Platelet Function and Pathophysiology

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Disclosures

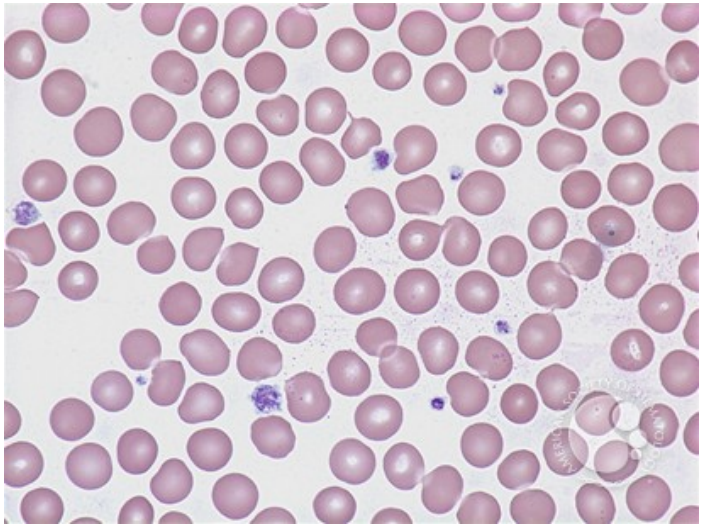
- none

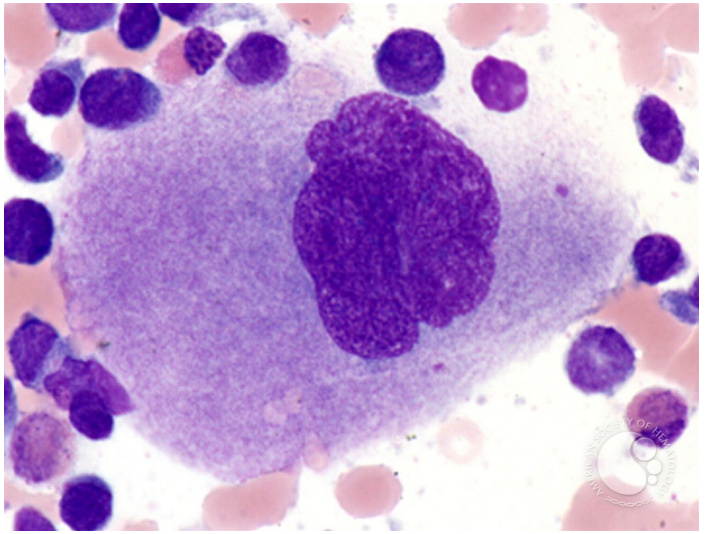
Objectives

- **Platelet basics**
- **Primary hemostasis**
  - Adhesion
  - Activation/secretion
  - Aggregation
  - Review key agonists/mediators
- **Antiplatelet medications**
- **Lab testing for platelet dysfunction**
  - PFA 100
  - Light transmission aggregometry
- **Inherited Platelet function disorders**
- **Acquired Platelet function disorders**

Platelets

- Anuclear, subcellular fragments derived from megakaryocytes
- Regulate hemostasis and vascular integrity
- Lifespan: 7-10 days

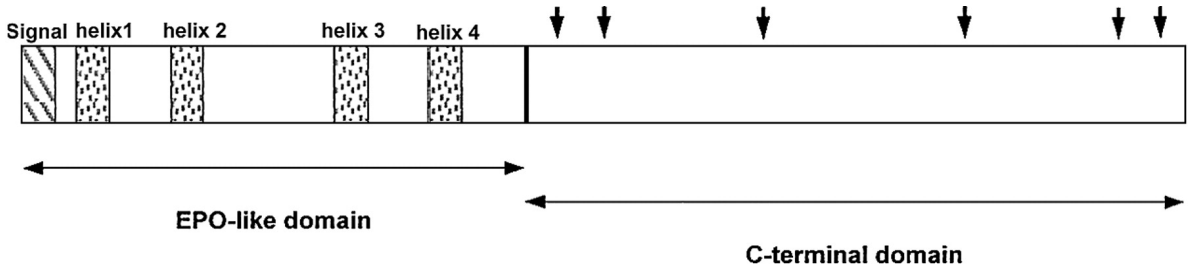




Maslak P, American Society of Hematology 2019

Platelets – Thrombopoietin (TPO)

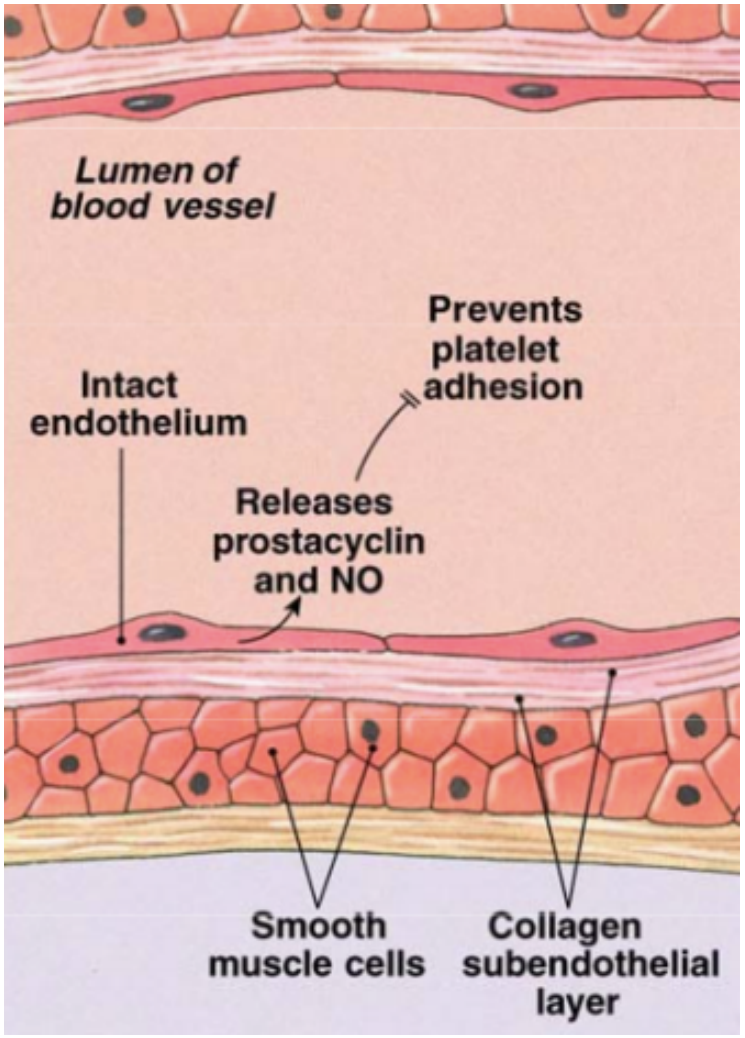
- **TPO:** cytokine, major regulator of plt production
- **TPO receptor (c-mpl)** on a variety of hematopoietic tissues
  - stem cells, mega CFC, myeloid/erythroid precursors, megas, plts
- Made by **liver (steady state)**, cleared by TPO-R's on plts
- **TPO regulated by platelet biomass**
  - Low plts -> ⇧ TPO exposure to undifferentiated bone marrow cells -> differentiation of megas -> ⇧ plt production



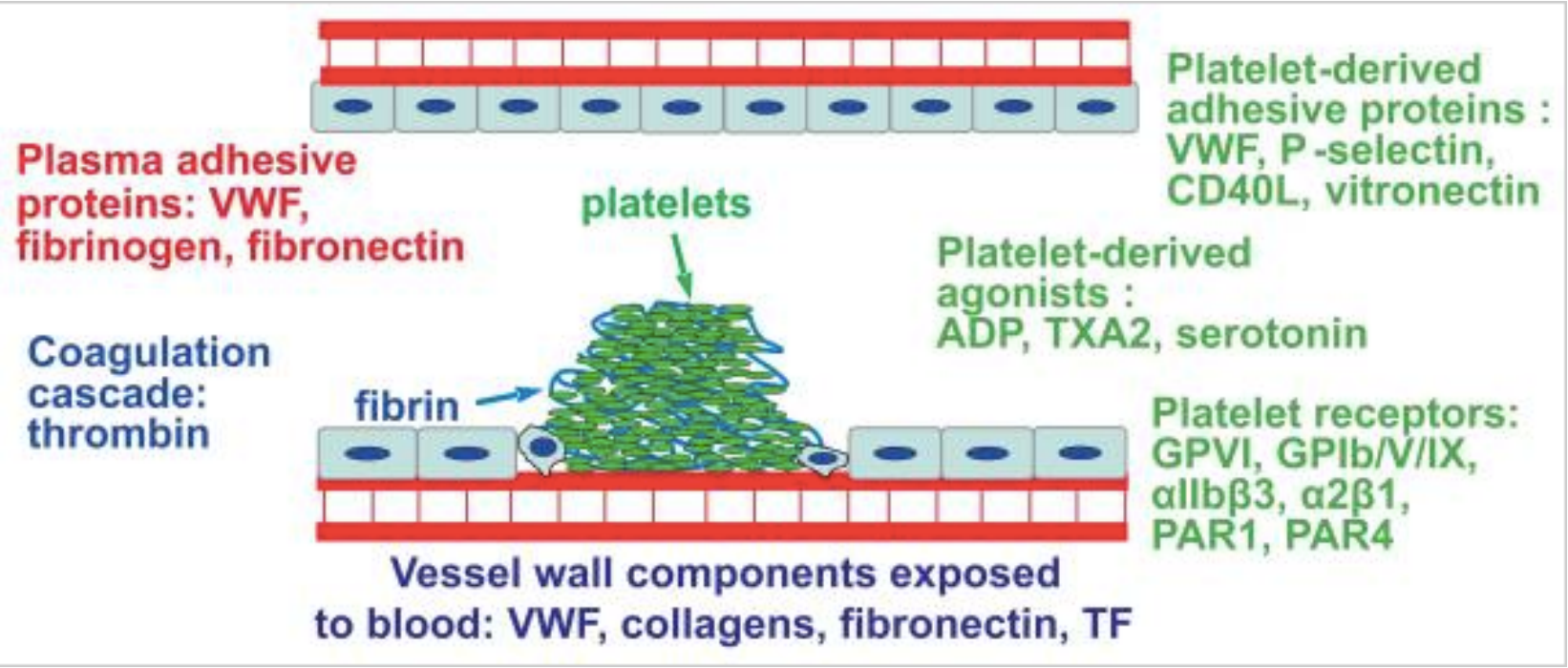
Kuter DJ, Begley CG Blood 2002

Platelets in Circulation

- Do not interact with intact endothelium
- **Nitric oxide** (NO), **prostacyclin** (PGI_2)
  - Endothelium-derived
  - Reduce plt reactivity
  - Prevent inappropriate plt activation



Primary Hemostasis



Platelet Adhesion: GPIb to immobilized vWF, GPVI to collagen

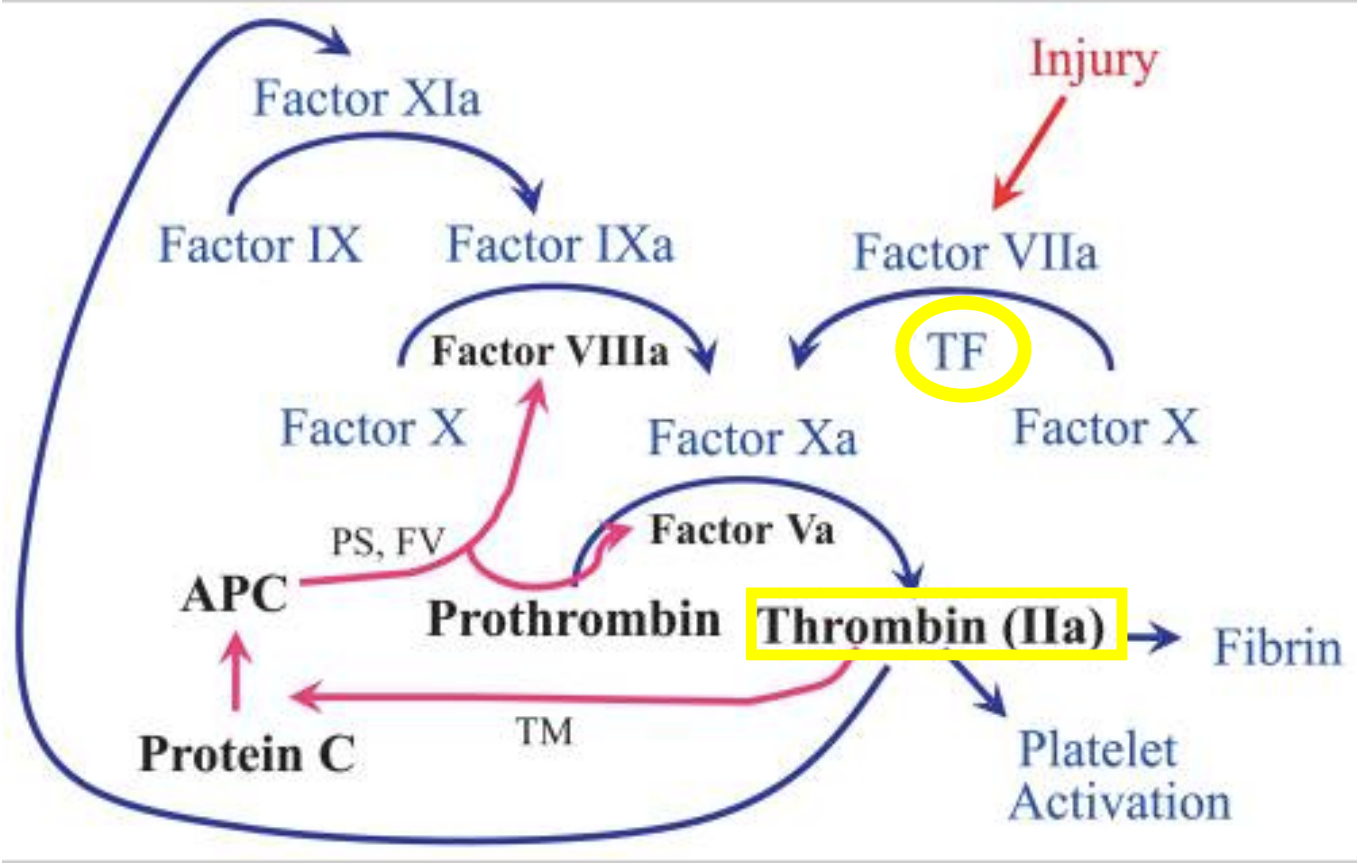
Platelet Activation/Secretion: plt shape change, activate integrin αIIbβ3 (GPIIb/IIIa); secrete ADP, serotonin, form TXA2

Platelet Aggregation: GPIIb/IIIa binding fibrinogen, vWF

Coagulation: help activate coag cascade (thrombin), plt plug stabilized by fibrin

Gale AJ, Toxicol Pathol 2011

Secondary Hemostasis



Coagulation cascade: Injury exposes TF, leads to thrombin formation

Thrombin -> fibrin generation, plt activation (via PAR), positive feedback activation of intrinsic pathway, negative feedback activation of APC

Gale AJ, Toxicol Pathol 2011

Primary Hemostasis -Platelet Response

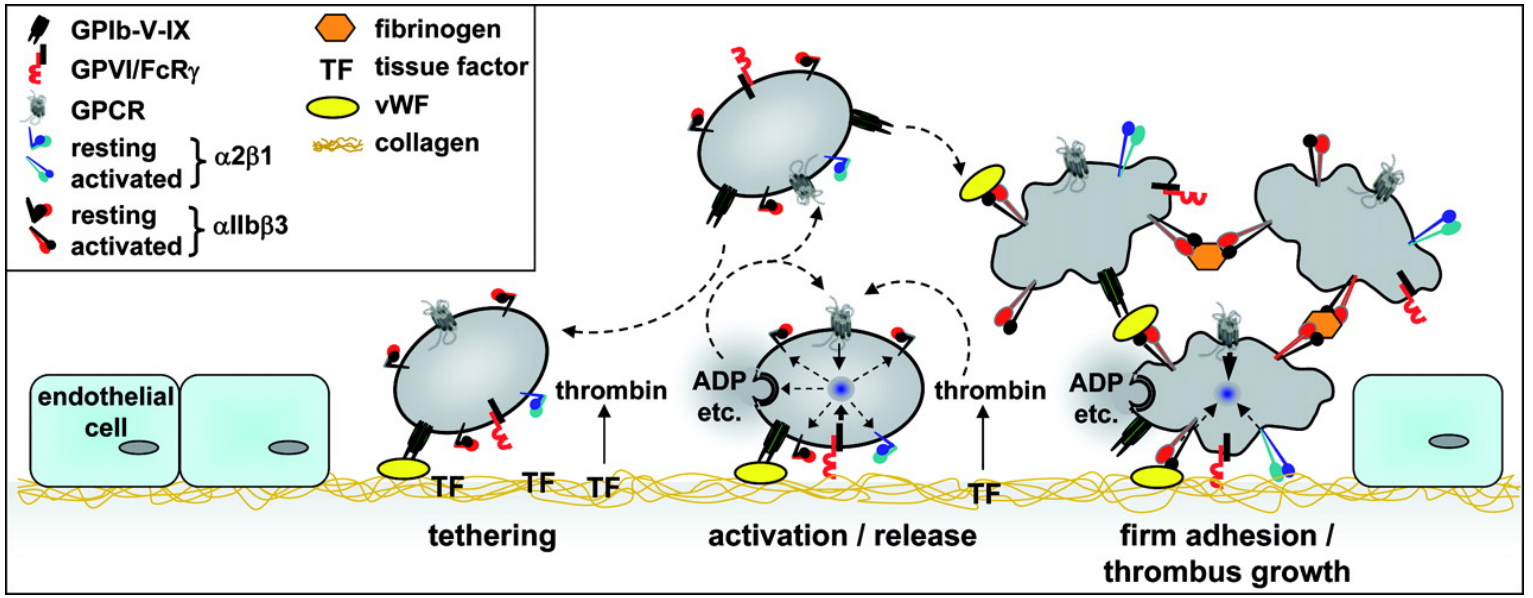
- **Adhesion**- platelets adhere to exposed ECM
  - Key players: GP1b-V-IX, vWF, GPVI, collagen
- Activation/Secretion- plt shape change, recruit more platelets, support coagulation cascade
  - Key players: ADP, ATP, Ca^{+2}, serotonin, TXA2, thrombin
- Aggregation – form plt plug
  - Key players: integrin αIIbβ3 (GPIIb/IIIa), fibrinogen, vWF

Platelet Adhesion: Von Willebrand Factor

- Large, multimeric glycoprotein
  - Stored in **Weibel-Palade bodies** in endothelial cells, **α-granules** in megas/plts
  - Size correlates with ability to induce plt thrombi
- Roles in Thrombus formation:
  - Latches to exposed subendothelium (ie **collagen**)
  - Mediate **plt adhesion** to ECM via **GP1b-V-IX**
  - Role in aggregation via binding of GPIIb/IIIa
  - Carries **FVIII**, prevent clearance

Platelet Adhesion

- **GP1b-V-IX** (on plt) binds **vWF** immobilized on **collagen**
  - Initial capture, but rapidly reversible
- **GP-VI** (transmembrane receptor, plt specific) binds **collagen**
  - Firm, stable adhesion; mediates plt activation/secretion
- **GPIa/IIa** (integrin α2β1 on plt) binds **collagen**



Varga-Szabo D, Arterioscler Thromb Vasc Biol 2008

Primary Hemostasis -Platelet Response

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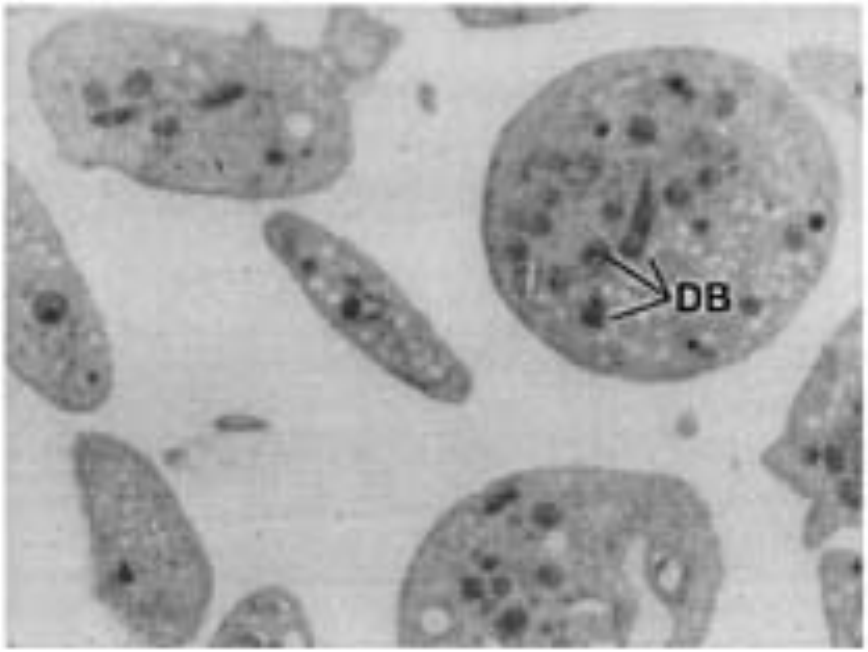
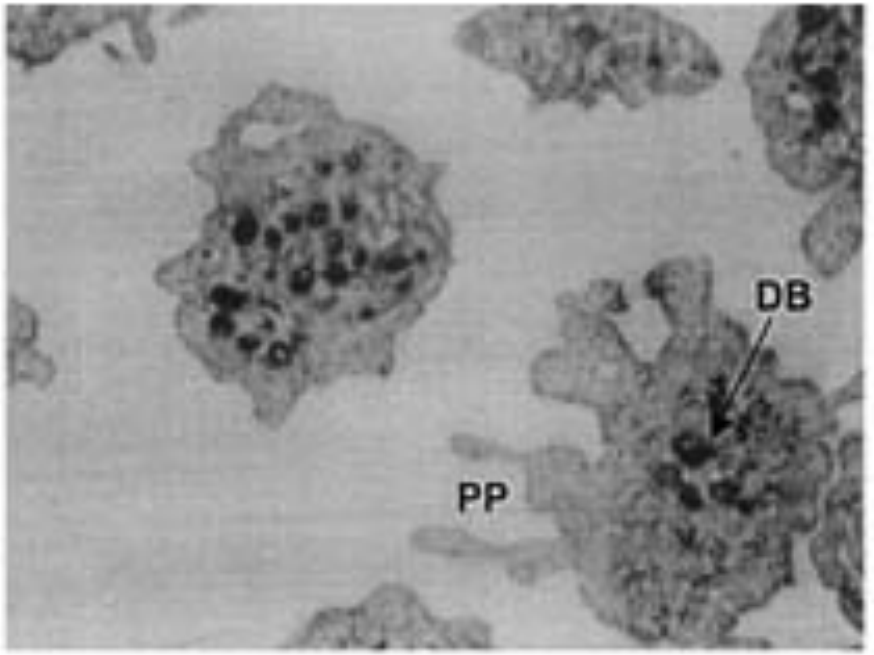
Platelet Activation – Shape change



Resting platelet



Activated platelet: form pseudopodia, ⇧ surface area, centralize granules, expose phospholipids for coag cascade

Jurk K, Semin Thromb Hemost 2005

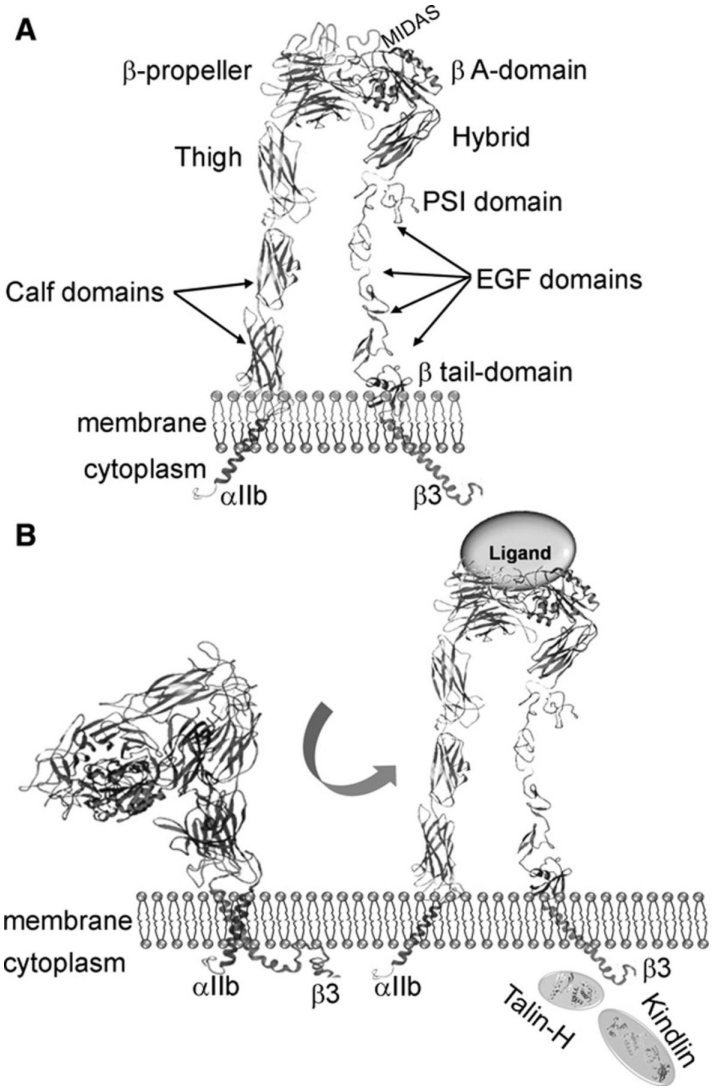
Platelet Activation

- Activation via adhesion and agonists leads to:
  - Change in plt shape
  - **Plt integrins to high-affinity state** (**GPIIb/IIIa**)
  - **Granule secretion** (ie **ADP**, Serotonin)
  - Synthesis of thromboxane A2 (**TXA2**)

- Amplify platelet activation, recruit additional platelets, generate thrombin

Platelet Activation - αIIbβ3 (GPIIb/IIIa)

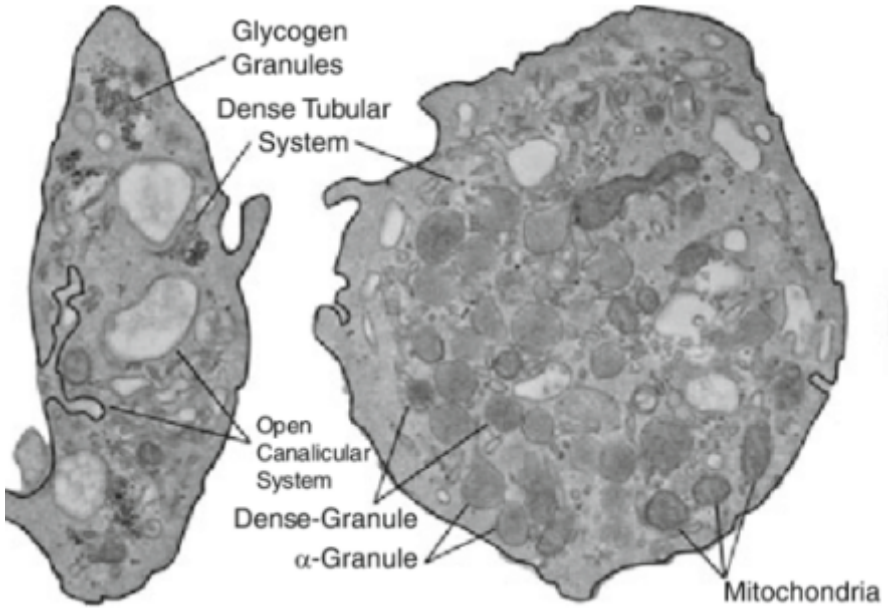
- **Integrin αIIbβ3 (GPIIb/IIIa)**
  - Integrin: heterodimeric transmembrane proteins
  - Most abundant receptor on plt (40,000-80,000/plt)
  - Low affinity at rest
- Activation by '**inside out'** (plt agonists, GPCRs, cytosolic Ca^{2+}) & **'outside in'** (ligand binding) **signaling**'
- Binds **fibrinogen**, vWF, thrombospondin, etc



Bledzka K, Circ Res 2013

Platelet Secretion

- **Tightly regulated**
  - Signaling pathways lead to ⇧cytosolic Ca^{+2}
  - Granules fuse with plasma membrane & release contents
- **Alpha (α) granules**
  - Primary hemostasis, coagulation, wound repair, inflammation, angiogenesis
- **Dense (δ) bodies**
  - Primary hemostasis via feedback (esp ADP)



Hartwig JH, Thromb Haemost 1999

Platelet Secretion- granules

Secretory granule	Representative contents	Functions	Defects/disorders
Alpha (α) 50-80/plt	- vWF, fibrinogen, FV, XI, XIII, prothrombin -TFPI, PS, plasmin -P-selectin, PF-4 (CXCL4), CXCL7 - VEGF, PDGF	- Coagulation - Hemostatic balance - Inflammation - Angiogenesis	Gray Platelet Syndrome Quebec platelet disorder
Dense (δ) 3-5/plt	**ADP**, ATP, GDP, Serotonin, Calcium	Platelet activation	Hermansky-Pudlak Chediak-Higashi
Lysosome Few/plt	Acid hydrolases	Clot remodeling Digestion, Phagocytosis	

Primary Hemostasis -Platelet Response

- Adhesion- platelets adhere to exposed ECM
  - Key players: GP1b-V-IX, vWF, GPVI, collagen
- Activation/Secretion- plt shape change, recruit more platelets, support coagulation cascade
  - Key players: ADP, ATP, Ca^{+2}, serotonin, TXA2, thrombin
- **Aggregation** – form plt plug
  - Key players: integrin αIIbβ3 (GPIIb/IIIa), fibrinogen, vWF

Aggregation -Platelet plug formation

Activated plts bind **fibrinogen** via **GPIIb/IIIa** -> plts linked by fibrinogen bridges

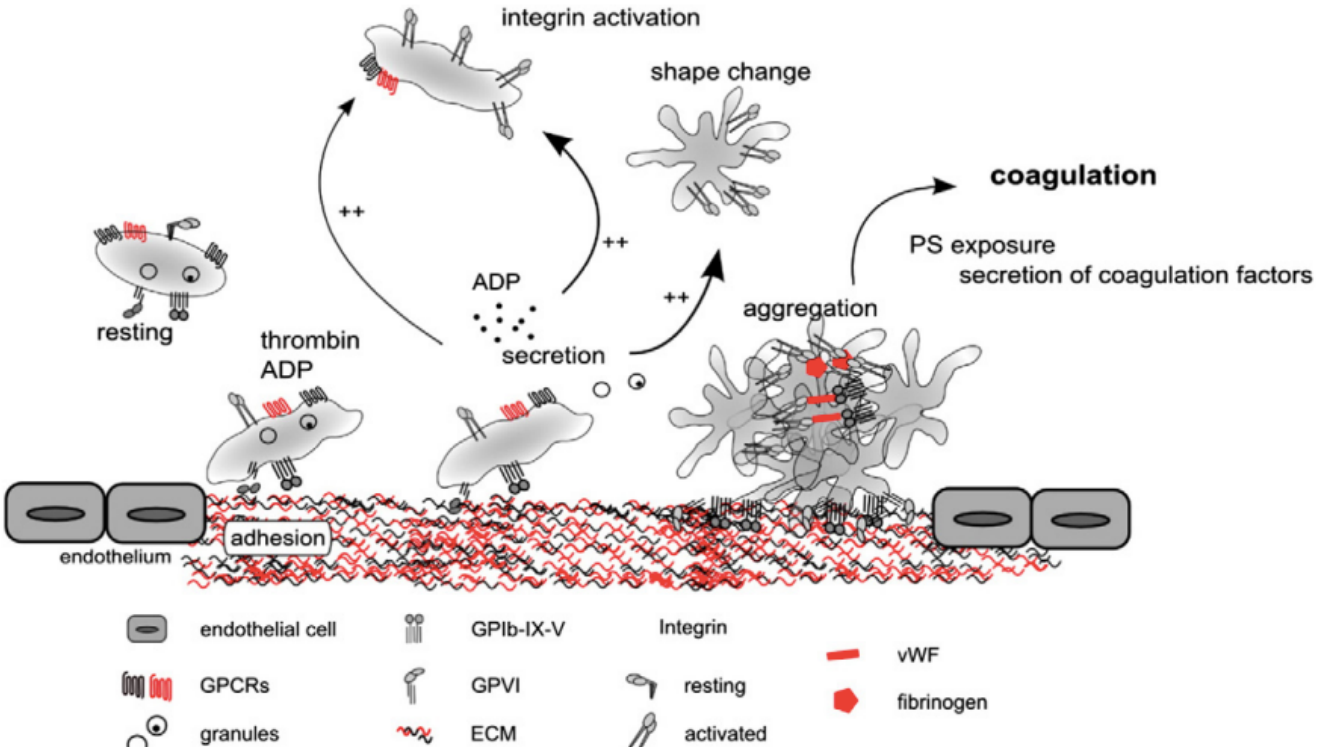
Endothelial injury

Plt adhesion: GP1b-vWF, GPVI-collagen

Plt activation: shape change, secrete agonists, form TXA2, GPIIb/IIIa activation

GPIIb/IIIa binds fibrinogen

Plt plug stabilized by fibrin



Golebiewska EM, Poole AW. Blood Reviews 2015

Key Agonists, Mediators

Thromboxane A2 (TXA2)

- Major product of AA metabolism
- Made & released from plts
- Amplifies plt activation, vasoconstriction
- **ASA**: inhibits mainly COX1 (convert AA -> prostaglandin H2 leading to TXA2 production)

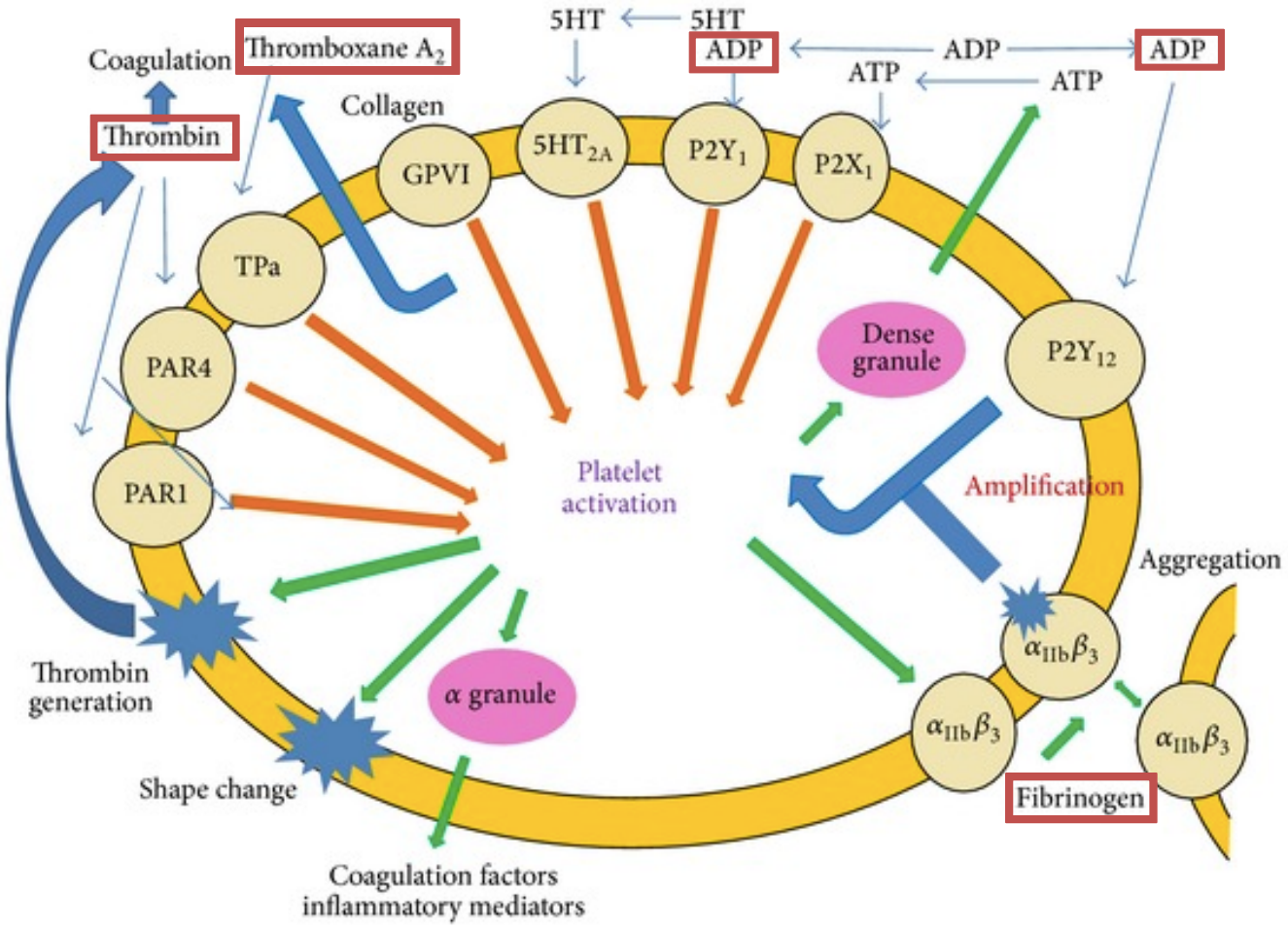
ADP

- Released by plt dense bodies
- Bind plt **P2Y12** & P2Y1 receptors
- Sustain/amplify plt aggregation
- **Thienopyridines** (ie plavix) inhibit P2Y12

Thrombin (Factor IIa)

- Formed via coag cascade (extrinsic pathway) & on plt surface
- Binds **PAR-1, PAR-4** on plts = activation of GPIIb/IIIa, plt agg
- Fibrinogen -> fibrin
- Positive feedback activation of intrinsic pathway

Key Agonists, Mediators

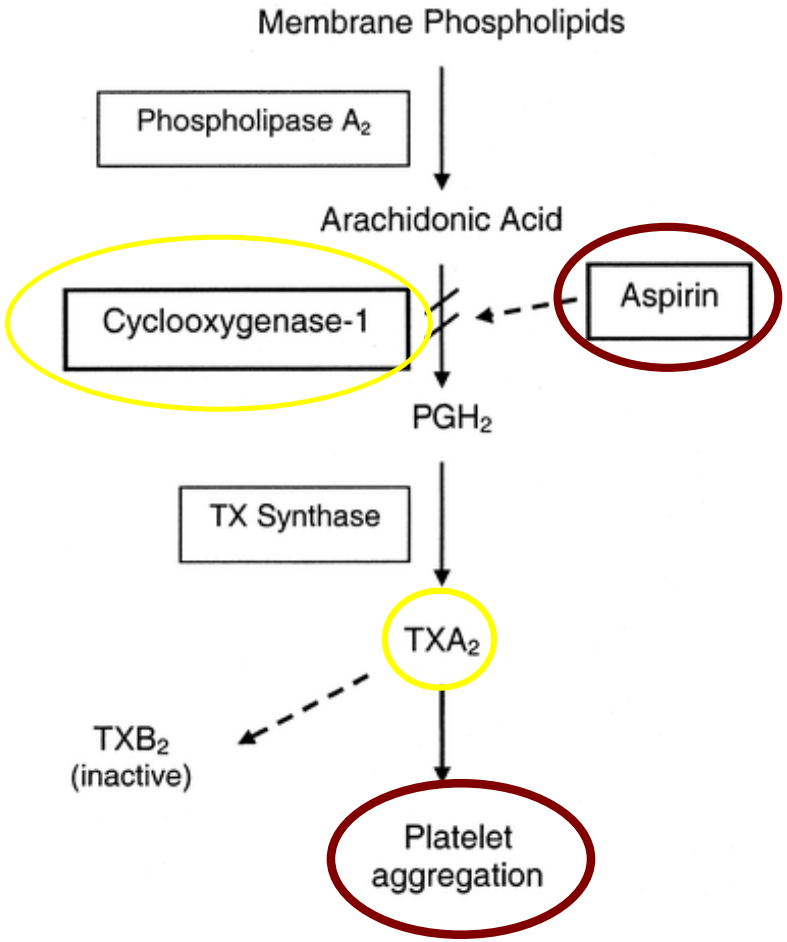


Ghoshal K, Bhattacharyya M. ScientificworldJournal, 2014

Platelet Pathology

- Cannot distinguish between traumatic and pathological vessel damage
  - May block diseased vessels = infarct, ischemia
  - Restenosis after angioplasty
  - **Antiplatelet agents** for coronary and cerebral artery disease

Antiplatelet Medications - ASA

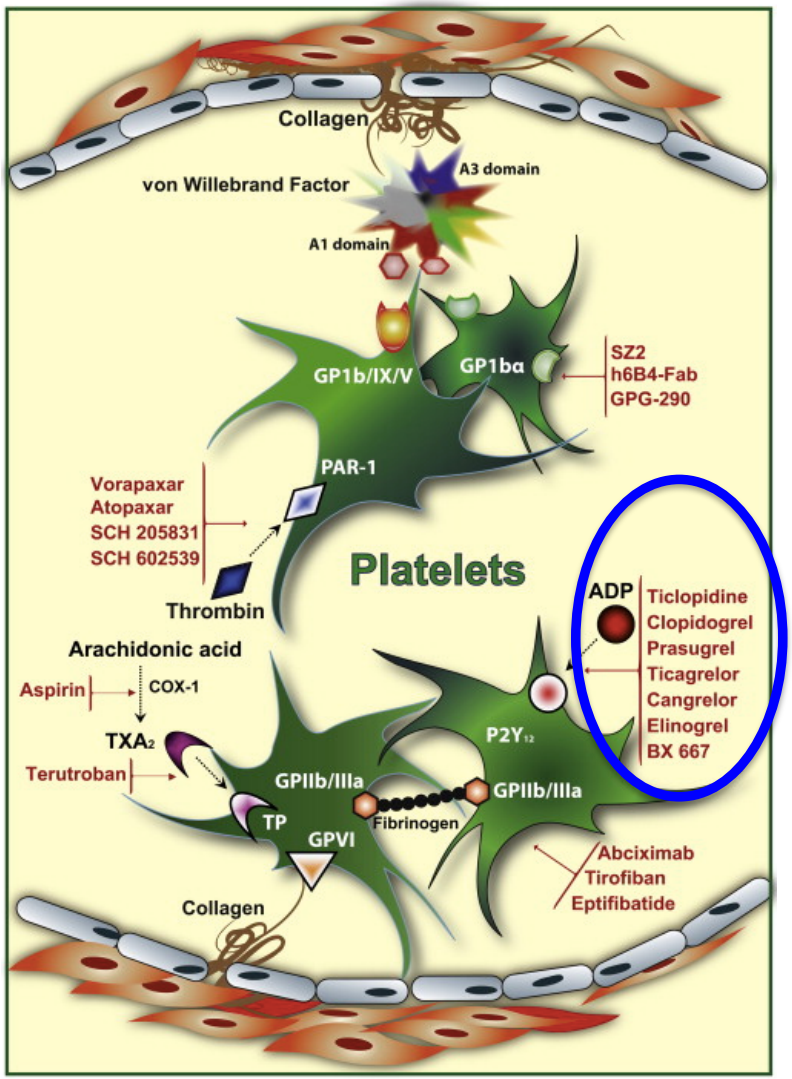


Maree AO, JACC 2005

- **Target**: Mainly COX-1, some COX-2 (dose dependent), irreversible inhibition
- **Effect**: ↓ Prostaglandin H2 synthesis, ↓ TXA2 = inhibited plt aggregation, blunted pro-inflammatory responses
- **Duration**: Lifetime of plt (8-10 days). About 10% of plts replaced daily (ie COX recovers 10%/day post-ASA)

Antiplatelet Medications – Clopidogrel

- **Target**: P2Y12 receptor, selective and irreversible inhibition
- **Effect**: Blocks ADP binding to P2Y12, suppress amplified plt response to other agonist, impair plt aggregation
- **Duration**: lifetime of plt (but recovery of plt function ~5 days)



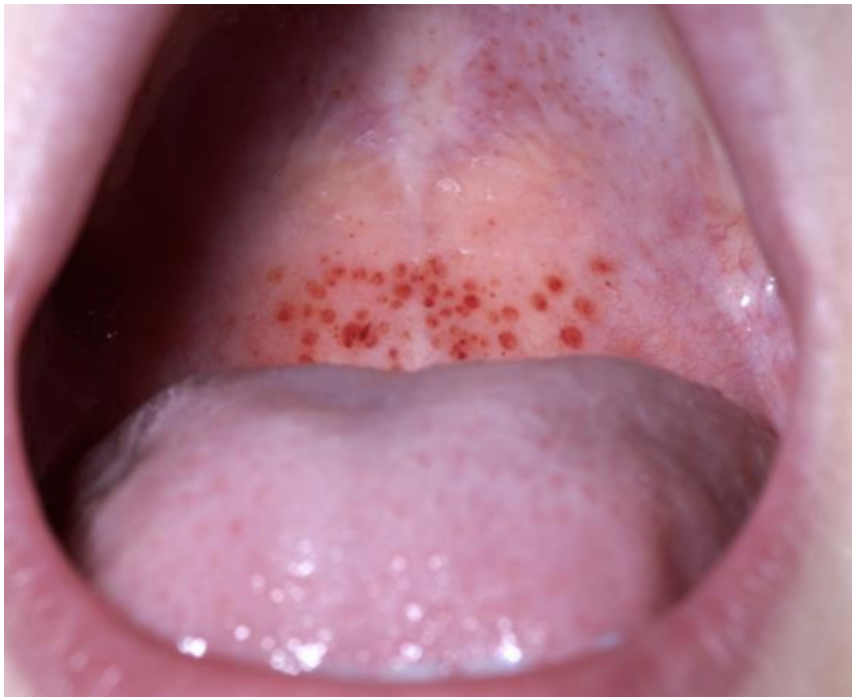
Siller-Matula JM, JACC: Cardiovascular Interventions, 2013

Antiplatelet Medications

Target	How it works	Medication Name
COX1	TXA2 involved in plt activation Irreversible inhibition COX1 Decrease TXA2 production	ASA
P2Y12 (plt receptor ADP)	Blocks ADP mediated amplification of plt activation/aggregation Irreversible blockade Prodrug (active metabolite via liver)	Thienopyridines: Ticlopidine (Ticlid®), Clopidogrel (Plavix®), Prasugrel (Effient®)
P2Y12	Direct, reversible antagonists	Ticagrelor (Brillinta®) Cangrelor (Kengreal®)
GPIIb/IIIa	Inhibit GPIIb/IIIa, blocks fibrinogen mediated plt aggregation	Tirofiban (Aggrastat®): Eptifibatide (Integrillin®) Abciximab (ReoPro®)
PAR1	Inhibits thrombin mediated platelet activation/aggregation	Vorapaxar (Zontivity®)

Platelet Function Disorders (PFD)

- **Acquired** (ie medicines, medical illness) or **inherited**
- **Mucocutaneous bleeding** (skin, mucous membranes)
  - Petechiae: < 3mm
  - Purpura: 3-10mm
  - Ecchymoses: > 1cm



Petechiae on soft palate

Marazzi P, Merck Manual

PFD – Diagnostic evaluation

- **Bleeding History**
  - Spontaneous, mucocutaneous, hemostatic challenges
  - Family history of bleeding
  - Medications, comorbidities
- **Clinical Exam**
- **Laboratory Testing**
  - CBC with diff, coags + fibrinogen, vWF studies
  - **PFA-100** (helpful for severe plt defects – ie BSS, GT, plt type vWD, poor sensitivity/specificity for less severe)
  - **Light transmission aggregometry (LTA)**
  - Specialized studies: **flow cytometry**, **EM**, **genetic testing**

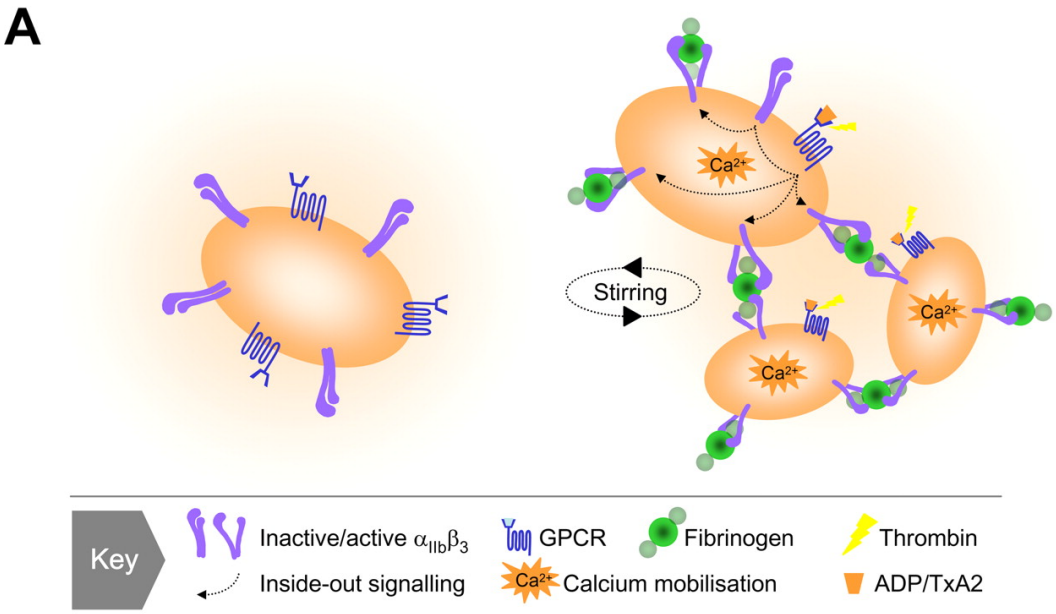
Platelet Aggregometry - LTA

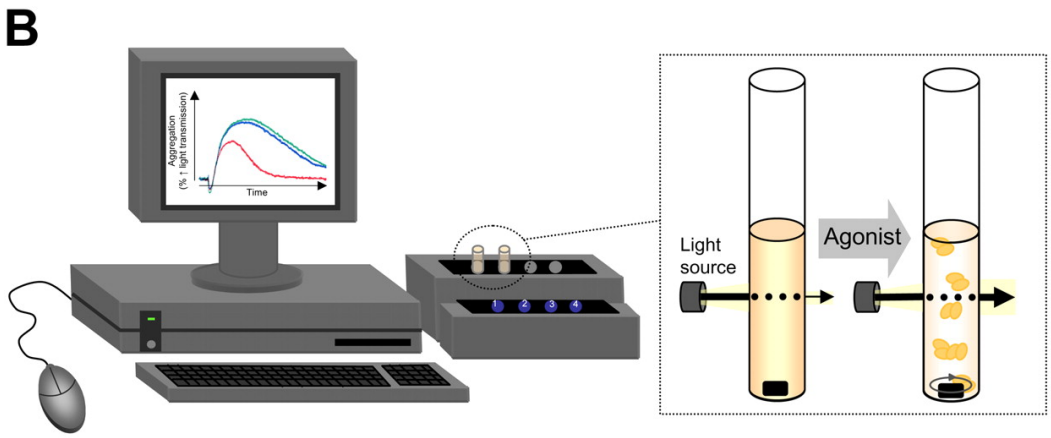
Light Transmission Aggregometry:

-Plt rich plasma in cuvette between light + photocell

- Stir plts in presence of agonist (ie ADP, AA, coll, epi, ristocetin)

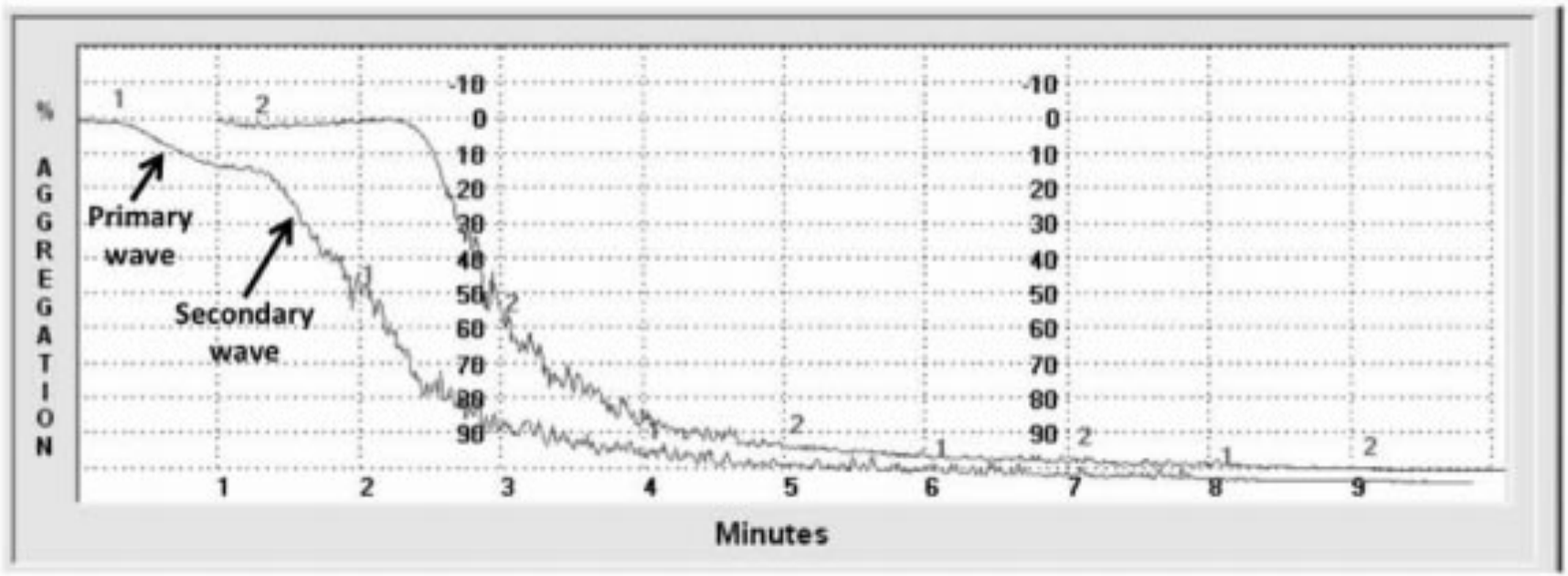
- Plts aggregate = ⇧light transmission, recorded as function of time





Jackson SP, Blood 2007

Platelet Aggregometry – LTA normal



Primary wave: response to addition of exogenous agonist

Secondary wave: aggregation in response to plt activation and secretion of endogenous pool of agonists

Cuker A, Ask the Hematologist, 2014

Platelet Aggregometry – LTA normal

1) Baseline pre agonist

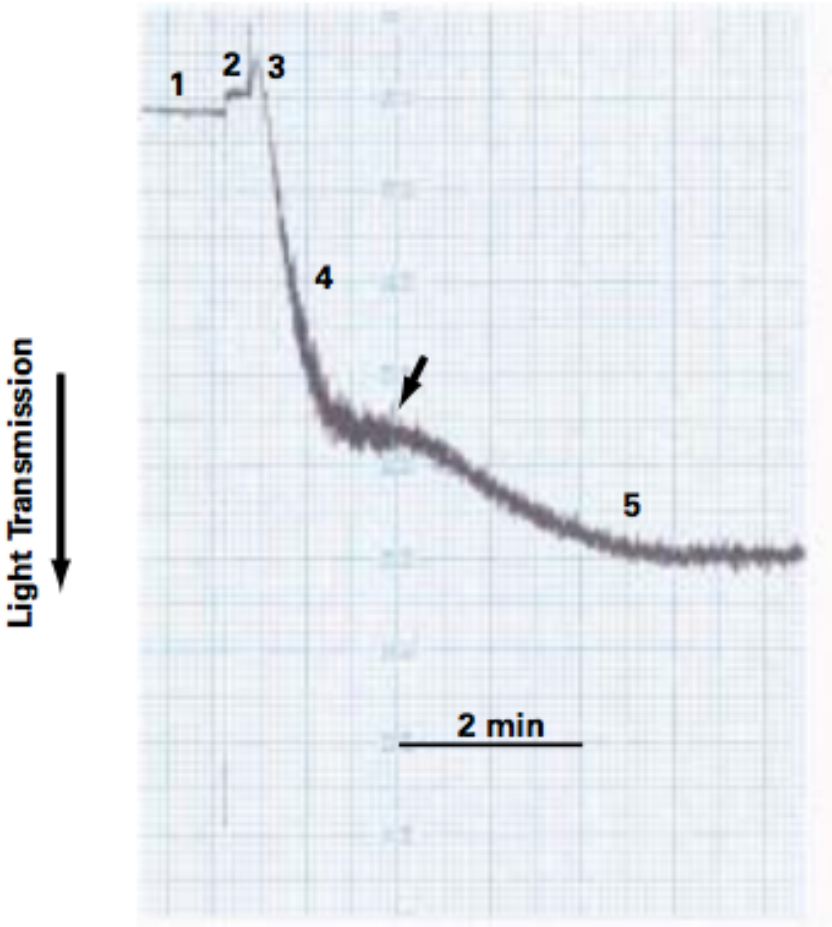
2) Plt agonist added

3) Plt shape change =slight ↓ in light transmission

4) Primary aggregation

5) Secondary aggregation (TXA formation, granule secretion)

Very strong agonists -> may not see differentiation between primary and secondary waves



ADP induced plt aggregation

Zhou L, Am J Clin Pathol 2005

Platelet Aggregometry - Agonists

Platelet Agonist	Target/Receptor
ADP	P2Y1, P2Y12 Low dose -> primary aggregation High dose -> secondary aggregation
Collagen	GPVI, GPIa/IIa
Ristocetin	vWF, GP Ib/IX/V complex
Epinephrine	Adrenergic receptors (leads to release of Ca^{+2})
Arachidonic Acid	Plt agg mediated via TXA2 synthesis (AA precursor of TXA2, involves COX1, COX2, prostaglandin H2)

Platelet Aggregometry - LTA Abnormal

Characteristic LTA Patterns of Selected PFD's

Disorder	Primary wave ADP	Secondary wave ADP	Epinephrine	AA	Collagen	Ristocetin
GT	Absent	Absent	Absent	Absent	Absent	Normal
BSS	Normal	Normal	Normal	Normal	Normal	Absent
Dense (δ) granule SPD	Normal	Decreased or Absent	Variable	Normal	Normal	Normal
ASA use	Normal	Decreased or Absent	Decreased or Absent	Absent	Decreased or Absent	Normal
P2Y12 inhibitor	Decreased or Absent	Absent	Normal	Normal	Normal	Normal
GPIIb/IIIa inhibitor	Absent	Absent	Absent	Absent	Absent	Normal

GT: Glanzmann thrombasthenia; BSS: Bernard Soulier Syndrome; SPD: storage pool disorder

Adapted from Cuker A, Ask the Hematologist, 2014

Glanzmann Thrombasthenia

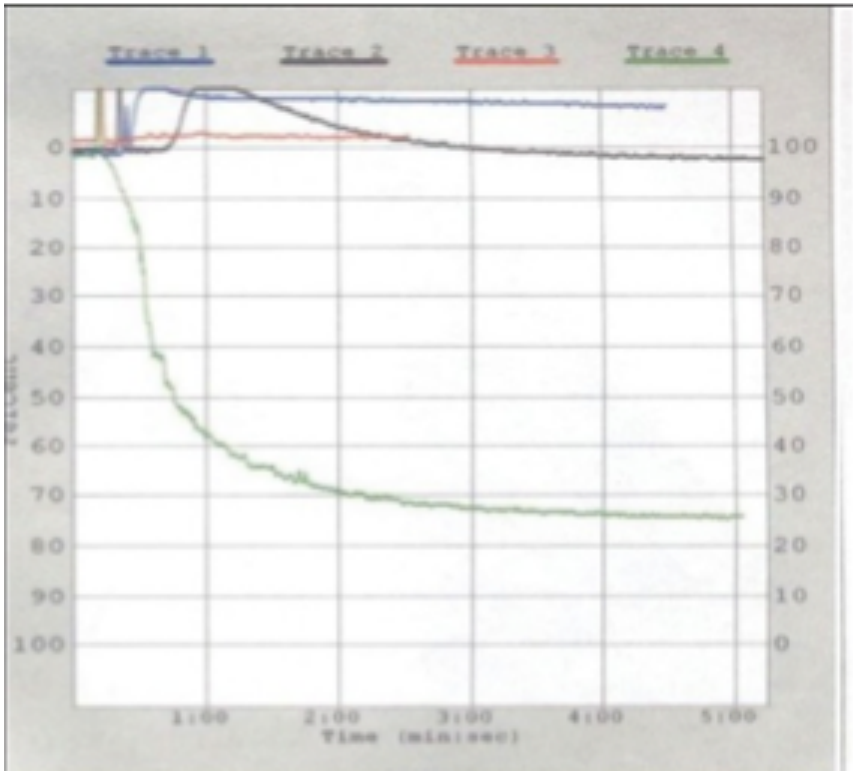
- **Genetics**: Autosomal recessive
  - Mutations *ITGA2B, ITGB3*
- **Incidence**: ~1/million; up to 1/200K in high consanguinity
- **Molecular**: Absent/non-functioning **GPIIb/IIIa**
  - Plts stick to collagen but no plt cross-linking
- **Clinical**: Mod to severe mucocutaneous bleeding
  - Incidence of severe bleeding decreases with age, no correlation b/w GPIIb/IIIa levels and bleeding severity

Glanzmann Thrombasthenia

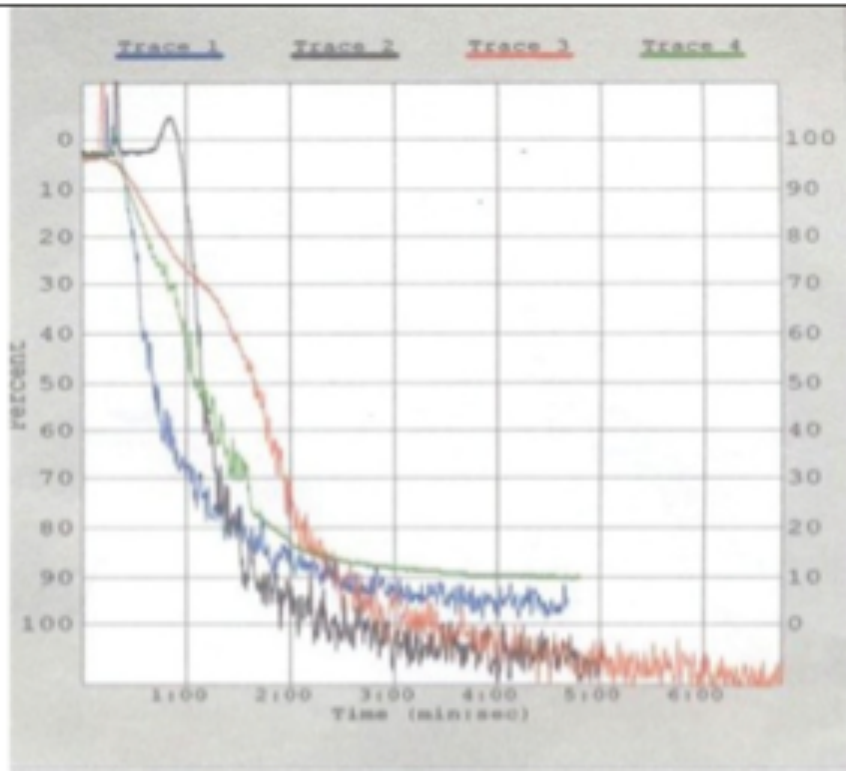
- **Diagnosis**:
  - Normal plt count
  - **LTA** - absent response to all agonists except ristocetin
  - **Flow**: low or absent GPIIb/IIIa
- **Treatment**:
  - anti-fibrinolytics, ?DDAVP, recombinant FVIIa, plt transfusion- HLA matched (risk of alloimmunization)

Glanzmann Thrombasthenia

Patient with GT



Control with normal LTA



LTA in Glanzmann Thrombasthenia: Normal aggregation with Ristocetin (green), decreased with other agonists

Ristocetin: causes vWF to bind to plt GP1b, plt agg/agglutination

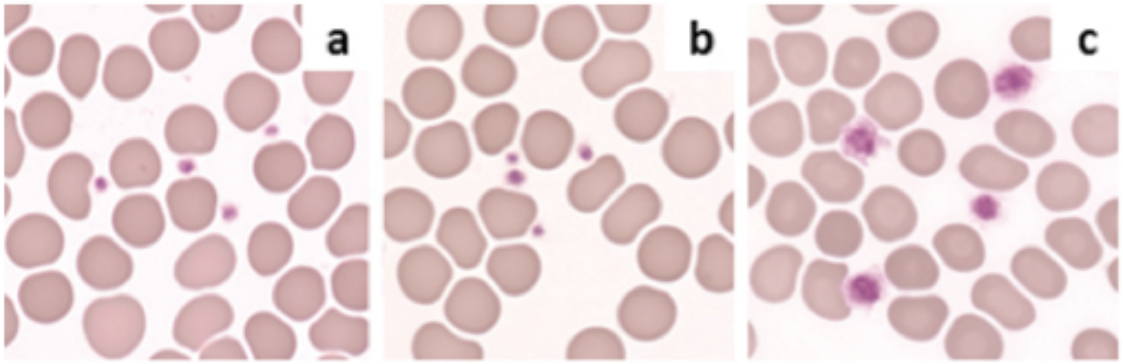
Belurkar S, Ann Nigerian Med 2012

Bernard Soulier Syndrome

- **Genetics**: Autosomal recessive
  - GP1b-V-IX complex composed of 4 subunits
  - Mutations in *GP1bα*, *GP1bβ*, *GP9*
- **Incidence**: < 1 per million
- **Molecular**: Dysfunctional GP1b-V-IX
  - Adhesion defect (plt binding to vWF on ECM)
- **Clinical**: Variable mucocutaneous bleeding

Bernard Soulier Syndrome

- **Diagnosis**:
  - Macrothrombocytopenia
  - **LTA:** no ristocetin response, normal to other agonists
  - **Flow cytometry**: decreased surface expression of GP1b
- **Treatment**:
  - anti-fibrinolytics, plt transfusion-HLA matched



a,b: normal platelets; **c: giant platelets**

Balduini CL, Semin Thromb Hemost 2013

Platelet-type von Willebrand disease

- **Genetics**: Autosomal dominant
  - Gain of function mutation of GPIb-V-IX (GP1bα)
- **Molecular**:
  - Spontaneous binding of vWF to plts and increased clearance of vWF-platelet complexes
- **Clinical:** Mild-mod mucocutaneous bleeding, mild macrothrombocytopenia

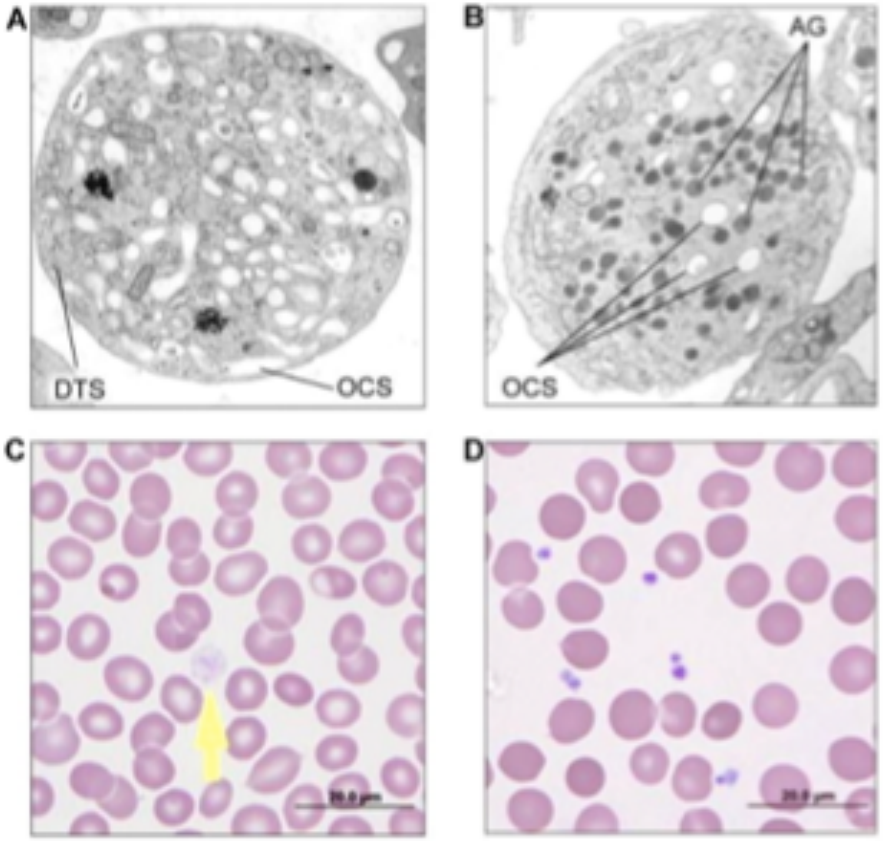
Platelet-type von Willebrand disease

- **Must distinguish from Type 2B vWD**
- Platelet type vWD: treat with platelet replacement, **NOT** responsive to vWF replacement

- **Diagnosis**: ↓vWF activity, ↓ HMW vWF multimers, specialized RIPA mixing studies, genetic testing (GP1bα, vWF)

Gray platelet syndrome

- **Genetics**: Autosomal recessive
  - mutation in *NBEAL2*
- **Clinical**:
  - Mild to moderate bleeding
  - Associated w/myelofibrosis splenomegaly
- **Diagnosis**:
  - Large platelets
  - **Lack α granules**
  - **Gray** appearance of plts by light microscopy



A: Plts lack α granules, B: normal α granules
C: Pale gray plts, D: normal smear

Meral Gunay-Aygun et al. Blood 2010;116:4990-5001

Hermansky-Pudlak Syndrome

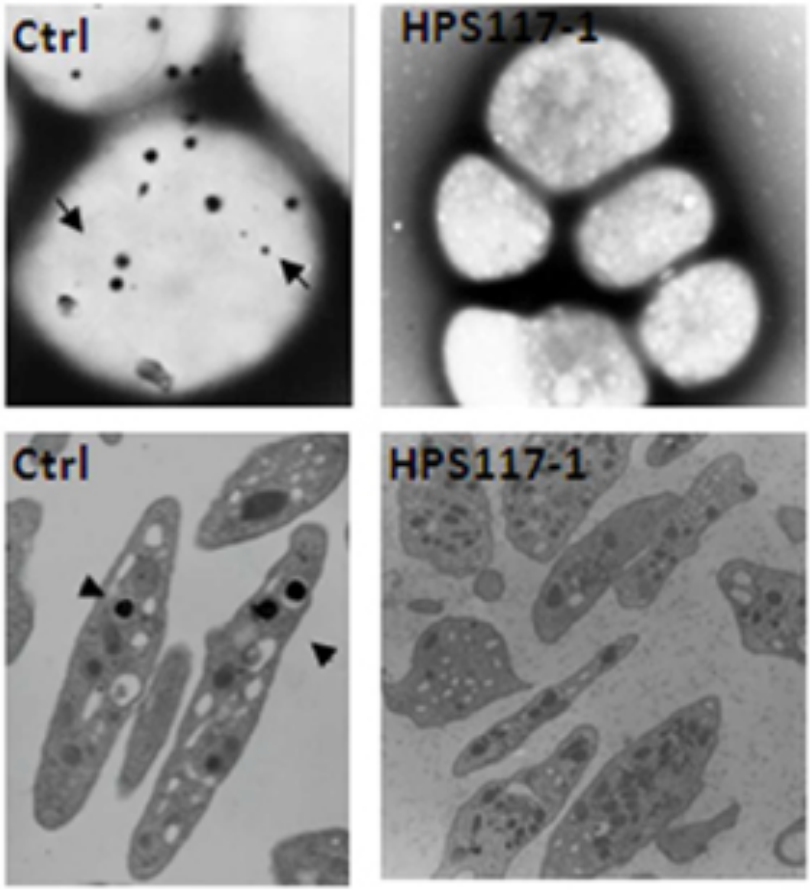
- **Genetics**: Autosomal recessive
  - Mutations in *HPS1* most common
  - Most common in northwestern Puerto Rico (1:1800)

- **Clinical:** Mod-severe bleeding, **Oculocutaneous albinism**
  - Granulomatous colitis, pulmonary fibrosis, immunodeficiency associated with some subtypes
  - Plt defect (**lack δ granules**) part of a larger syndrome

Pt with HPS with mother

Loredana Asztalos M et al, Pediatr Dermatol 2017

Hermansky-Pudlak Syndrome



EM showing absence of plt δ granules

Diagnosis:

- Normal plt count
- LTA: absent second wave of aggregation
- Electron microscopy: absent/few dense (δ) granules

Carmona-Rivera C et al, J Invest Dermatol 2011

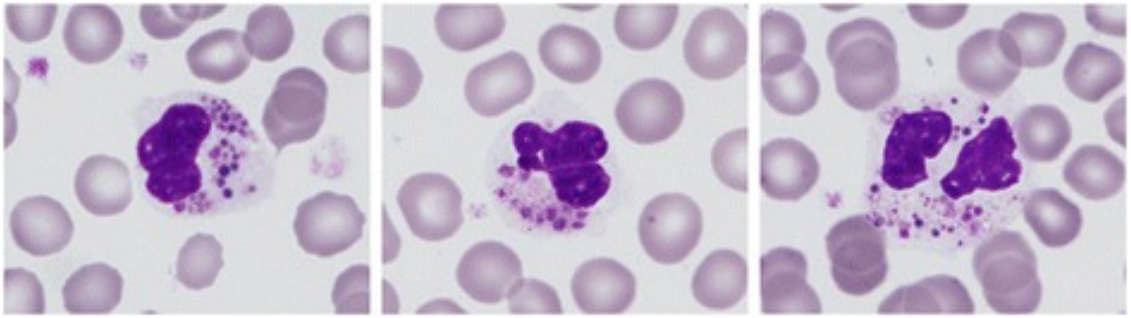
Chediak-Higashi Syndrome

- **Genetics**: Autosomal recessive
  - mutation in *CHS/LYST* gene
- **Clinical**: Mod-severe bleeding, oculocutaneous albinism, severe immunodeficiency, neurological dysfunction
  - Plt defect (**absent δ granules**) part of a larger syndromic disease

Chediak-Higashi Syndrome

Diagnosis:

- LTA: can have ↓ response to collagen, AA and thrombin, lack second wave of aggregation
- Smear: **giant inclusions** in leukocytes
- EM **absent dense granules**



Peripheral smear (Wright Giemsa stain): giant intracytoplasmic granules in leukocytes

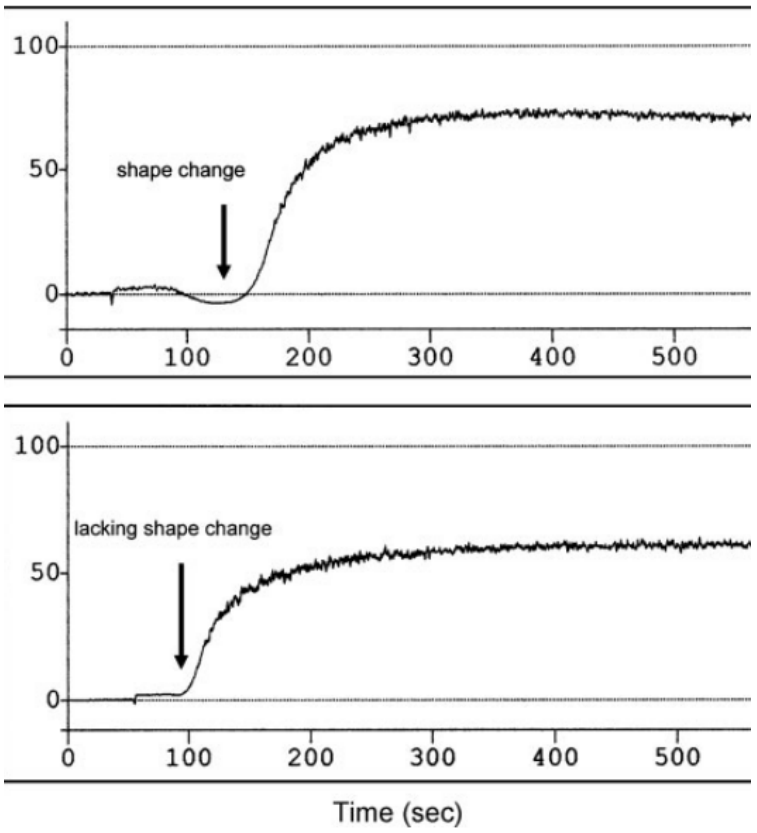
Lozano ML, Orphanet J Rare Dis, 2014

MYH-9 Related Disorders

Previously known as May-Hegglin anomaly, Sebastian, Fechtner, or Epstein syndrome

- **Genetics**: Autosomal dominant
  - Mutations in MYH9 (nonmuscle myosin IIA heavy chain); involved in cell motility/shape maintenance
- **Molecular**:
  - Dysfunctional MYH9 -> defective megakaryocyte maturation, abnormal cytoplasmic transport
- **Clinical**: Mild-mod bleeding, plts 30-100K, macrothrombocytopenia, nephritis, hearing loss

MYH-9 Related Disorders

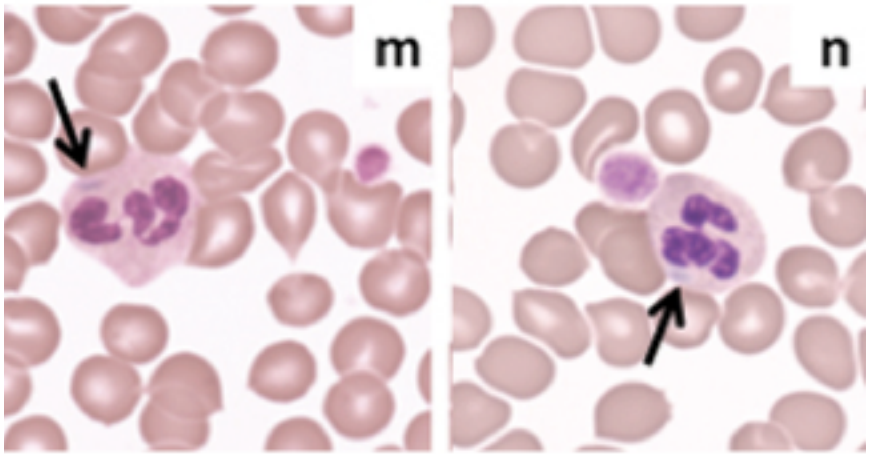


Top: normal aggregation
Bottom: MYH-9, slightly impaired response to collagen, no shape change

Althaus K, Semin Thromb Hemost, 2009

Diagnosis:

- large **Döhle-like bodies** in leukocytes, giant plts
- **LTA**: impaired collagen response, no shape change
- Immunoflourescence (NMM-IIA inclusion bodies)



Balduini CL, Semin Thromb Hemost 2013

Wiskott-Aldrich Syndrome

- **Genetics**: X linked recessive
  - Mutation in *WAS* gene
  - WASp: hematopoietic-specific regulator of actin polymerization
- **Clinical**: **microthrombocytopenia**, **eczema**, recurrent infections due to severe **immune deficiency**, increased risk of lymphoid malignancy
- **Diagnosis**: low IgG/IgA/IgM, flow for WASp expression, gene sequencing

Inherited Platelet Function Disorders

Disorder	Genetic Alteration	LTA response	Clinical features
Disorders of plt aggregation			
Glanzmann Thrombasthenia	*ITGA2B, ITGB3* (GPIIb/IIIa defects)	Absent to all but ristocetin	Mod-severe bleeding
Disorders of plt adhesion			
Bernard Soulier Syndrome	*GP1Bα, GP1Bβ, GP9* (GPIb/IX/V defects)	Absent response to ristocetin	Large plts, mild thrombocytopenia
Platelet type vWD	GOF mutation in *GP1BA* (GP1bα)	Increased agglutination to low dose ristocetin	Large plts, decreased HMW vWF multimers
α Granule disorders			
Gray plt syndrome	*NBEAL2* (lack α granules)	Decreased response thrombin, collagen	Large plts, myelofibrosis
Quebec plt disorder	Duplication of *PLAU* Excess uPA = α granule proteolysis	Decreased response thrombin, collagen	Delayed onset bleeding, responds to anti-fibrinolytics

Inherited Platelet Function Disorders

Disorder	Genetic Alteration	LTA response	Clinical features
Dense (δ) Granule defects/secretion defects			
Hermansky-Pudlak Syndrome	*HPS1 – HPS 8* (absent δ granules)	+/- Decreased response to ADP, coll, epi. Absent secondary aggregation	Oculocutaneous albinism, strabismus, pulmonary fibrosis
Chediak-Higashi Syndrome	*LYST* (absent δ granules)	+/- Decreased response to ADP, coll, epi. Absent secondary aggregation	Partial albinism, immunodeficiency, neurologic dysfunct Inclusion bodies in granulocytes
Cytoskeletal defects			
Wiskott-Aldrich Syndrome	*WAS* (WASp needed to maintain integrity of actin cytoskeleton)		X-linked recessive. Eczema, low + small plts, immune deficiency

Acquired Platelet Function Disorders

- **Medications**
- **Acquired von Willebrand Syndrome** (AVWS)
  - Clonal hematopoietic disorders, AS, autoimmune
- **Systemic Disorders**
  - Renal disease/uremeia, paraproteinemias, bypass

Acquired Platelet Function Disorders

Medications

- Antiplatelet medications, NSAIDs
- β-Lactam antibiotics (penicillins, cephalosporins)
- In vitro effects: statins, SSRIs, herbals

Acquired von Willebrand Syndrome (AVWS)

- **Clonal hematological disorders** (MPN, ET): adsorption of vWF to plts
- **Autoimmune**: Ab mediated vWF clearance
- **Shear stress**/proteolysis (ie Aortic Stenosis, LVAD)

Acquired Platelet Function Disorders
Systemic Disorders

- **ESRD/Uremia**
  - ↑ substances (ie NO) inhibit plt adhesion, activation, aggregation
  - Anemia attenuates plt/vessel wall interactions
  - Accumulation of medications

- **Plasma cell dyscrasias**
  - Paraproteins stick to platelets, impair plt-plt interactions
  - Paraproteins can cause AVWS

- **Cardiopulmonary bypass**
  - Plts activated and degranulate in circuit
  - Hypothermia compromises plt function

Thank You!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FROZEN

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