIA, a receptor for the constant fragment (Fc) of IgG. When activated and bound to IgG opsonised bacteria, the platelets subsequently release reactive oxygen species (ROS), antimicrobial peptides, defensins, kinocidins and proteases, killing the bacteria directly.[42] Platelets also secrete proinflammatory and procoagulant mediators such as inorganic polyphosphates or platelet factor 4 (PF4), connecting innate and adaptive immune responses.[42][43]

Signs and symptoms of disorders

Spontaneous and excessive bleeding can occur because of platelet disorders. This bleeding can be caused by deficient numbers of platelets, dysfunctional platelets, or very excessive numbers of platelets: over 1.0 million/microliter. (The excessive numbers create a relative von Willebrand factor deficiency due to

sequestration.)[44][45]

One can get a clue as to whether bleeding is due to a platelet disorder or a coagulation factor disorder by the characteristics and location of the bleeding.[4]:815,Table 39-4 All of the following suggest platelet bleeding, not coagulation bleeding: the bleeding from a skin cut such as a razor nick is prompt and excessive, but can be controlled by pressure; spontaneous bleeding into the skin which causes a purplish stain named by its size: petechiae, purpura, ecchymoses; bleeding into mucous membranes causing bleeding gums, nose bleed, and gastrointestinal bleeding; menorrhagia; and intraretinal and intracranial bleeding.

Excessive numbers of platelets, and/or normal platelets responding to abnormal vessel walls, can result in venous thrombosis and arterial thrombosis. The symptoms depend on the site of thrombosis.

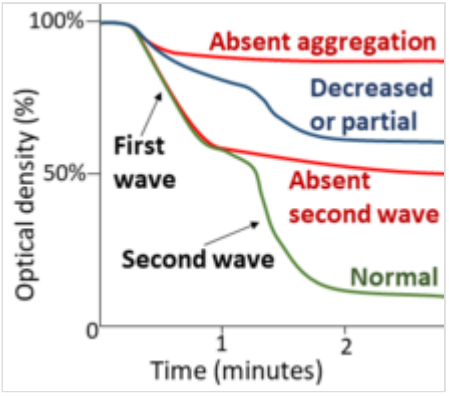
Measurement and Testing

Measurement

Platelet concentration in the blood (i.e. platelet count), is measured either manually using a hemocytometer, or by placing blood in an automated platelet analyzer using particle counting, such as a Coulter counter or optical methods.[46] Most common blood testing methods include platelet count in their measurements, usually reported as (PLT).[47]

Platelet concentrations vary between individuals and over time, with the population average being between 250,000 and 260,000 cells per mm^3 (equivalent to per microliter), but the typical laboratory accepted normal range is between 150,000 to 400,000 cells per mm^3 or 150–400 × 10^9 per liter.[47][46]

On a stained blood smear, platelets appear as dark purple spots, about 20% the diameter of red blood cells. The smear is used to examine platelets for size, shape, qualitative number, and clumping. A healthy adult typically has 10 to 20 times more red blood cells than platelets.



On for example optical densitometry, a first and second wave of platelet aggregation is seen, in this case for an ADP-initiated aggregation.

Bleeding time

Bleeding time was first developed as a test of platelet function by Duke in 1910.[48] Duke's test measured the time taken for bleeding to stop from a standardized wound in the ear lobe which was blotted every 30 seconds. The normal time for bleeding to stop was less than 3 minutes.[49] More modern techniques are now used. A normal bleeding time reflects sufficient platelet numbers and function, plus normal microvasculature.

Multiple electrode aggregometry

In multiple electrode aggregometry, anticoagulated whole blood is mixed with saline and a platelet agonist in a single-use cuvette with two pairs of electrodes. The increase in impedance between the electrodes as platelets aggregate onto them, is measured and visualized as a curve.[50][51]

Platelet aggregation function by disorders and agonists

	ADP	Epinephrine	Collagen	Ristocetin
P2Y receptor defect[52] (including Clopidogrel)	**Decreased**	Normal	Normal	Normal
Adrenergic receptor defect[52]	Normal	**Decreased**	Normal	Normal
Collagen receptor defect[52]	Normal	Normal	**Decreased or absent**	Normal
▪ **Von Willebrand disease[53]** ▪ **Bernard–Soulier syndrome[52]**	Normal	Normal	Normal	**Decreased or absent**
▪ **Glanzmann's thrombasthenia[52]** ▪ **Afibrinogenemia**	**Decreased**	**Decreased**	**Decreased**	Normal or **decreased**
Storage pool deficiency[53]	**Absent second wave**			**Partial**
Aspirin or aspirin-like disorder	**Absent second wave**		**Absent**	Normal

Light transmission aggregometry

In light transmission aggregometry (LTA), platelet-rich plasma is placed between a light source and a photocell. Unaggregated plasma allows relatively little light to pass through. After adding an agonist, the platelets aggregate, resulting in greater light transmission, which is detected by the photocell.[54]

PFA-100

The PFA-100 (Platelet Function Assay – 100) is a system for analysing platelet function in which citrated whole blood is aspirated through a disposable cartridge containing an aperture within a membrane coated with either collagen and epinephrine or collagen and ADP. These agonists induce platelet adhesion, activation and aggregation, leading to rapid occlusion of the aperture and cessation of blood flow termed the closure time (CT). An elevated CT with EPI and collagen can indicate intrinsic defects such as von Willebrand disease, uremia, or circulating platelet inhibitors. The follow-up test involving collagen and ADP is used to indicate if the abnormal CT with collagen and EPI was caused by the effects of acetyl sulfosalicylic acid (aspirin) or medications containing inhibitors.[55]

Disorders

Adapted from:[4]:vii

Low platelet concentration is called thrombocytopenia, and is due to either *decreased production* or *increased destruction*. Elevated platelet concentration is called thrombocytosis, and is either *congenital*, *reactive* (to cytokines), or due to *unregulated production*: one of the *myeloproliferative neoplasms* or certain other myeloid neoplasms. A disorder of platelet function is called a thrombocytopathy or a platelet function disorder.

Normal platelets can respond to an *abnormality on the vessel wall* rather than to hemorrhage, resulting in inappropriate platelet adhesion/activation and thrombosis: the formation of a clot within an intact vessel. This type of thrombosis arises by mechanisms different from those of a normal clot: namely, extending the fibrin of venous thrombosis; extending an unstable or ruptured arterial plaque, causing arterial thrombosis; and microcirculatory thrombosis. An arterial thrombus may partially obstruct blood flow, causing downstream ischemia, or may completely obstruct it, causing downstream tissue death.

The three broad categories of platelet disorders are "not enough", "dysfunctional", and "too many".[4]:vii

Thrombocytopenia

- Immune thrombocytopenia (ITP) – formerly known as immune thrombocytopenic purpura and idiopathic thrombocytopenic purpura
- Splenomegaly
  - Gaucher's disease
- Familial thrombocytopenia[56][57]
- Chemotherapy
- Babesiosis
- Dengue fever
- Onyalai
- Thrombotic thrombocytopenic purpura
- HELLP syndrome
- Hemolytic–uremic syndrome
- Drug-induced thrombocytopenic purpura (five known drugs – most problematic is heparin-induced thrombocytopenia (HIT)
- Pregnancy-associated
- Neonatal alloimmune associated
- Aplastic anemia
- Transfusion-associated
- Pseudothrombocytopenia
- Vaccine-induced immune thrombotic thrombocytopenia (VITT)

Altered platelet function (thrombocytopathy)

- Congenital
  - Disorders of adhesion
    - Bernard–Soulier syndrome
  - Disorders of activation
    - Disorders of granule amount or release
    - Hermansky–Pudlak syndrome
    - Gray platelet syndrome
    - ADP receptor defect
    - Decreased cyclooxygenase activity
    - Platelet storage pool deficiency

    - Disorders of aggregation
        - Glanzmann's thrombasthenia
        - Wiskott–Aldrich syndrome
    - Disorders of coagulant activity
        - COAT platelet defect
        - Scott syndrome
- Acquired
    - Disorders of adhesion
        - Paroxysmal nocturnal hemoglobinuria
        - Asthma[58]
        - Aspirin-exacerbated respiratory disease (AERD/Samter's triad)[59]
        - Cancer[60]
        - Malaria[61]
        - Decreased cyclooxygenase activity

Thrombocytosis and thrombocythemia

- Reactive
    - Chronic infection
    - Chronic inflammation
    - Malignancy
    - Hyposplenism (post-splenectomy)
    - Iron deficiency
    - Acute blood loss
- Myeloproliferative neoplasms – platelets are both elevated and activated
    - Essential thrombocythemia
    - Polycythemia vera
- Associated with other myeloid neoplasms
- Congenital

Pharmacology

Anti-inflammatory drugs

Some drugs used to treat inflammation have the unwanted side effect of suppressing normal platelet function. These are the non-steroidal anti-inflammatory drugs (NSAIDS). Aspirin irreversibly disrupts platelet function by inhibiting cyclooxygenase-1 (COX1), and hence normal hemostasis. The resulting platelets are unable to produce new cyclooxygenase because they have no DNA. Normal platelet function will not return until the use of aspirin has ceased and enough of the affected platelets have been replaced by

new ones, which can take over a week. Ibuprofen, another NSAID, does not have such a long duration effect, with platelet function usually returning within 24 hours,[62] and taking ibuprofen before aspirin prevents the irreversible effects of aspirin.[63]

Drugs that suppress platelet function

These drugs are used to prevent thrombus formation.

Oral agents

- Aspirin
- Cilostazol
- Clopidogrel
- Prasugrel
- Ticagrelor
- Ticlopidine

Drugs that stimulate platelet production

- Desmopressin
- Factor VIIa
- Thrombopoietin mimetics

Intravenous agents

- Abciximab
- Eptifibatide
- Tirofiban
- Others: oprelvekin, romiplostim, eltrombopag, argatroban

Therapies

Transfusion

Indications

Platelet transfusion is most frequently used to correct unusually low platelet counts, either to prevent spontaneous bleeding (typically at counts below 10×10^9/L) or in anticipation of medical procedures that will necessarily involve some bleeding. For example, in patients undergoing surgery, a level below 50×10^9/L is associated with abnormal surgical bleeding, and regional anaesthetic procedures such as epidurals are avoided for levels below 80×10^9/L.[64] Platelets may also be transfused when the platelet count is normal but the platelets are dysfunctional, such as when an individual is taking aspirin or clopidogrel.[65] Finally, platelets may be transfused as part of a massive transfusion protocol, in which the

three major blood components (red blood cells, plasma, and platelets) are transfused to address severe hemorrhage. Platelet transfusion is contraindicated in thrombotic thrombocytopenic purpura (TTP), as it fuels the coagulopathy.

Collection


Platelet concentrate

Platelets are either isolated from collected units of whole blood and pooled to make a therapeutic dose, or collected by platelet apheresis: blood is taken from the donor, passed through a device which removes the platelets, and the remainder is returned to the donor in a closed loop. The industry standard is for platelets to be tested for bacteria before transfusion to avoid septic reactions, which can be fatal. Recently the AABB Industry Standards for Blood Banks and Transfusion Services (5.1.5.1) has allowed use of pathogen reduction technology as an alternative to bacterial screenings in platelets.[66]

Pooled whole-blood platelets, sometimes called "random" platelets, are separated by one of two methods.[67] In the US, a unit of whole blood is placed into a large centrifuge in what is referred to as a "soft spin". At these settings, the platelets remain suspended in the plasma. The platelet-rich plasma (PRP) is removed from the red cells, then centrifuged at a faster setting to harvest the platelets from the plasma. In other regions of the world, the unit of whole blood is centrifuged using settings that cause the platelets to become suspended in the "buffy coat" layer, which includes the platelets and the white blood cells. The "buffy coat" is isolated in a sterile bag, suspended in a small amount of red blood cells and plasma, then centrifuged again to separate the platelets and plasma from the red and white blood cells. Regardless of the initial method of preparation, multiple donations may be combined into one container using a sterile connection device to manufacture a single product with the desired therapeutic dose.

Apheresis platelets are collected using a mechanical device that draws blood from the donor and centrifuges the collected blood to separate out the platelets and other components to be collected. The remaining blood is returned to the donor. The advantage to this method is that a single donation provides at least one therapeutic dose, as opposed to the multiple donations for whole-blood platelets. This means that a recipient is not exposed to as many different donors and has less risk of transfusion-transmitted disease and other complications. Sometimes a person such as a cancer patient who requires routine transfusions of platelets will receive repeated donations from a specific donor to further minimize the risk. Pathogen reduction of platelets using for example, riboflavin and UV light treatments can also be carried out to reduce the infectious load of pathogens contained in donated blood products, thereby reducing the risk of transmission of transfusion-transmitted diseases.[68][69] Another photochemical treatment process utilizing amotosalen and UVA light has been developed for the inactivation of viruses, bacteria, parasites, and leukocytes that can contaminate blood components intended for transfusion.[70] In addition, apheresis platelets tend to contain fewer contaminating red blood cells because the collection method is more efficient than "soft spin" centrifugation at isolating the desired blood component.

Storage

Platelets collected by either method have a very short shelf life, typically five days. This results in frequent problems with short supply, as testing the donations often requires up to a full day. Since there are no effective preservative solutions for platelets, they lose potency quickly and are best when fresh.

Platelets are stored under constant agitation at 20–24 °C (68–75.2 °F). Units can not be refrigerated as this causes platelets to change shape and lose function. Storage at room temperature provides an environment where any bacteria that are introduced to the blood component during the collection process may proliferate and subsequently cause bacteremia in the patient. Regulations are in place in the United States that require products to be tested for the presence of bacterial contamination before transfusion.[71]

Delivery to recipients

Platelets do not need to belong to the same A-B-O blood group as the recipient or be cross-matched to ensure immune compatibility between donor and recipient unless they contain a significant amount of red blood cells (RBCs). The presence of RBCs imparts a reddish-orange color to the product and is usually associated with whole-blood platelets. An effort is sometimes made to issue type specific platelets, but this is not critical, as it is with RBCs.

Platelets collected by using apheresis at an American Red Cross donation center

Prior to issuing platelets to the recipient, they may be irradiated to prevent transfusion-associated graft versus host disease or they may be washed to remove the plasma if indicated.

The change in the recipient's platelet count after transfusion is termed the "increment" and is calculated by subtracting the pre-transfusion platelet count from the post-transfusion platelet count. Many factors affect the increment including the recipient's body size, the number of platelets transfused, and clinical features that may cause premature destruction of the transfused platelets. When recipients fail to demonstrate an adequate post-transfusion increment, this is termed platelet transfusion refractoriness.

Platelets, either apheresis-derived or random-donor, can be processed through a *volume reduction* process. In this process, the platelets are spun in a centrifuge and the excess plasma is removed, leaving 10 to 100 mL of platelet concentrate. Such volume-reduced platelets are normally transfused only to neonatal and pediatric patients when a large volume of plasma could overload the child's small circulatory system. The lower volume of plasma also reduces the chances of an adverse transfusion reaction to plasma proteins.[72] Volume reduced platelets have a shelf life of only four hours.[73]

Wound repair

The blood clot is only a temporary solution to stop bleeding; tissue repair is needed. Small interruptions in the endothelium are handled by physiological mechanisms; large interruptions by the trauma surgeon.[74] The fibrin is slowly dissolved by the fibrinolytic enzyme, plasmin, and the platelets are cleared by phagocytosis.[75]

Platelets release platelet-derived growth factor (PDGF), a potent chemotactic agent; and TGF beta, which stimulates the deposition of extracellular matrix; fibroblast growth factor, insulin-like growth factor 1, platelet-derived epidermal growth factor, and vascular endothelial growth factor. Local application of these

factors in increased concentrations through platelet-rich plasma (PRP) is used as an adjunct in wound healing.[76]

Other animals

Instead of platelets, non-mammalian vertebrates have nucleated thrombocytes, which resemble B lymphocytes in morphology. They aggregate in response to thrombin, but not to ADP, serotonin, nor adrenaline, as platelets do.[77][78]

History

- George Gulliver in 1841 drew pictures of platelets[79] using the twin lens (compound) microscope invented in 1830 by Joseph Jackson Lister.[80] This microscope improved resolution sufficiently to make it possible to see platelets for the first time.
- William Addison in 1842 drew pictures of a platelet-fibrin clot.[81]
- Lionel Beale in 1864 was the first to publish a drawing showing platelets.[82]
- Max Schultze in 1865 described what he called "spherules", which he noted were much smaller than red blood cells, occasionally clumped, and were sometimes found in collections of fibrin material.[83]
- Giulio Bizzozero in 1882 studied the blood of amphibians microscopically *in vivo*. He named Schultze's spherules (lt.) *piastrine*: little plates.[84][85] An article in *Scientific American* suggests Bizzozero proposed the name Blutplattchen.[86]
- William Osler observed platelets and, in published lectures in 1886, called them a *third corpuscle* and a blood *plaque*; and described them as "a colorless protoplasmic disc".[87]
- James Wright examined blood smears using the stain named for him, and used the term *plates* in his 1906 publication[88] but changed to *platelets* in his 1910 publication[89] which has become the universally accepted term.

The term *thrombocyte* (clot cell) came into use in the early 1900s and is sometimes used as a synonym for platelet; but not generally in the scientific literature, except as a root word for other terms related to platelets (e.g. *thrombocytopenia* meaning low platelets).[4]:v3 The term thrombocytes are proper for mononuclear cells found in the blood of non-mammalian vertebrates: they are the functional equivalent of platelets, but circulate as intact cells rather than cytoplasmic fragments of bone marrow megakaryocytes.[4]:3

In some contexts, the word *thrombus* is used interchangeably with the word *clot*, regardless of its composition (white, red, or mixed). In other contexts it is used to contrast a normal from an abnormal clot: *thrombus* arises from physiologic hemostasis, *thrombosis* arises from a pathologic and excessive quantity of clot.[90] In a third context it is used to contrast the result from the process: *thrombus* is the result, *thrombosis* is the process.

See also

- List of distinct cell types in the adult human body

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