Platelet Structure and Function

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Today's Discussion

Platelet Structure

Origin

Platelet Membrane

Platelet Granules

Platelet Function

Platelet Activation Pathways

Platelets

Cells consisting of granular cytoplasm with no nucleus

On average 2.5 um in diameter

Normal reference ranges:

- Platelet count= 150-450 (x10/uL)
- Mean platelet volume= 8-10 fL

Turnover of platelets averages 8-9 days in peripheral blood

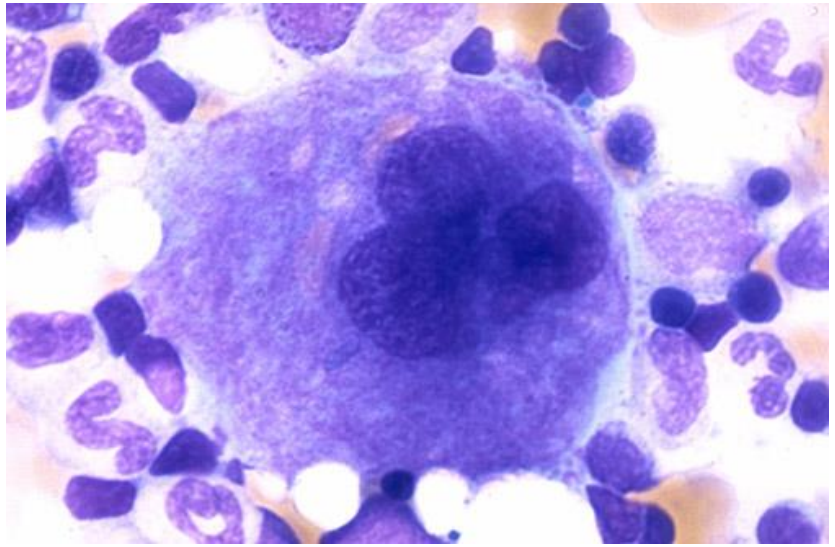
Location of platelets

- 70%-80% circulate in the blood
- 20%-30% pool in the spleen

Platelets “round up” in blood collected in EDTA

Megakaryocytopoiesis

- Platelets arise from megakaryocytes
- Undergo endomitosis
  - DNA replication and cytoplasmic maturation are normal, but cells lose ability to divide
- Terminal megakaryocyte differentiation
- Megakaryocyte membrane receptors and markers
  - MPL- TPO receptor site present at all maturation stages
  - CD Markers (ex. CD 34) appear/disappear with maturation
- Hormones and cytokines of megakaryocytes
  - Thrombopoietin (TPO)
    - Circulates as a hormone in plasma and binds to MPL
    - Plasma concentration inversely proportional to platelet and megakaryocyte mass
  - IL-3, IL-6, IL-11



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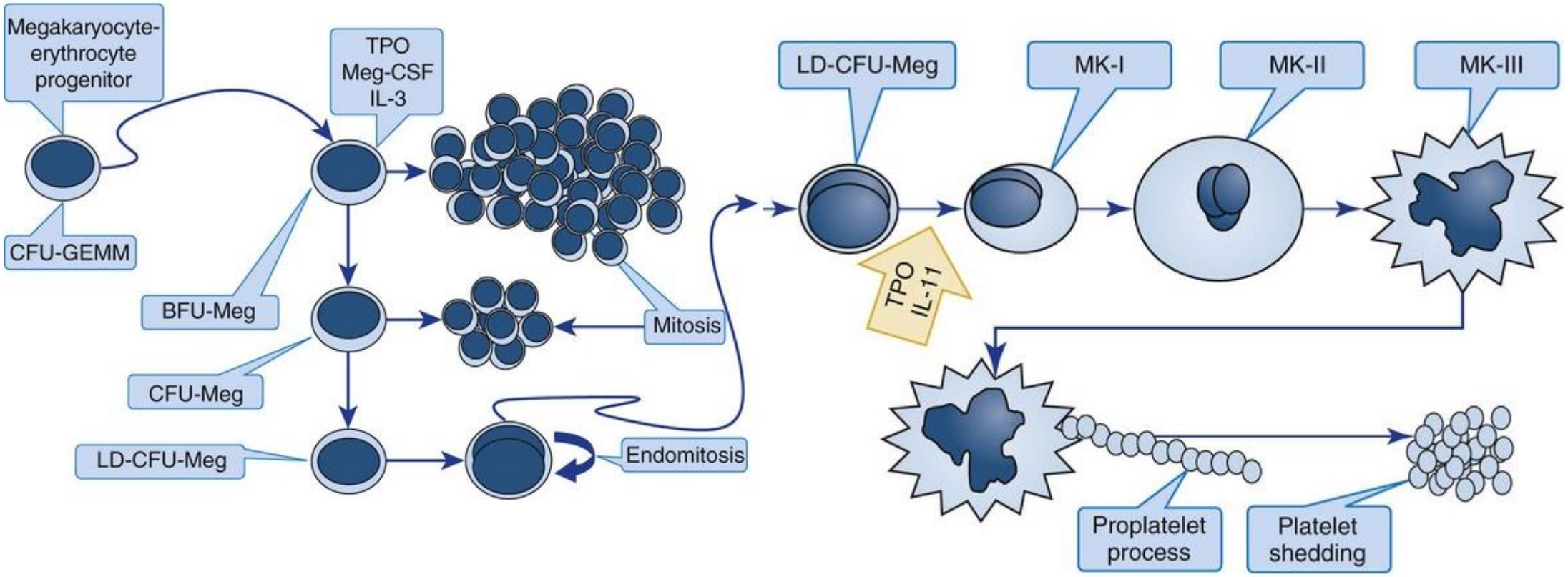
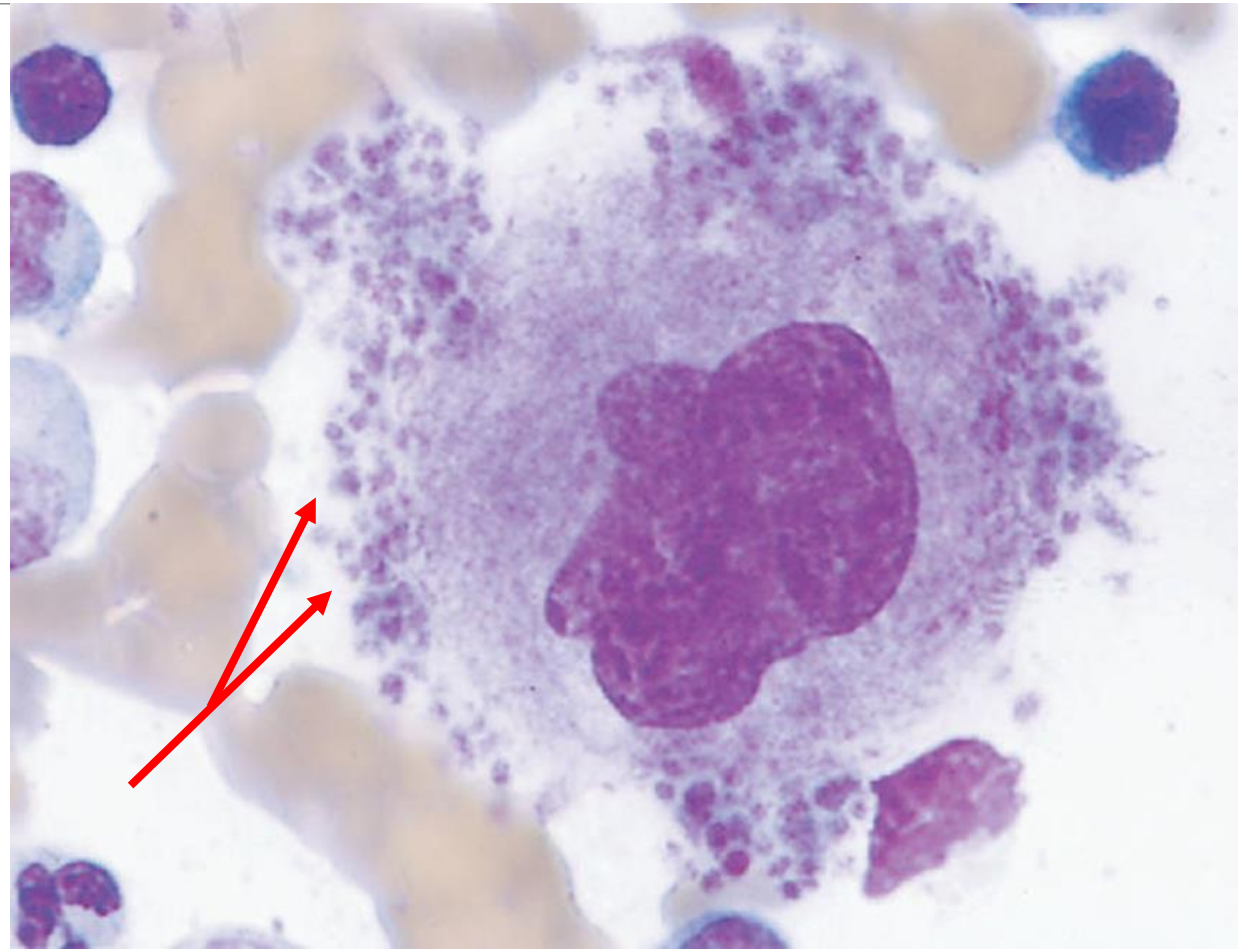
Megakaryocytopoiesis



https://oncohemakey.com/platelet-production-structure-and-function/

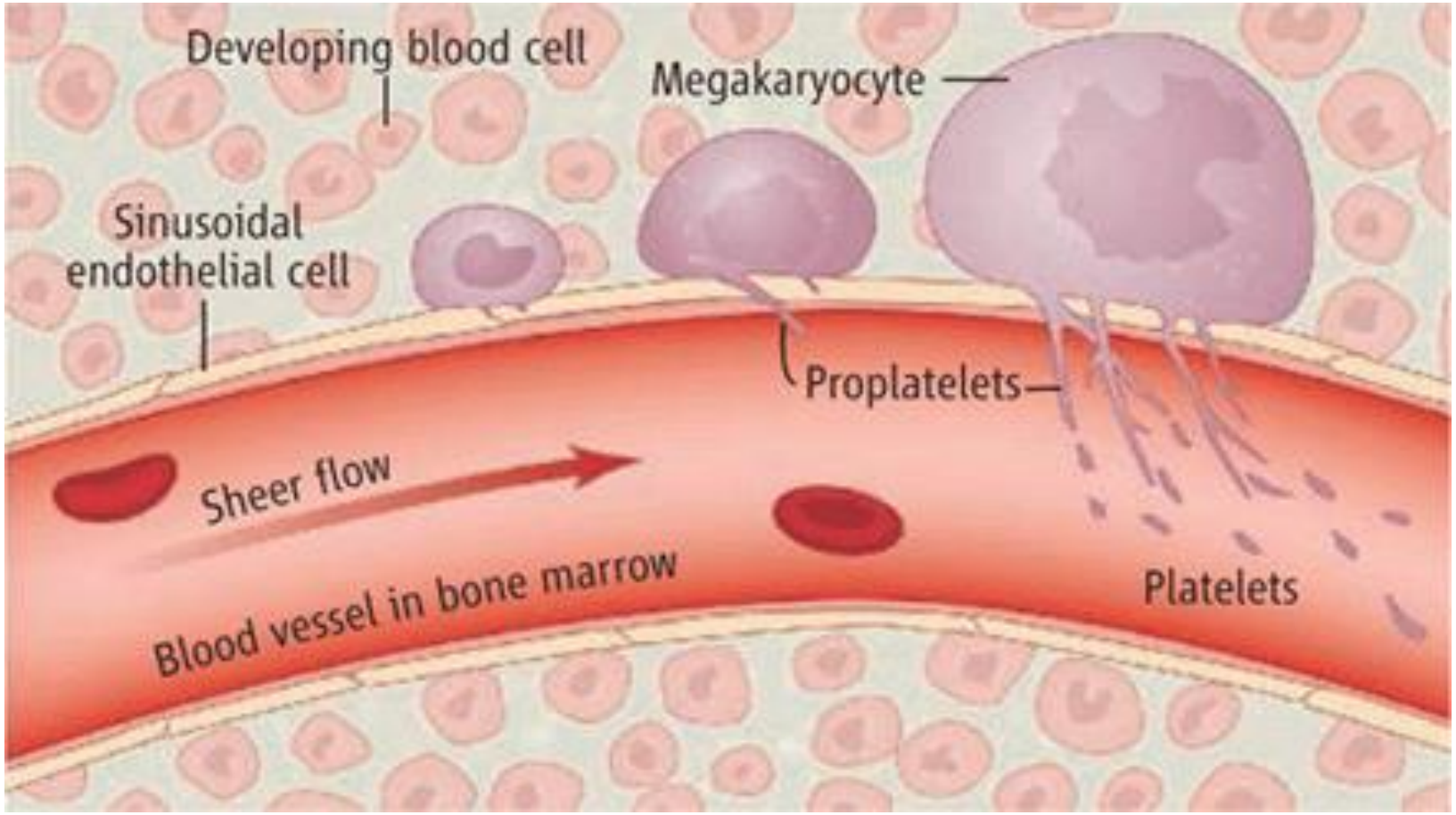
Thrombocytopoiesis

- "Platelet shedding"
- Single megakaryocyte can shed 2,000-4,000 platelets
- Normal adult of average-size will have 10^8 megakaryocytes producing 10^{11} platelets per day
- Platelet lifespan is approximately 8-9 days
  - Will have a continual renewal of platelets



https://medical-dictionary.thefreedictionary.com/megakaryocyte

Proplatelet Process



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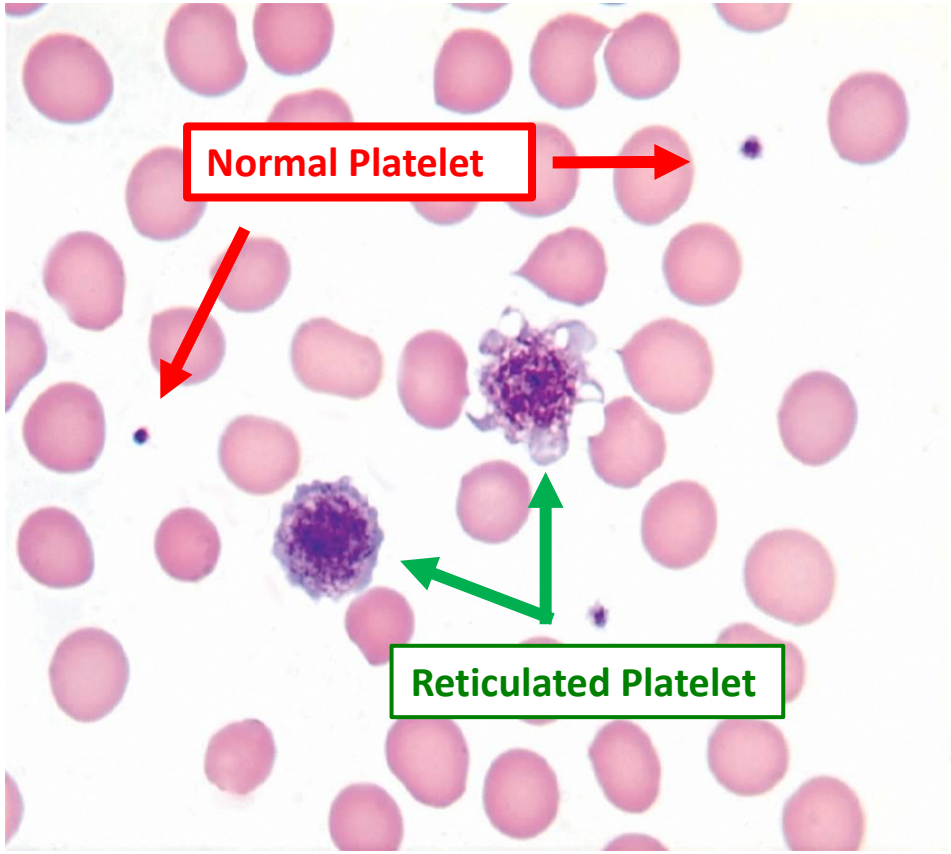
Reticulated vs. Normal Platelet

- Reticulated platelets
  - Aka “stress platelets”
  - Appear in compensation for thrombocytopenia
  - Marked larger size (>6 um in diameter)
    - MPV can reach 12-14 fL
  - Carry free ribosome and fragments of RER



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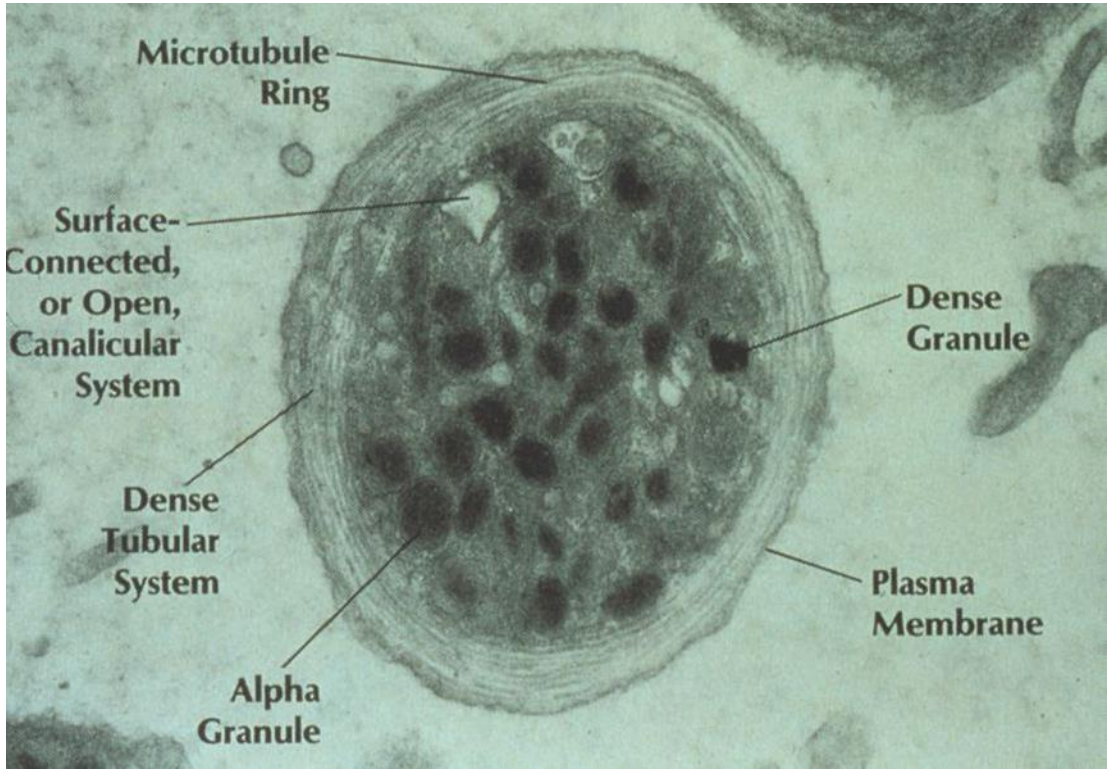
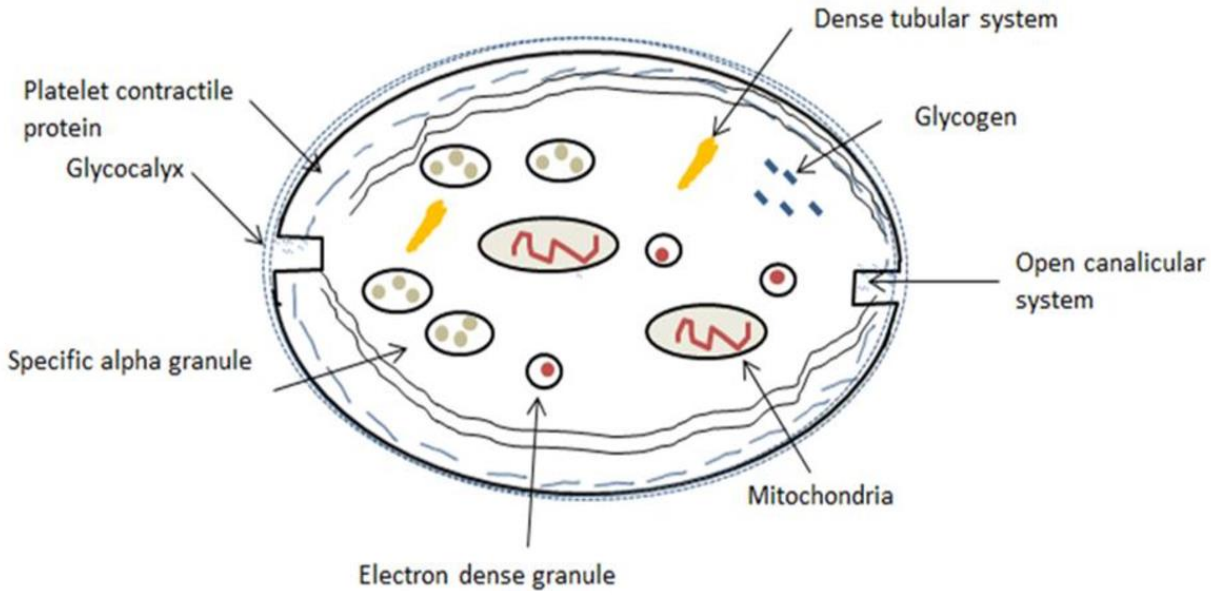
Platelet Ultrastructure

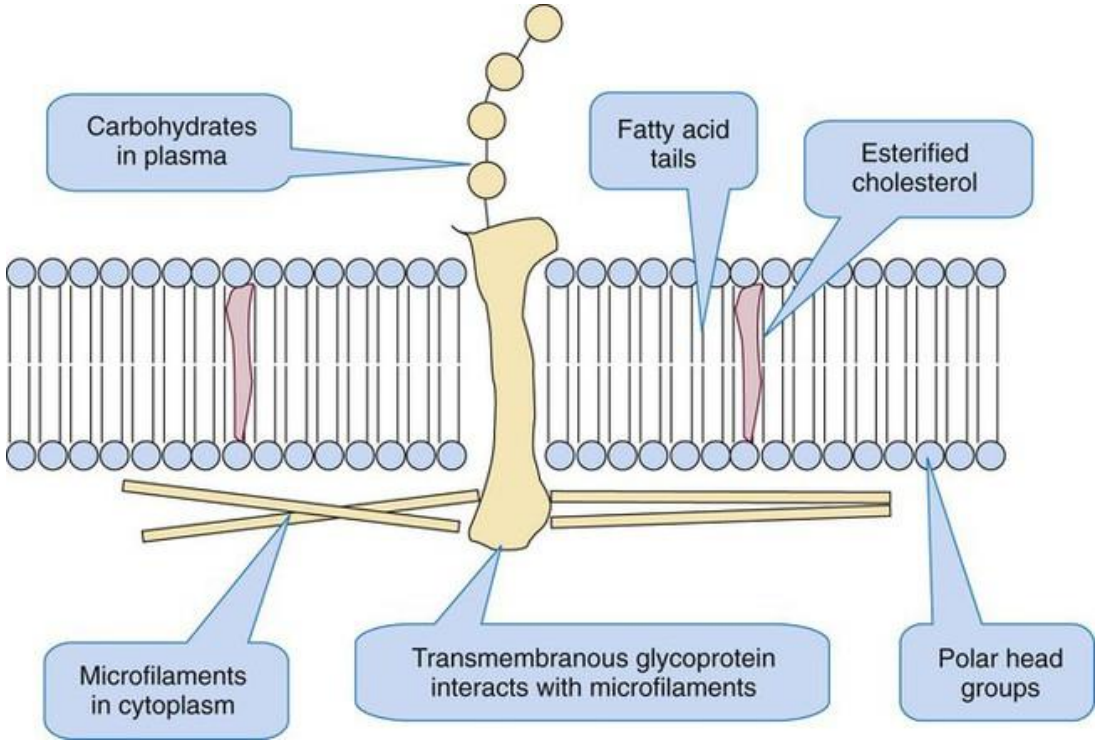


Picture from Kandice Kottke-Marchant



https://www.semanticscholar.org/paper/The-effect-of-the-flavonols-quercetin-and-3%27%2C-4%27-on-Mosawy/8a7aa8d766a86900fa85d7f48c2fcfa27812486f/figure/2

Glycocalyx and Plasma Membrane



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Glycocalyx

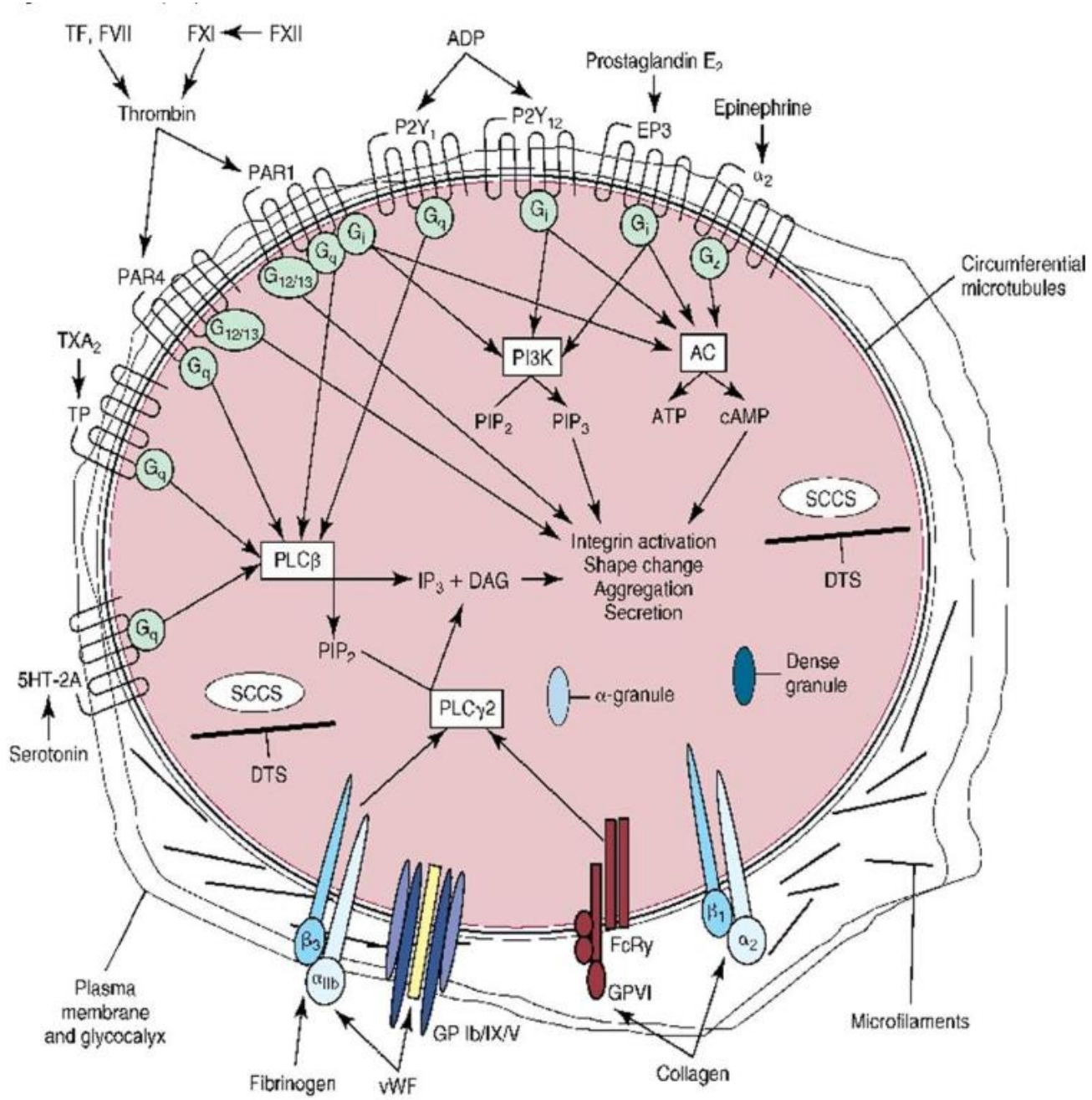
- Integral Membrane Glycoproteins

Membrane

- Phospholipid bilayer
- Membrane systems
  - Dense tubular system
  - Surface-connected canalicular system (SCCS)

Plasma Membrane

- Phospholipid bilayer
  - Polar head groups and non-polar fatty acid tails
    - Neutral phospholipids: phosphatidylcholine and sphingomyelin
    - Anionic or polar phospholipids: phosphatidylinositol, phosphatidylethanolamine, phosphatidylserine
  - Stability and support to platelet
- Surface-Connected Canalicular System
  - Twist sponge like (stores additional hemostatic proteins found in glycocalyx)
  - Route for endocytosis and secretion of α-granules
- Dense Tubular System
  - Remnant of RER
  - Sequesters Ca^{2+}
  - Contain enzymes that support platelet activation
    - Phospholipase A_2, cyclooxygenase, thromboxane synthetase
      - These support production of:
        - Thromboxane A_2, and phospholipase C
          - These support production of signaling molecules inositol triphosphate (IP_3) and diacylglycerol (DAG)



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Glycoprotein Platelet Membrane Receptors

Glycoprotein	Receptor for	Results in
GP IIb/IIIa ($\alpha_{IIb}\beta_3$ integrin)	Fibrinogen and VWF	Aggregation, low shear adhesion
GP VI	Collagen	Triggers activation and release of agonists
GP Ib/IX/V	VWF and Thrombin	Aggregation, high shear adhesion
GP Ia/IIa	Collagen	Adhesion and activation

Other Important membrane receptors

Seven-transmembrane receptor family (STRs)

- Ligands with their receptors:
  - Thrombin- PAR1 and PAR4
  - ADP- $P2Y_1$ and $P2Y_{12}$
  - TXA_2-TP_α and TP_β
  - Epinephrine- α_2 adrenergic
  - PGI_2 –IP
  - Serotonin- $5HT_{2A}$

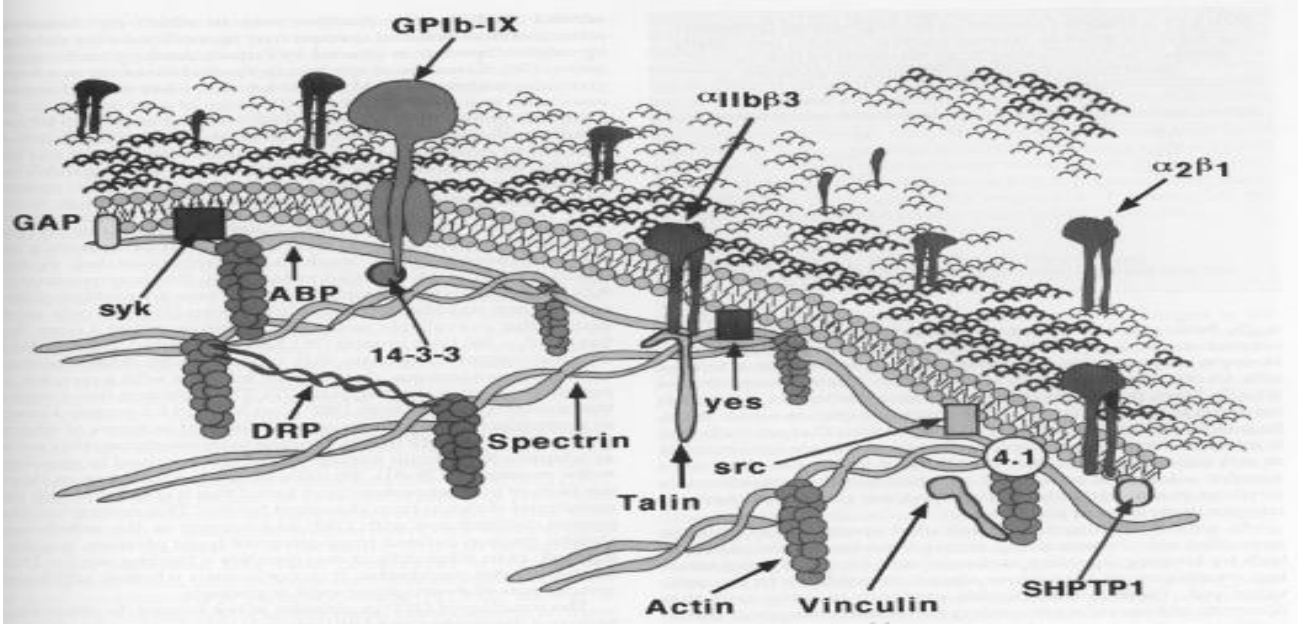
Cytoskeleton (Sol-Gel Zone)

Microtubules

- Maintain platelet discoid shape
- Reside just within plasma membrane
- 8-20 tubules per platelet
  - Composed of tubulin (disassemble with colchicine)
- Move inward on platelet activation
  - Enables α-granule expression
  - Rigidity to pseudopods

Microfilaments

- Lies between plasma membrane and microtubules
- Composed of Actin
  - Contractile and anchors glycoproteins and proteoglycans
- Actin also found in cytoplasm of platelet



Picture courtesy of Kandice-Kottke Marchant

Platelet Granules

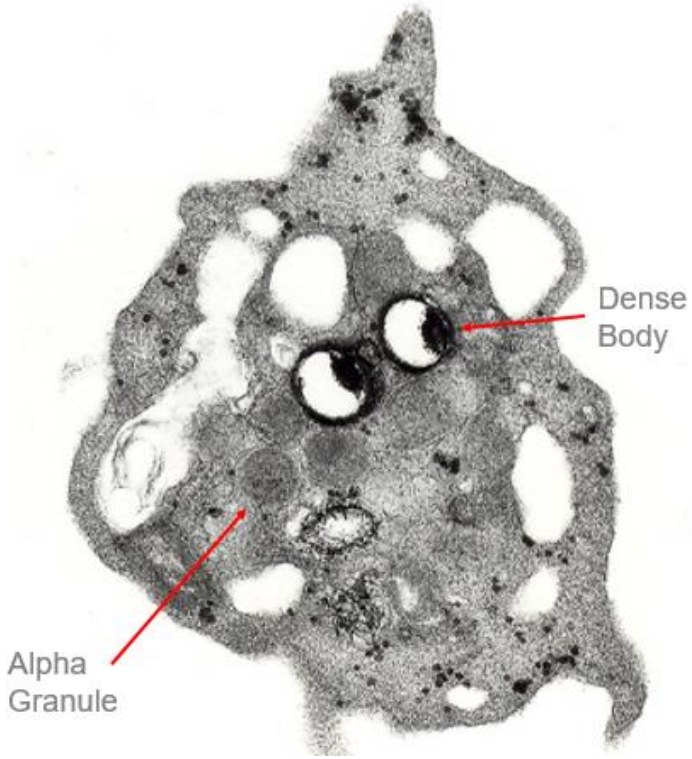
ALPHA GRANULES

Contents flow to surrounding microenvironment where participate in adhesion, aggregation, and plasma coagulation

- Platelet specific proteins
  - Platelet Factor 4, B thromboglobulin
    - Heparin binding proteins
- Coagulation proteins
  - Fibrinogen, vWF, fV
- PAI-1
  - Fibrinolytic inhibitor
- Platelet Derived Growth Factor
- Adhesive Protein
  - Fibronectin, thrombospondin
- Integral Membrane Proteins
  - P-selectin

DENSE GRANULES

- ATP
- ADP-nonmetabolic
- Serotonin
- Ca^{2+} and Mg^{2+}



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Platelet Function

Adhesion

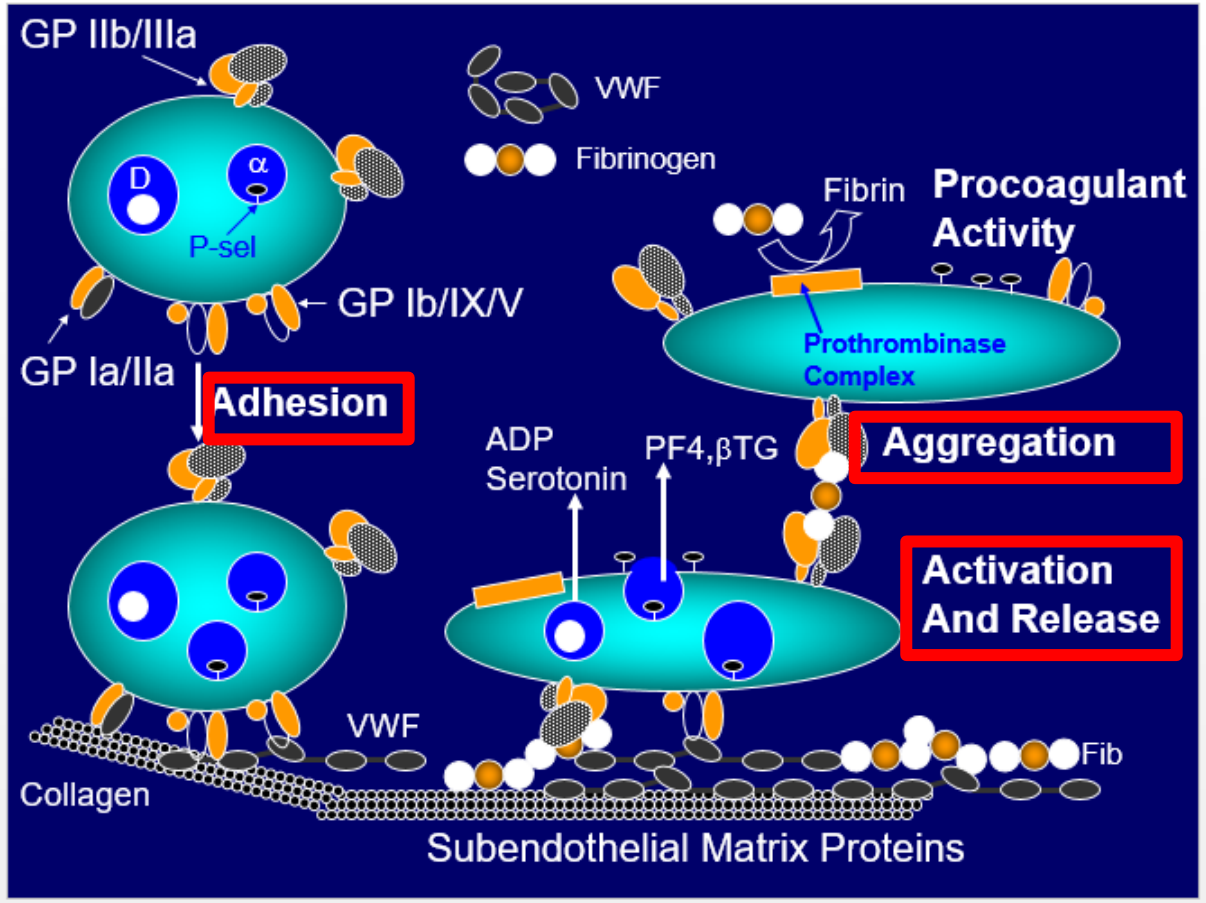
- Interaction of platelet surface glycoproteins with elements of subendothelium (collagen)
- Initial binding of collagen from ECM through GP Ia/IIa
- Result in linking of VWF via high shear stress to GP Ib/IX/V
- Reversible

Activation and Secretion

- Expression of platelet membrane integrins along which causes a contractile shape change and subsequent granule release
  - Procoagulants released (fV, VWF, fVIII, fibrinogen) and Ca2+
- Irreversible

Aggregation

- Platelet shape change includes pseudopods and conformational change of GP IIb/IIIa
  - Allows binding of fibrinogen and formation of fibrinogen bridges
- Irreversible



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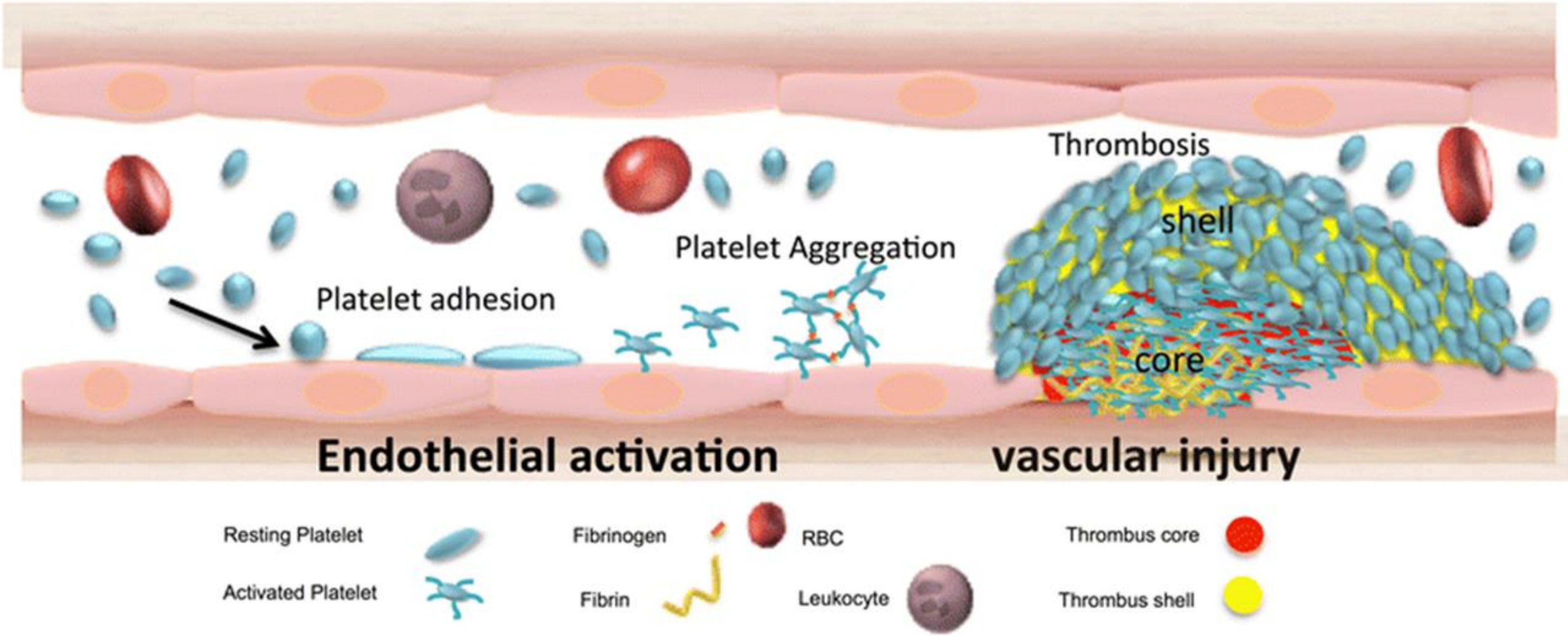
Platelet role in hemostasis and thrombosis



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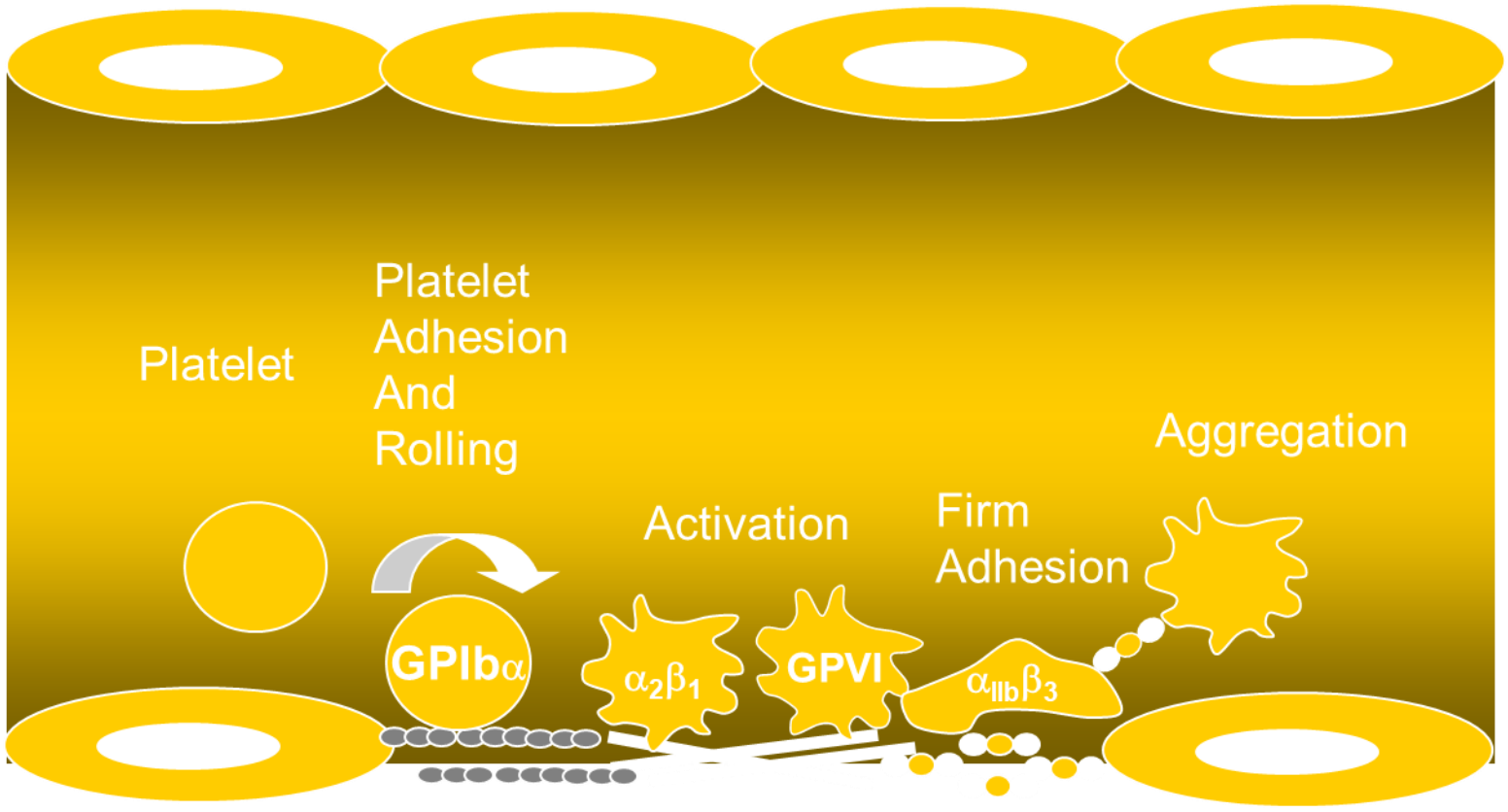
Role of Platelet Surface Receptors in Platelet Function



Picture courtesy of Kandice-Kottke Marchant

Von Willebrand factor

The GP 1bα portion of the GP Ib/IX/V is the von Willebrand factor (VWF) receptor site and binds VWF

- Will allow GP VI to further bind collagen

The bound GP VI to collagen initiates the release of thromboxane A_2 (TXA_2) and adenosine diphosphate (ADP)

- Activates $\alpha_2\beta_1$(GP Ia/IIa), an additional collagen receptor, stabilizing platelet adhesion
- Activates $\alpha_{IIb}\beta_3$ (GP IIb/IIIa), the arginine-glycine-aspartate (RGD) receptor site that binds fibrinogen and VWF to support platelet aggregation

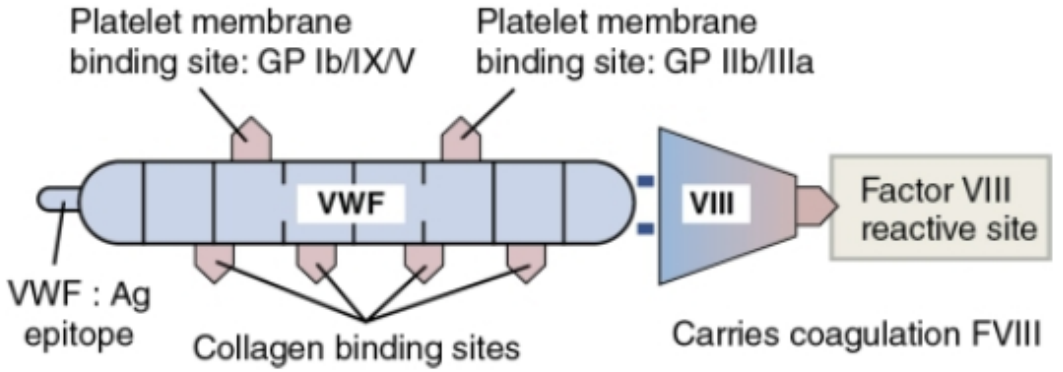
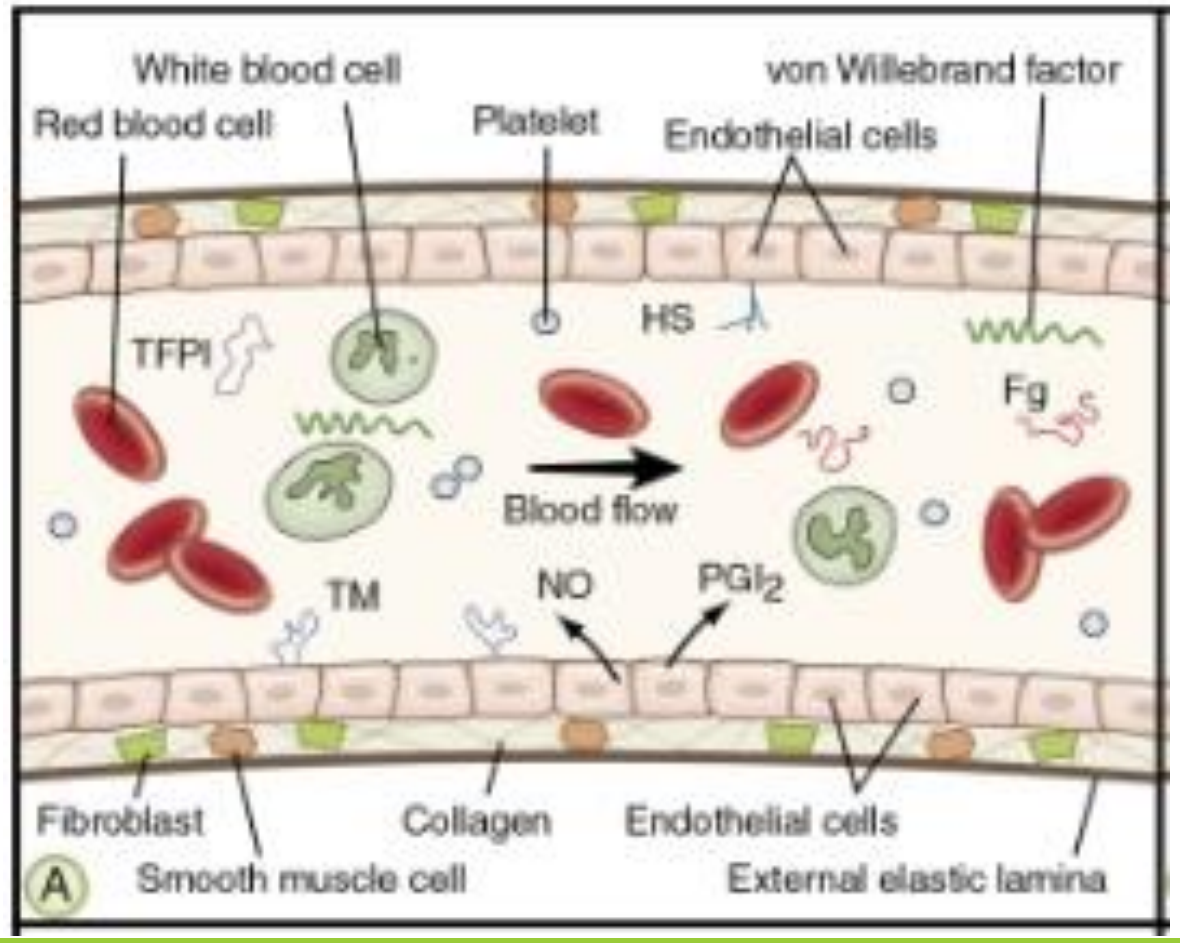


FIGURE 35.7 Von Willebrand Factor *(VWF)*-Factor VIII Complex. VWF molecules of various lengths from 0.5 to 20 mDaltons are in blood circulation. Factor VIII circulates covalently bound to VWF. VWF provides three other active receptor sites: VWF binds to collagen; it binds to glycoprotein *(GP)* Ib/IX/V to support platelet adhesion; and it binds to GP IIb/IIIa to facilitate platelet aggregation. VWF:Ag epitope is the target of quantitative immunoassays.

Figure 35.7 Rodak's Hematology 6th edition

Primary Hemostasis



Normal Blood Flow

- RBCs and platelets flow near the center and WBCs go to the edge and roll evenly along the endothelium
- Endothelial cells and subendothelial matrix, which contains collagen, smooth muscle cells and collagen-producing fibroblasts, have several mechanisms by which they can limit blood clotting and platelet activation

Figure 10.9
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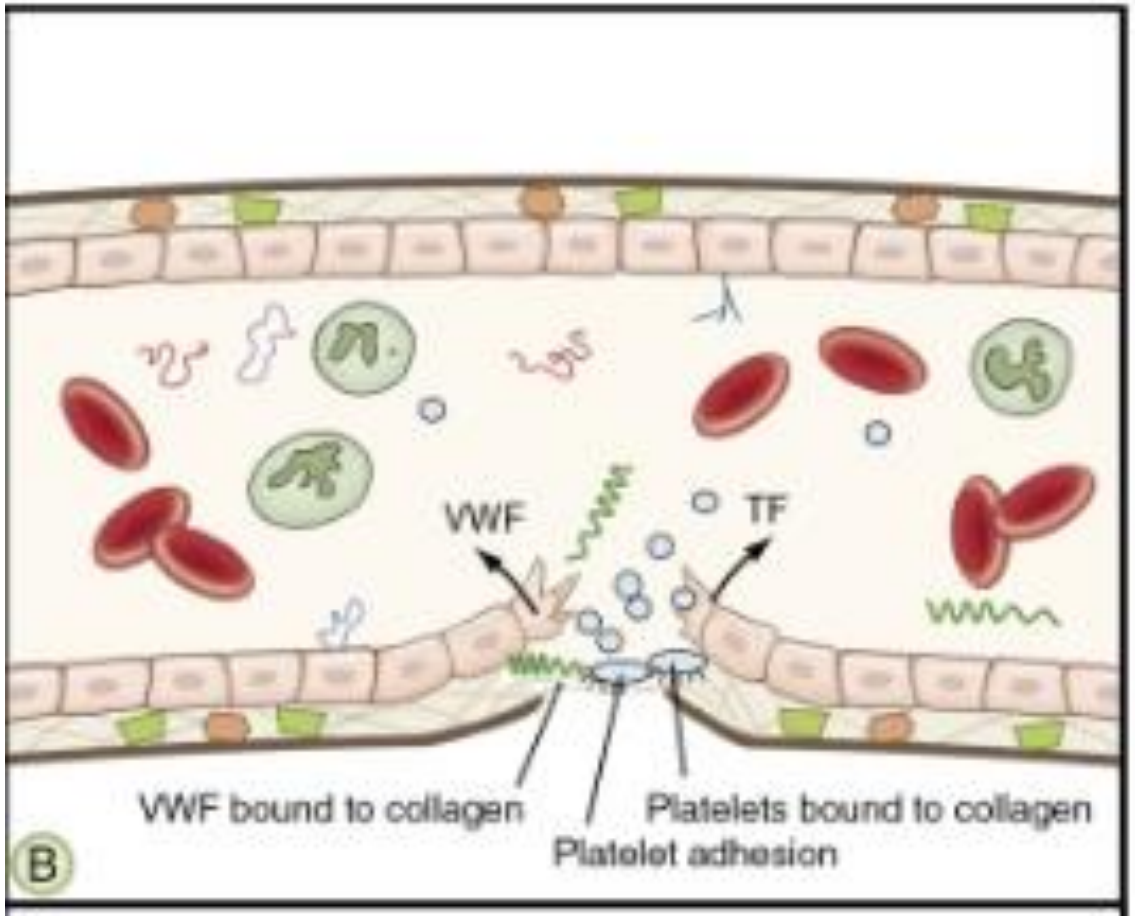
Primary Hemostasis



Trauma to blood vessel wall

Exposure of subendothelial collagen and tissue factor triggering platelet adhesion

Figure 10.9
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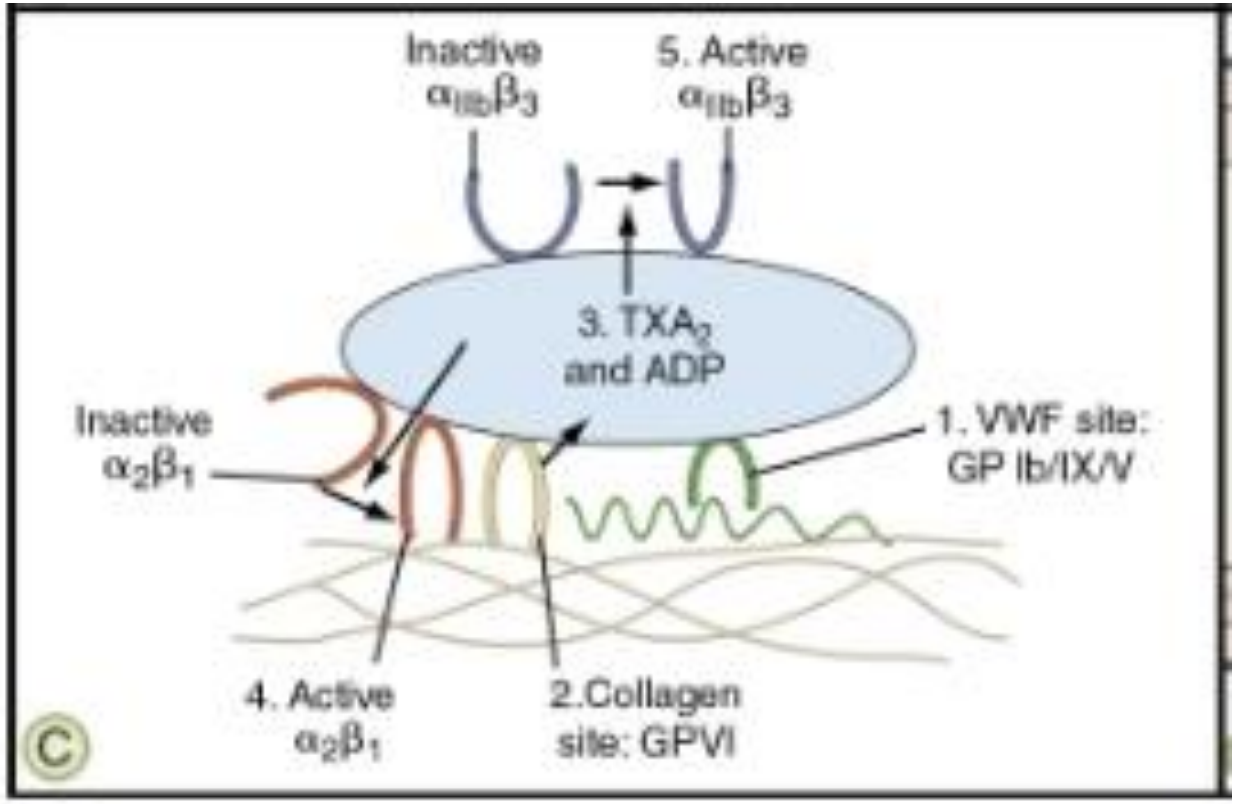
Primary Hemostasis



Von Willebrand Factor

- VWF serves as a bridge between subendothelial collagen and the platelet GP Ib/IX/V receptor
- Platelet interaction with collagen via $\alpha_2\beta_1$ and GP VI receptors triggers release of TXA_2 and ADP
- Activation of the $\alpha_{IIb}\beta_3$ receptor

Figure 10.9
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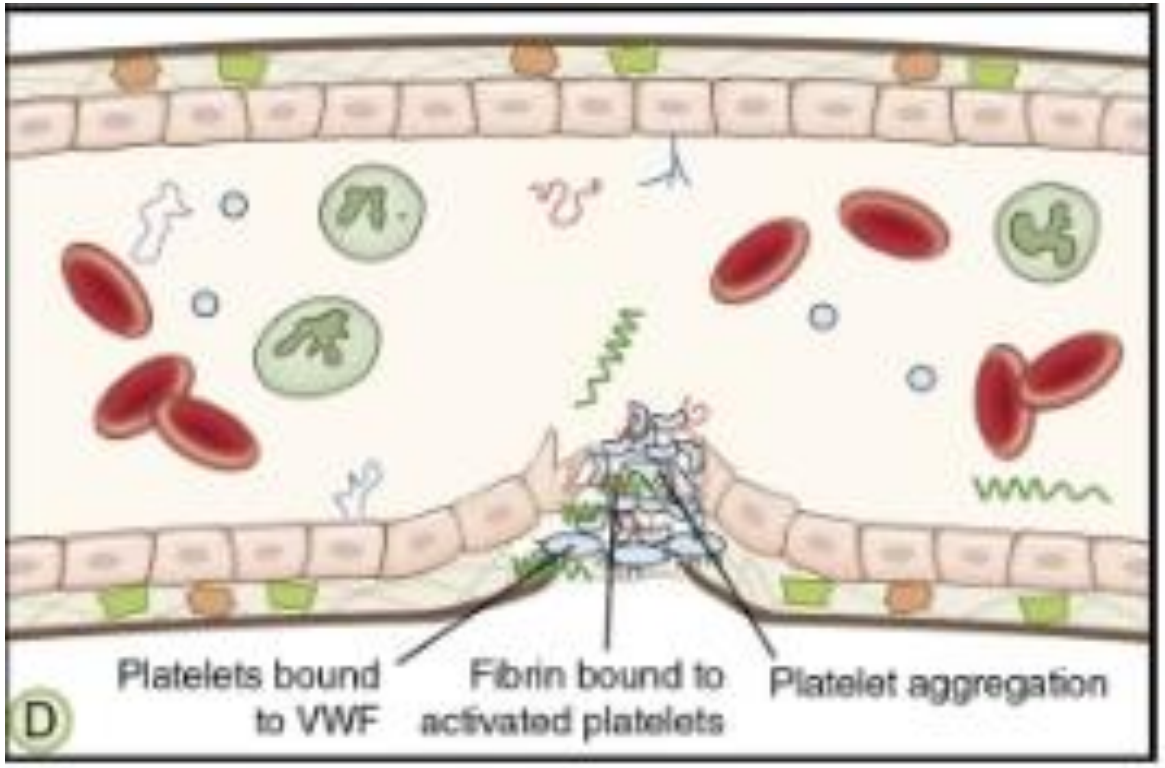
Primary Hemostasis



Platelet-Platelet Aggregation

- Activation of $\alpha_{IIb}\beta_3$ supports aggregation through binding of arginine –glycine-asparate (RGD) - containing ligands like fibrinogen and VWF

Figure 10.9
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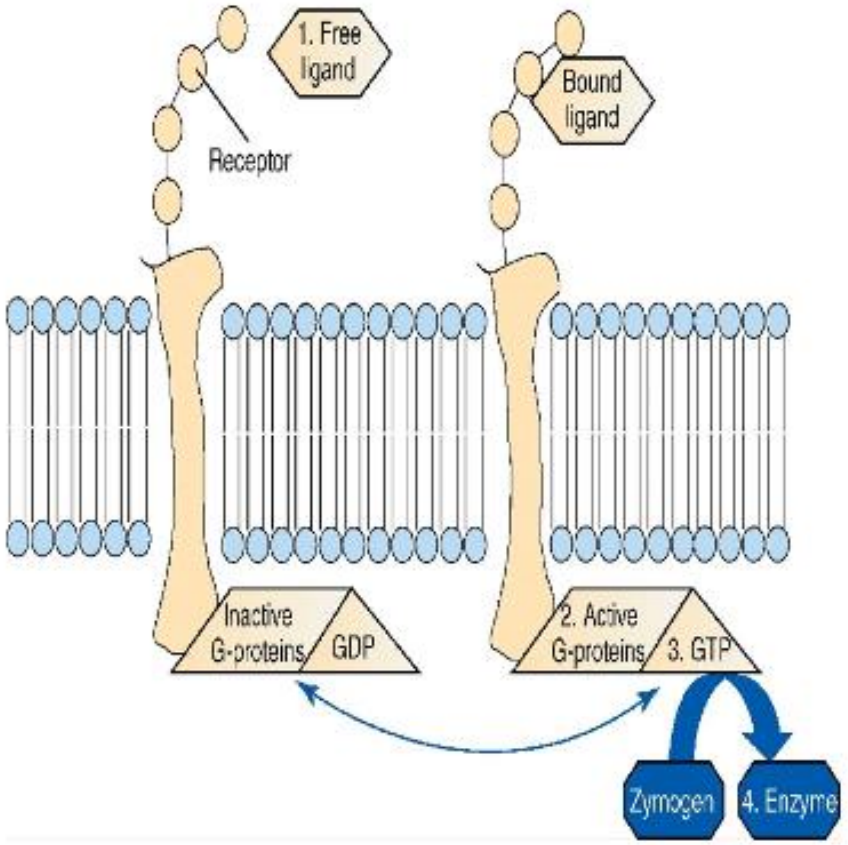
Platelet Activation Pathways

G- proteins

Eicosanoid Synthesis

Inositol Triphosphate- Diacylglycerol Activation

G- Protein Couple Mechanism for Platelet Activation



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Eicosanoid Synthesis Pathway

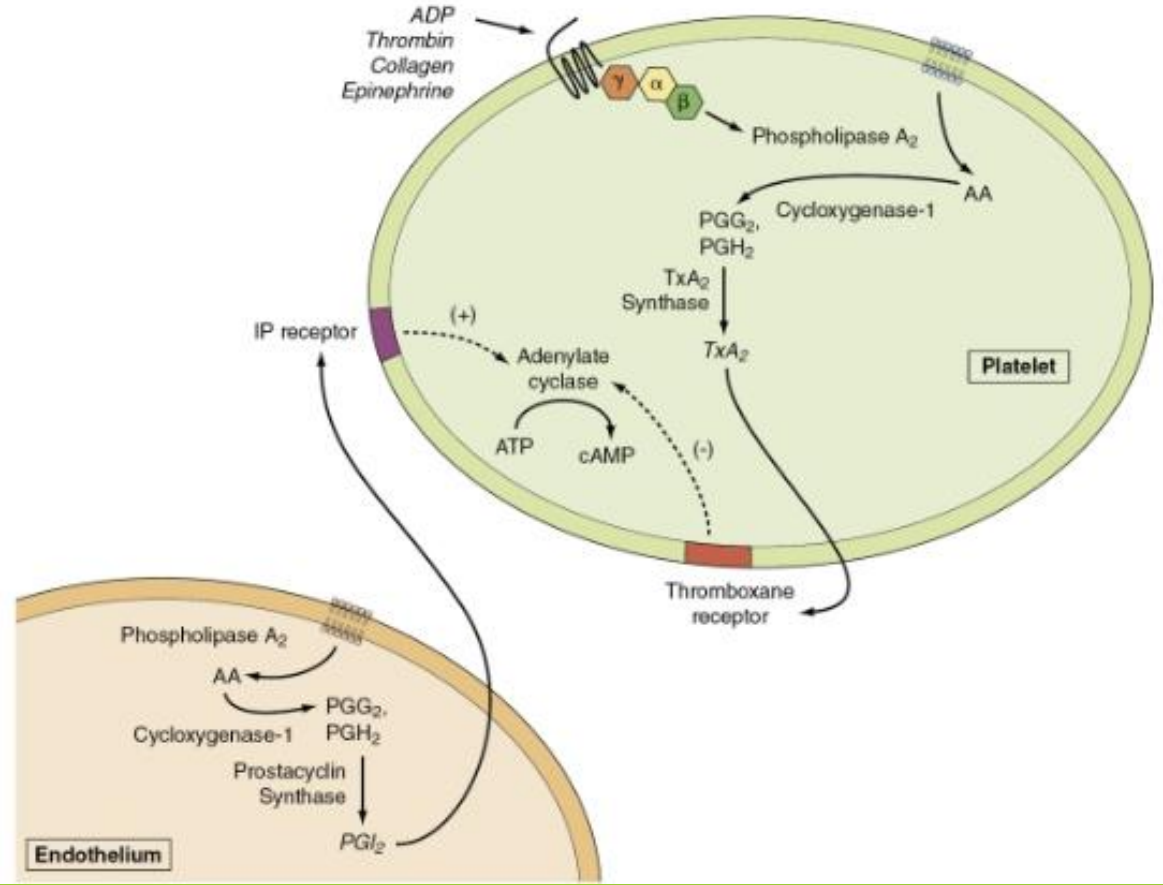

Figure 10.12
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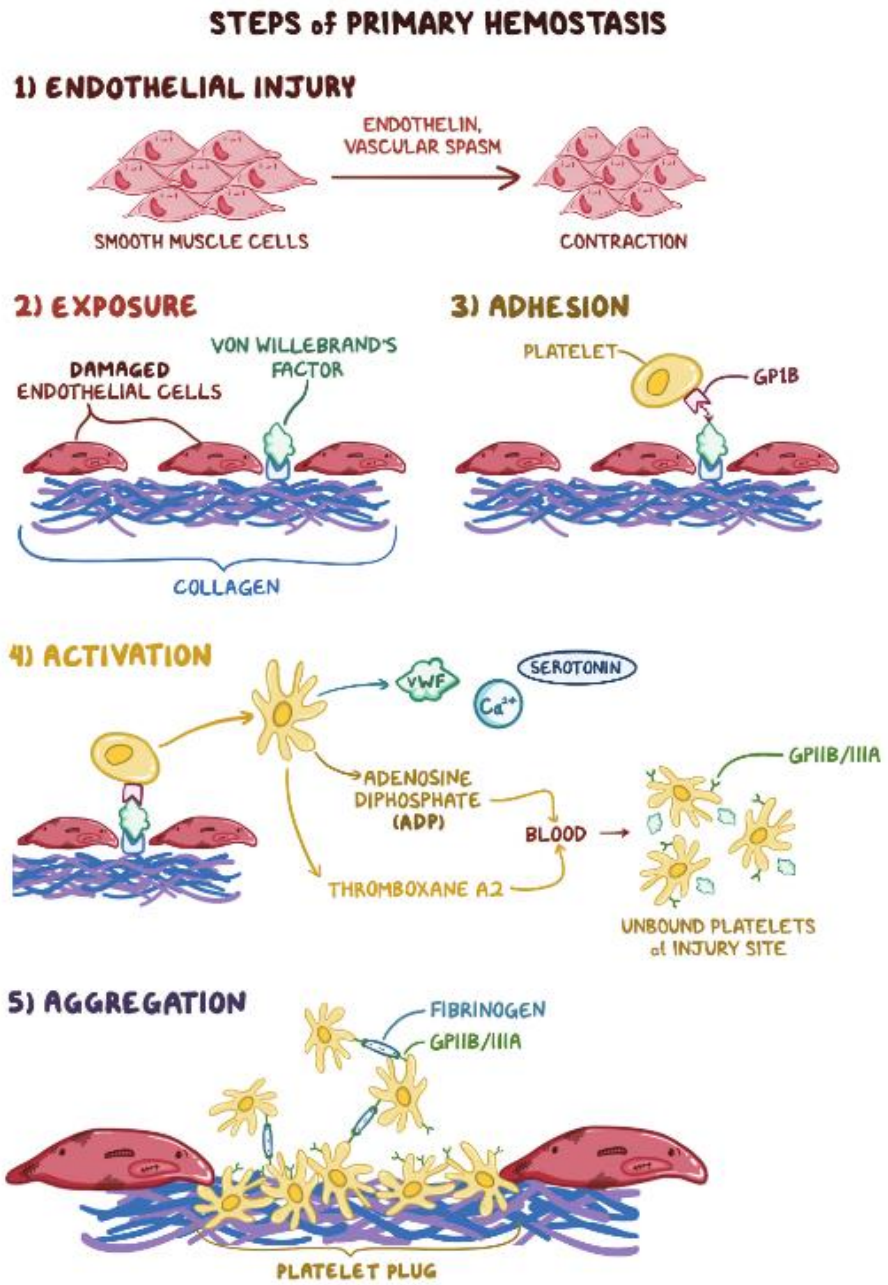

Figure 43.3 Platelet plug formation steps.

https://www.osmosis.org/notes/Blood_Components_and_Function#page-1

References

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