Platelet Structure and Function

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LEARNING OBJECTIVES

1. Diagram platelet structure, including glycocalyx, plasma membrane, filaments, microtubules, and granules.
2. Illustrate platelet adhesion, including the role of von Willebrand factor
3. Illustrate platelet aggregation, including the role of fibrinogen
4. List the secretions of platelet dense bodies and α-granules
5. Demonstrate the relationship of platelets and the plasma coagulation mechanism.

ABBRVIATIONS: ADP-adenosine diphosphate; ATP-adenosine triphosphate; CAM-cell adhesion molecule; cAMP-cyclic adenosine monophosphate; DAG-diacylglycerol; DTS-dense tubular system; ECM-extracellular matrix; EGF-endothelial growth factor; GMP-guanidine monophosphate; GP-glycoprotein; HMWK-high-molecular-weight kininogen; Ig-immunoglobulin; IP_3-inositol triphosphate; IP-PGI_2 receptor; MPV-mean platelet volume; $P2Y_1$ and $P2Y_{12}$-ADP receptors; PAI-1-plasminogen activator inhibitor-1; PAR-protease-activated receptor; PF_4-platelet factor 4; PGG_2-prostaglandin G2; PGH_2-prostaglandin H2; PDCI-platelet-derived collagenase inhibitor; PDGF-platelet-derived growth factor; PECAM-1-platelet–endothelial cell adhesion molecule-1; PGI_2-prostaglandin I_2 (prostacyclin); RGD-arginine-glycine-aspartic acid receptor target; SCCS-surface-connected canalicular system; STR-seven-transmembrane repeat receptor; TGF-β-transforming growth factor-β; TPα and TPβ-thromboxane receptors; TXA_2-thromboxane A2; VEGF/VPF-vascular endothelial growth factor/vascular permeability factor; VWF-von Willebrand factor

INDEX TERMS: Cell adhesion molecules, eicosanoid synthesis, glycoprotein, ligands, prostaglandin, platelet adhesion, platelet aggregation, platelet agonists, platelet count, platelet function, platelet production, platelet secretion, platelet structure

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Platelets are blood cells that are released from bone marrow megakaryocytes and circulate for approximately 10 days. They possess granular cytoplasm with no nucleus and their diameter when seen in a Wright-stained peripheral blood film averages 2.5 um with a subpopulation of larger cells, 4–5 um. Mean platelet volume (MPV), as measured in a buffered isotonic suspension flowing through the impedance-based detector cell of a clinical profiling instrument, is 8–10 fL.

Circulating, resting platelets are biconvex, although in EDTA blood they tend to "round up." On a blood film, platelets appear circular to irregular, lavender, and granular, although their diminutive size makes them hard to examine for internal structure.[1] In the blood, their surface is even, and they flow smoothly through veins, arteries, and capillaries.

The normal peripheral blood platelet count is 150–400,000/μL. This count represents only two thirds of available platelets because the spleen sequesters the remainder. In hypersplenism or splenomegaly, increased sequestration may cause a relative thrombocytopenia. Under conditions of hemostatic need, platelets move from the spleen to the peripheral blood and answer cellular and humoral stimuli by becoming irregular and sticky, extending pseudopods, and adhering to neighboring structures or aggregating with one another.

Platelet Structure

Platelet Plasma Membrane

The platelet plasma membrane is a standard bilayer composed of proteins and lipids (Figure 1). The predominant lipids are phospholipids, which form the basic structure, and cholesterol, which distributes asymmetrically throughout the phospholipids. The phospholipids form a bilayer with their polar heads oriented toward aqueous environments—toward the plasma externally and the cytoplasm internally. Their fatty acid chains, esterified to carbons 1 and 2 of the phospholipid triglyceride backbone, orient toward each other, perpendicular to the plane of the membrane, to form a hydrophobic barrier sandwiched within the hydrophilic layers.

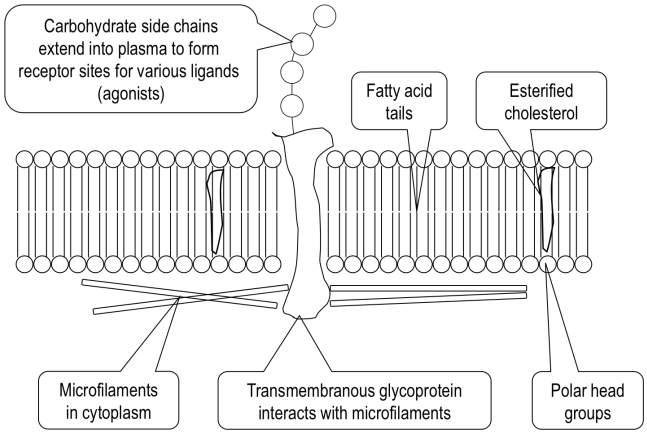


Figure 1. The platelet possesses a standard biological membrane composed of a phospholipid bilayer with polar head groups oriented toward the aqueous plasma and cytoplasm and nonpolar fatty acid tails that orient toward the center. The phospholipid backbone is interspersed with esterified cholesterol. A series of transmembranous proteins communicate with microfilaments and enzymes.

The neutral phospholipids phosphatidylcholine and sphingomyelin predominate in the plasma layer; the anionic or polar phospholipids phosphatidylinositol, phosphatidylethanolamine, and phosphatidylserine predominate in the inner, cytoplasmic layer. These phospholipids, especially phosphatidylinositol, support platelet activation by supplying arachidonic acid, an unsaturated fatty acid that becomes converted to the eicosanoids prostaglandin and thromboxane A_2 during platelet activation. Phosphatidylserine flips to the outer surface upon activation and is the charged phospholipid surface on which the coagulation enzymes, especially coagulation factor complex VIII and IX and coagulation factor complex X and V, assemble.[2,3]

Esterified cholesterol moves freely throughout the hydrophobic internal layer, exchanging with unesterified cholesterol from the surrounding plasma. Cholesterol stabilizes the membrane, maintains fluidity, and helps control the transmembranous passage of materials.

Anchored within the membrane are glycoproteins and proteoglycans; these support surface glycosaminoglycans, oligosaccharides, and glycolipids. The platelet membrane surface, called the glycocalyx, also absorbs albumin, fibrinogen, and other plasma proteins, in many instances transporting them to storage organelles within using a process called endocytosis.

At 20–30 nm, the platelet glycocalyx is thicker than the analogous surface layer of leukocytes or erythrocytes. This thick layer is adhesive and responds readily to hemostatic demands. The platelet carries its functional environment with it, meanwhile maintaining a negative surface charge that repels other platelets, other blood cells, and the endothelial cells that line the blood vessels.

The plasma membrane is selectively permeable, and the membrane bilayer provides phospholipids that support platelet activation internally and plasma coagulation externally. The anchored glycoproteins support essential plasma surface–oriented glycosylated receptors that respond to cellular and humoral stimuli, called ligands or agonists, transmitting their stimulus through the membrane to internal activation organelles.

Surface-Connected Canalicular System

The plasma membrane invades the platelet interior, producing its unique surface-connected canalicular system (SCCS; Figure 2). The SCCS twists sponge-like throughout the platelet, storing additional quantities of the same hemostatic proteins in the glycocalyx.

Dense Tubular System

Parallel and closely aligned to the SCCS is the dense tubular system (DTS), a remnant of the rough endoplasmic reticulum. The DTS sequesters Ca^{2+} and bears enzymes that support platelet activation. These enzymes include phospholipase A_2, cyclooxygenase, and thromboxane synthetase, which support the eicosanoid synthesis pathway that produces thromboxane A_2.

Cyclooxygenase is the enzyme that is inactivated by aspirin acetylation.

Platelet Plasma Membrane Receptors That Provide for Adhesion

The platelet membrane supports more than 50 categories of receptors; Tables 1 and 2 list representative receptors that support platelet adhesion and aggregation. The receptors most often involved in laboratory tests are $P2Y_{12}$, the ADP receptor that is blocked by thienopyridine drugs clopidogrel, prasugrel, and ticagrelor; GP IIb-IIIa, the fibrinogen receptor that is suppressed by the glycoprotein inhibitors; GP Ib-V-IX, the von Willebrand factor receptor; and the collagen receptors GP Ia-IIa and GP VI.

Platelet Cytoskeleton: Microfilaments and Microtubules

A circumferential bundle of microtubules maintains the platelet's discoid shape. The circumferential microtubules parallel the plane of the outer surface of the platelet and reside just within, although not touching, the plasma membrane. When microtubules disassemble in the cold, platelets become round, but upon warming to 37C, they recover their original disc shape. On cross section, microtubules are cylindrical, with a diameter of 25 nm. They also reassemble in long parallel bundles during platelet shape change to provide rigidity to pseudopods.

In the narrow area between the microtubules and the membrane lies a thick meshwork of microfilaments composed of actin. Actin is contractile in platelets (as in muscle) and anchors the plasma membrane glycoproteins and proteoglycans.

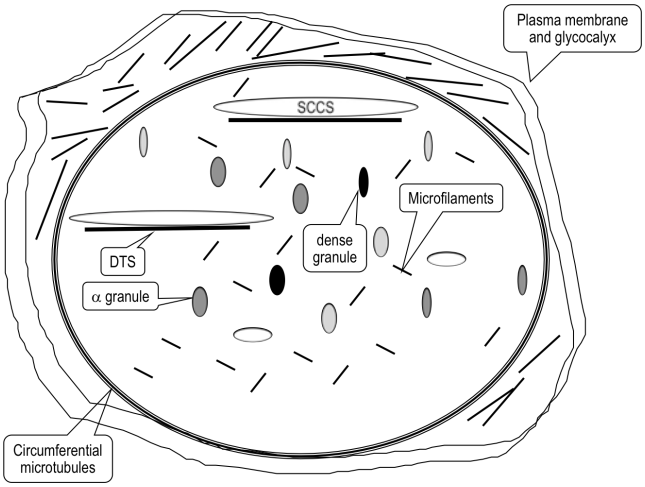


Figure 2. Diagram of a circulating platelet illustrating α-granules, dense granules, dense tubular system (DTS) surface-connected canalicular system (SCCS), circumferential microtubules.

Table 1. Glycoprotein Platelet Membrane Receptors That Participate in Adhesion and in the Initiation of Aggregation by Binding Specific Ligands

Electrophoresis Nomenclature	Current Nomenclature	Ligand	Cluster Designation	Comments
GP Ia-IIa	Integrin: $\alpha_2\beta_1$	Collagen	CD29, CD49b	Avidity is upregulated via "inside-out" activation that depends on collagen binding to GP VI
	Integrin: $\alpha_v\beta_1$	Vitronectin		
	Integrin: $\alpha_5\beta_1$	Laminin	CD29, CD49e	
	Integrin: $\alpha_6\beta_1$	Fibronectin	CD29, CD49f	
GP VI	CAM of the immunoglobulin gene family	Collagen		Key collagen receptor, triggers activation, release of agonists that increase the avidity of integrins $\alpha_2\beta_1$and $\alpha_{IIb}\beta_3$.
GP Ib-IX-V	CAM of the leucine-rich repeat family	VWF and thrombin bind GP Ibα; thrombin cleaves a site on GP V	CD42a, CD42b, CD42c, CD42d	GP Ib-IX-V is a 2:2:2:1 complex of GP Ibα and Ibβ, GP IX, and GP V. There are 25,000 copies on the resting platelet membrane surface, 5% to 10% on the α-granule membrane, but few on the SCCS membrane. GP Ibα is the VWF-specific site. Fifty percent of GP Ibα/Ibβ is cleared from the membrane on activation. Bernard-Soulier syndrome mutations are identified for all but GP V. Bound to subsurface actin-binding protein.
GP IIb-IIIa	Integrin: $\alpha_{IIb}\beta_3$	Fibrinogen, VWF	CD41, CD61	GP IIb and IIIa are distributed on the surface membrane, SCCS, and α-granule membranes (30%). Heterodimer forms on activation.

CAM, Cell adhesion molecule; GP, glycoprotein; SCCS, surface-connected canalicular system; VWF, von Willebrand factor.

Table 2. Platelet STR Receptor-Ligand Interactions Coupled to G proteins

Receptor	Ligand	G Proteins
PAR1	Thrombin	Coupled to G_1 protein that reduces cAMP; coupled to G_q and G_{12} proteins that increase IP_3 and DAG
PAR4	Thrombin	Coupled to G_q and G_{12} proteins that increase IP_3 and DAG
$P2Y_1$	ADP	Coupled to G_q protein that increases IP_3 and DAG
$P2Y_{12}$	ADP	Coupled to G_1 protein that reduces cAMP
TPα and TPβ	TXA_2	Coupled to G_q protein that increases IP_3 and DAG
α_2-adrenergic	Epinephrine	Coupled to G_1 protein that reduces cAMP; potentiates effects of ADP, thrombin, and TXA_2
IP	PGI_2	Coupled to G_S protein that increases cAMP to inhibit activation

STRs are named for their peculiar "seven-transmembranous repeat" anchorage. These receptors mediate "outside-in" platelet activation by transmitting signals initiated by external ligand binding to internal G proteins.

ADP, Adenosine diphosphate; cAMP, cyclic adenosine monophosphate; DAG, diacylglycerol; IP_3, inositol triphosphate; PAR, protease-activated receptor; PGI_2, prostaglandin I_2 (prostacyclin); STR, seven-transmembrane repeat receptor; TXA_2, thromboxane A_2; $P2Y_1$ and $P2Y_{12}$, ADP receptors; TPα and TPβ, thromboxane receptors; IP, PGI_2 receptor.

The cytoplasm also contains intermediate filaments, ropelike polymers 8–12 nm in diameter, of desmin and vimentin. The intermediate filaments connect with actin and the tubules, maintaining the platelet shape. Microtubules, actin microfilaments, and intermediate microfilaments control platelet shape change, extension of pseudopods, and secretion of granule contents.

Platelet Granules: α-Granules, Dense Granules, and Lysosomes

There are 50 to 80 α-granules in each platelet. Unlike the nearly opaque dense granules, α-granules stain medium gray in osmium-dye transmission electron microscopy preparations. The α-granules are filled with proteins, some endocytosed, some synthesized within the megakaryocyte (Table 3). As the platelet becomes activated, α-granule membranes fuse with the SCCS. Their contents flow to the nearby microenvironment, where they participate in platelet adhesion and aggregation and support plasma coagulation.[4]

There are 2–7 dense granules per platelet. Also called dense bodies, these appear later than α-granules in megakaryocyte differentiation and stain black (opaque) when treated with osmium in transmission electron microscopy. Small molecules are endocytosed and are stored in the dense granules (Table 4).

Table 3. Representative Platelet α-Granule Proteins

	Coagulation Proteins	Non-coagulation Proteins
Proteins Present in Platelet Cytoplasm and α-Granules		
Endocytosed	Fibronectin	Albumin
	Fibrinogen	Immunoglobulins
Megakaryocyte-synthesized	Factor V	—
	Thrombospondin	—
	VWF	—
Proteins Present in α-Granules But Not Cytoplasm (Megakaryocyte-Synthesized)		
	β-thromboglobulin	EGF
	HMWK	Multimerin
	PAI-1	PDC1
	Plasminogen	PDGF
	PF4	TGF-β
	Protein C inhibitor	VEGF/VPF
Platelet Membrane-Bound Proteins		
Restricted to α-granule membrane	P-selectin	GMP33
	—	Osteonectin
In α-granule and plasma membrane	GP IIb-IIIa	cap1
	GP IV	CD9
	GP Ib-IX-V	PECAM-1

EGF, Endothelial growth factor; GMP, guanidine monophosphate; GP, glycoprotein; HMWK, high-molecular-weight kininogen; Ig, immunoglobulin; PAI-1, plasminogen activator inhibitor-1; PDCI, platelet-derived collagenase inhibitor; PDGF, platelet-derived growth factor; PECAM-1, platelet–endothelial cell adhesion molecule-1; PF4, platelet factor 4; TGF-β, transforming growth factor-β; VEGF/VPF, vascular endothelial growth factor/vascular permeability factor; VWF, von Willebrand factor; cap1, adenyl cyclase–associated protein.

Table 4: Dense-Granule (Dense Body) Contents

Small Molecule	Comment
ADP	Nonmetabolic, supports neighboring platelet aggregation by binding to ADP receptors $P2Y_1$, $P2Y_{12}$
ATP	Function unknown, but ATP release is detectable upon platelet activation
Serotonin	Vasoconstrictor that binds endothelial cells and platelet membranes
Ca^{2+} and Mg^{2+}	Divalent cations support platelet activation and coagulation

ADP, Adenosine diphosphate; ATP, adenosine triphosphate; $P2Y_1$ and $P2Y_{12}$, members of the purigenic receptor family (receptors that bind purines).

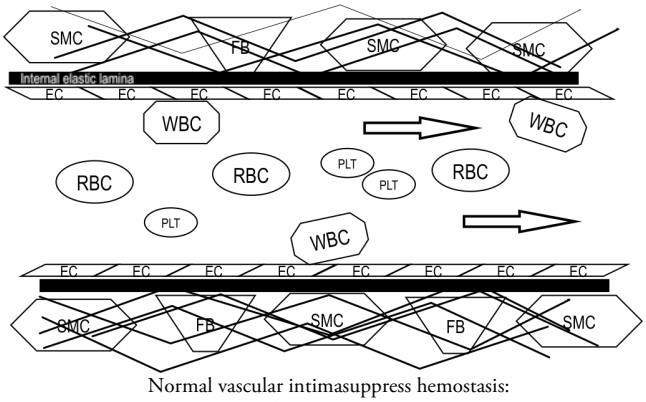
Platelets also have a few lysosomes, similar to those in neutrophils, 300-nm-diameter granules that stain positive for arylsulfatase, β-glucuronidase, acid phosphatase, and catalase. The lysosomes probably digest vessel wall matrix components during in vivo aggregation and may also digest autophagic debris.

Platelet Function

Although the following discussion seems to imply a linear and stepwise process, adhesion, aggregation, and secretion, collectively called platelet activation, are often simultaneous.[5,6]

Adhesion: Platelets Bind Elements of the Vascular Matrix

In arterioles, where the shear rate (viscosity) is over 1000 s^{-1}, platelet adhesion and aggregation require a sequence of events that involves collagen, tissue factor, phospholipid, VWF, and a number of platelet receptors, ligands and activators (Figure 3).[7]



Normal vascular intimasuppress hemostasis:

- Prostacyclin
- Heparan sulfate
- Tissue factor pathway inhibitor
- Nitric oxide
- Thrombomodulin

Figure 3. Normal blood flow in intact vessels. RBCs and platelets flow near the center, WBCs marginate and roll. Endothelial cells and the vascular intima provide the listed properties that suppress hemostasis.
Legend: EC, endothelial cell; FB, fibroblast; lines, collagen; PLT, platelet; RBC, red blood cell; SMC, smooth muscle cell; WBC, white blood cell.

Injury to the blood vessel wall disrupts the collagen of the extracellular matrix (ECM).[8] Damaged endothelial cells release VWF from cytoplasmic storage organelles (Figure 4).[9] VWF, whose molecular weight ranges from 800,000 to 2,000,000 Daltons "unrolls" like a carpet, adheres to the injured site, and exposes sites that partially bind the platelet membrane GP Ib-IX-V receptor. This is a reversible binding process that "tethers" or decelerates the platelet. Platelet and VWF interactions remain localized by a liver-secreted plasma enzyme, ADAMTS-13, also called VWF-cleaving protease, that digests "unused" VWF.

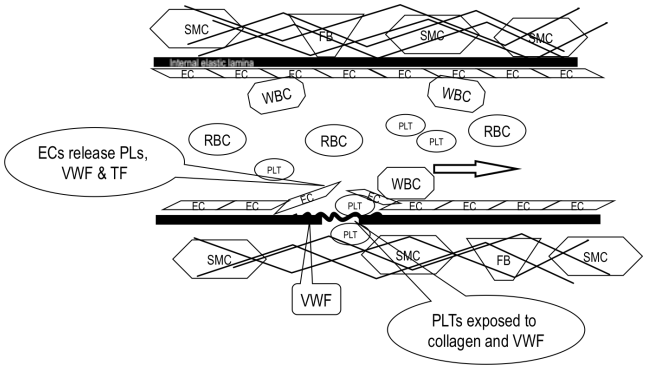


Figure 4. Trauma to the blood vessel wall exposes extracellular collagen and releases von Willebrand factor, triggering platelet adhesion and aggregation. Subendothelial tissue factor and phospholipids support coagulation.
Legend: EC, endothelial cell; FB, fibroblast; PL, phospholipid; PLT, platelet; RBC, red blood cell; SMC, smooth muscle cell; TF, tissue factor; VWF, von Willebrand factor; WBC, white blood cell.

At high shear rates, the VWF-GP Ibα tethering reaction is temporary, and the platelet rolls along the surface unless GPVI comes in contact with the exposed ECM collagen.[10] When type I fibrillar collagen binds platelet GPVI, the receptor triggers internal platelet activation pathways, releasing TXA_2 and ADP.[11] These agonists attach to their respective receptors: TPα and TPβ for TXA_2, and $P2Y_1$ and $P2Y_{12}$ for ADP, raising the affinity of GP Ia-IIa for collagen. The combined effect of GP Ib-IX-V, GP VI, and GP Ia-IIa causes the platelet to

become firmly affixed to the damaged surface, where it subsequently loses its discoid shape and spreads.[12]

The platelet activators TXA_2 and ADP are secreted from the platelet to the microenvironment, where they activate neighboring platelets through their respective receptors; and subsequently, GP IIb-IIIa, the key receptor site for fibrinogen, which assists in platelet aggregation.

Aggregation: Platelets Irreversibly Cohere

In addition to collagen exposure and VWF secretion, blood vessel injury releases constitutive (integral) tissue factor from fibroblasts and smooth muscle cells. Tissue factor triggers the production of thrombin, which reacts with platelet receptors PAR1 and PAR4. Meanwhile, GP IIb-IIIa assembles from its resting membrane units GP IIb and IIIa, binding arginine-glycine-aspartic acid (RGD) sequences of fibrinogen and VWF and supports platelet-to-platelet aggregation. Platelets lose their shape and extend pseudopods. Membrane phospholipids redeploy with the more polar molecules, especially phosphatidylserine, flipping to the outer layer, establishing a surface for the assembly of coagulation factor complexes. As platelet aggregation continues, membrane integrity is lost, and a syncytium of platelet cytoplasm forms as the platelets exhaust internal energy sources.

Platelet aggregation is a key part of primary hemostasis, which in arteries may end with the formation of a "white clot," a clot composed primarily of platelets and VWF.

The combination of polar phospholipid exposure on activated platelets, platelet fragmentation with cellular microparticle dispersion, and secretion of the platelet's α-granule and dense granule contents triggers secondary hemostasis, called coagulation. Fibrin and red blood cells deposit around and within the platelet syncytium, forming a bulky "red clot." The red clot is essential to wound repair, but it may also be characteristic of inappropriate coagulation in venules and veins, resulting in deep vein thrombosis and pulmonary emboli.

Secretion: Activated Platelets Release Granular Contents

Receptor-ligand interaction triggers actin microfilament contraction. Intermediate filaments also contract, moving microtubules inward and compressing the granules. Contents of α-granules and lysosomes flow through the SCCS, while dense granules migrate to the plasma membrane, where their contents are secreted. The dense granule contents are vasoconstrictors and platelet agonists that amplify primary hemostasis; most of the α-granule contents are coagulation proteins that participate in secondary hemostasis.

Platelets provide a localized cellular milieu that supports coagulation. Phosphatidylserine is the polar phospholipid on which two coagulation pathway complexes assemble: factor IX-VIII (tenase) and factor X-V (prothrombinase), both supported by ionic calcium secreted from the dense granules. The α-granule contents fibrinogen, factors V and VIII, and VWF are secreted and increase the localized concentrations of these essential coagulation proteins. Their presence further supports the action of tenase and prothrombinase. Platelet secretions provide for cell-based, controlled, localized coagulation.

Eicosanoid Synthesis

The eicosanoid synthesis pathway, alternatively called the prostaglandin, cyclooxygenase, or thromboxane pathway, is an essential platelet activation pathway. The platelet membrane's inner leaflet is rich in phosphatidylinositol, a phospholipid whose number 2 carbon binds, among other fatty acids, arachidonic acid. Membrane receptor-ligand binding triggers phospholipase A_2, a membrane enzyme that releases arachidonic acid to the cytoplasm, where it becomes the substrate for cyclooxygenase, anchored in the DTS. Cyclooxygenase converts arachidonic acid to a series of prostaglandins to ultimately produce TXA_2. TXA_2 binds membrane receptors TPα or TPβ to mobilize ionic calcium from the DTS (Figure 5). The rising cytoplasmic calcium level causes contraction of actin microfilaments and platelet activation.

TXA_2 has a half-life of 30 seconds, diffuses from the platelet, and becomes spontaneously reduced to thromboxane B_2, a stable, measurable plasma metabolite. Thromboxane B_2 is acted on by a variety of liver enzymes to produce an array of soluble urine metabolites, including 11-dehydrothromboxane B_2, which is stable and measurable, indicating platelet activation.[13,14]

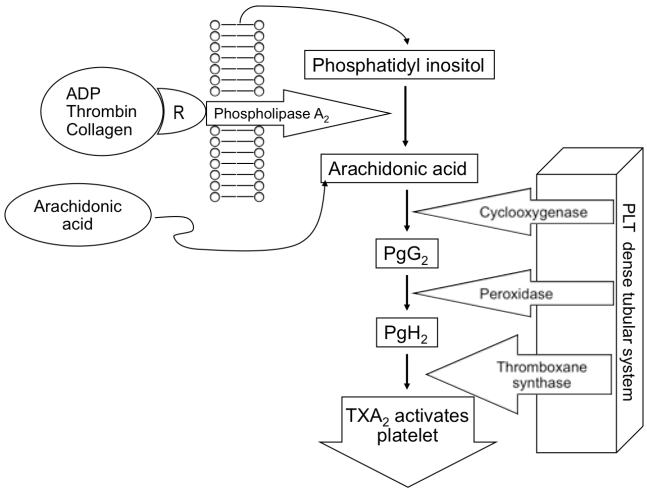


Figure 5. Eicosanoid synthesis. Ligands (agonists) ADP, thrombin, collagen, or epinephrine bind their respective membrane receptors. The combination activates phospholipase A_2. Phospholipase A_2 releases arachidonic acid from membrane phosphatidyl inositol. Arachidonic acid is acted upon by cyclooxygenase, peroxidase, and thromboxane synthase to produce TXA_2, which activates the platelet. When reagent arachidonic acid is used as an agonist, it bypasses the membrane and directly enters the eicosanoid synthesis pathway.
Legend: ADP, adenosine diphosphate; PgG_2, prostaglandin G_2; PgH_2, prostaglandin H_2; TXA_2, thromboxane A_2.

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