Lec 17

Storage Pool Disorders
Gray Platelet Syndrome

- Absence of **α-granules** , Molecular defect **unknown**, Mild mucocutaneous **bleeding**, Variably prolonged **bleeding time**, Moderate thrombocytopenia, Reticulin fibrosis of Bone Marrow, Large gray platelet

Quebec Platelet Disorder

- QPD is a rare, autosomal dominant bleeding disorder described in a family from the **province of Quebec in Canada**
- **large** amounts of the **fibrinolytic** enzyme urokinase-type plasminogen activator (**u-PA**) in platelets
- stored platelet **plasminogen** is converted to **plasmin**

Storage Pool Disorders
Dense Granule Disorders

- **Normal** dense granules, **3-6**/ platelet, **Serotonin**, ADP, ATP, Ca, **Heterogeneous** group of disorders, Molecular defect **unknown**, Mild to moderate **bleeding**

Storage Pool Disorders

- Two autosomal recessive syndromes associated with albinism
  - Chediak-Higash
  - Hermansky-Pudlack
- Non-albino syndromes
  - Wiskott-Aldrich
  - Thrombocytopenia absent radii
  - Osteogenesis imperfecta

Storage Pool Disorders

Chediak-Higashi

- Partial oculocutaneous albinism
- Frequent pyogenic infection
- Giant lysosomal granules in cells
- Thrombocytopenia
- Dense granule deficiency

Hermansky-Pudlak

- Oculocutaneous albinism
- Inclusions in the cells of reticuloendothelial system Thrombocytopenia
- Dense granule deficiency

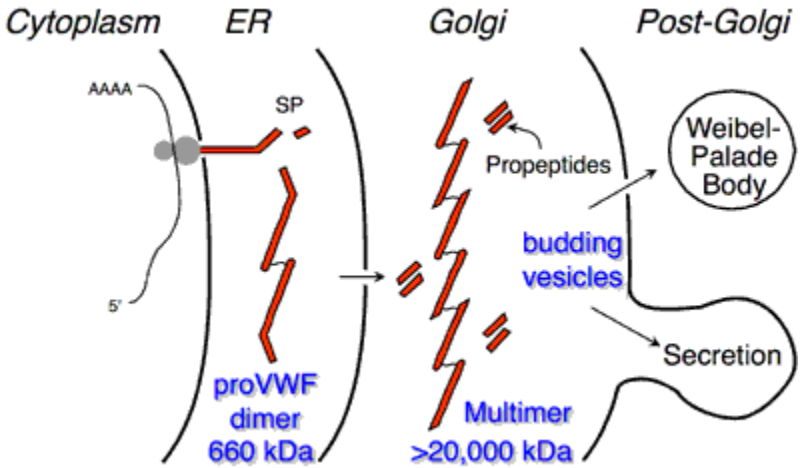
Storage Pool Disorders

Clinical presentation

- Platelet **morphology normal**
- Bleeding **time** usually, **not** always **prolonged**
- **Aggregation**
- Marked impairment with weak agonists ADP, epinephrine and low concentrations of collagen
- Response to higher concentration may be normal
- Absent second wave of aggregation when stimulated by ADP and epinephrine

Von Willebrand Factor

- The gene for vWF →chromosome **12p**.
- Synthesized in **endothelial cells** and **megakaryocytes** and stored in **Weibel-Palade bodies** and **platelet alpha granules**, respectively.
- vWF is initially formed in the **ER** as a **pre-pro VWF** molecule, which would assembly into homomultimeric protein after **glycosylation**, dimerization and **multimerization** in the **golgi** organelle and **storage places** in the cells.



Function of vWF

- Serves as the **carrier protein** for factor **VIII** (probably factor VIII and vWF are brought together in storage granules).
- Serves as the **ligand** that **binds to glycoptrotein Ib** receptor on platelets to **initiate platelet adhesion** to damaged blood vessel walls.
- vWF needs to be activated to be able to bind to **GP 1b receptor** on platelets (**Ristocetin**, high shear force, collagen, etc)

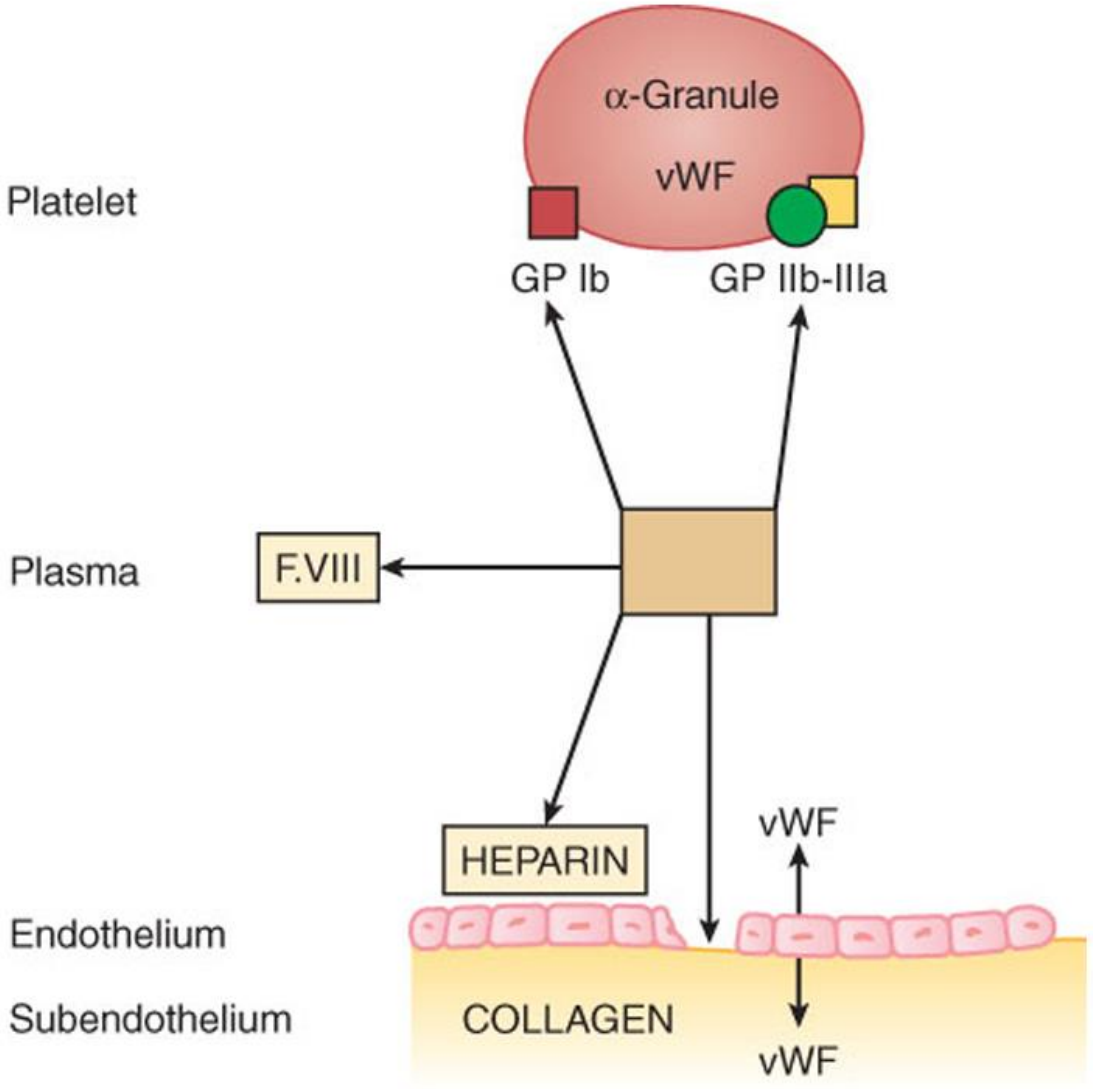
von Willebrand disease:

- *Pathogenesis: defect of platelet* ***GPIbα*** increased desire for normal vWF leading to the binding of the largest vWF multimers to resting platelets and to their clearance from the circulation results thrombocytopenia and adhesion defect.
- *Inheritance:* **autosomal dominant**
- *Laboratory findings:* - **prolonged** bleeding time

- **moderate** thrombocytopenia
- **loss** of large vWF multimers
- enhanced ristocetin-induced platelet aggregation

- ***Differential diagnosis:*** **from Type 2B vWD (molecular characterisation of platelet GPIb**a**)**
- ***Treatment:*** **platelet concentrate + vWF concentrate.**

VON WILLEBRAND DISESE



I/2. Disease associated platelet function disorders

- **Uremia**: *complex **hemostatic defect***

– thrombocytopenia, platelet dysfunction (adhesion, aggregation, secretion defects), mild coagulation abnormalities.

- **Hematopoetic** disorders:

– paraproteinemias, myeloproliferative disorders, myelodysplastic syndrome, leukemia.

- Cardiopulmonary bypass operation
- Platelet antibodies:

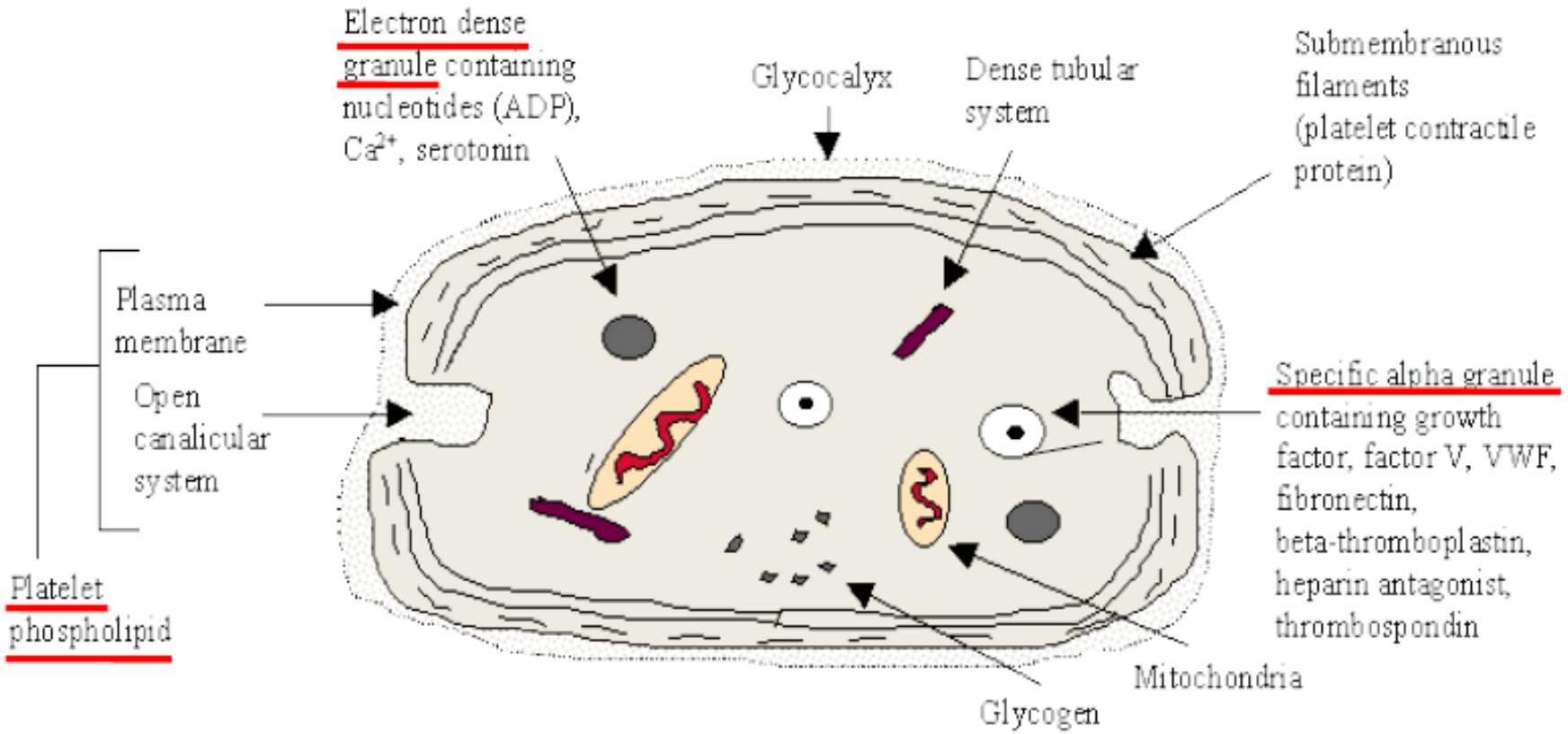
– auto-, alloantibodies

- Others:

– diabetes mellitus, liver disease, DIC

Collagen receptor deficiency

- *Pathogenesis:*
- abnormalities of platelet ***GPVI*** *and* ***GPIa-IIa*** (receptors for collagen)
- **defect** of adhesion and collagen-induced platelet aggregation.



Platelet ultrastructure

Defects of intracellular signal transduction and secretion

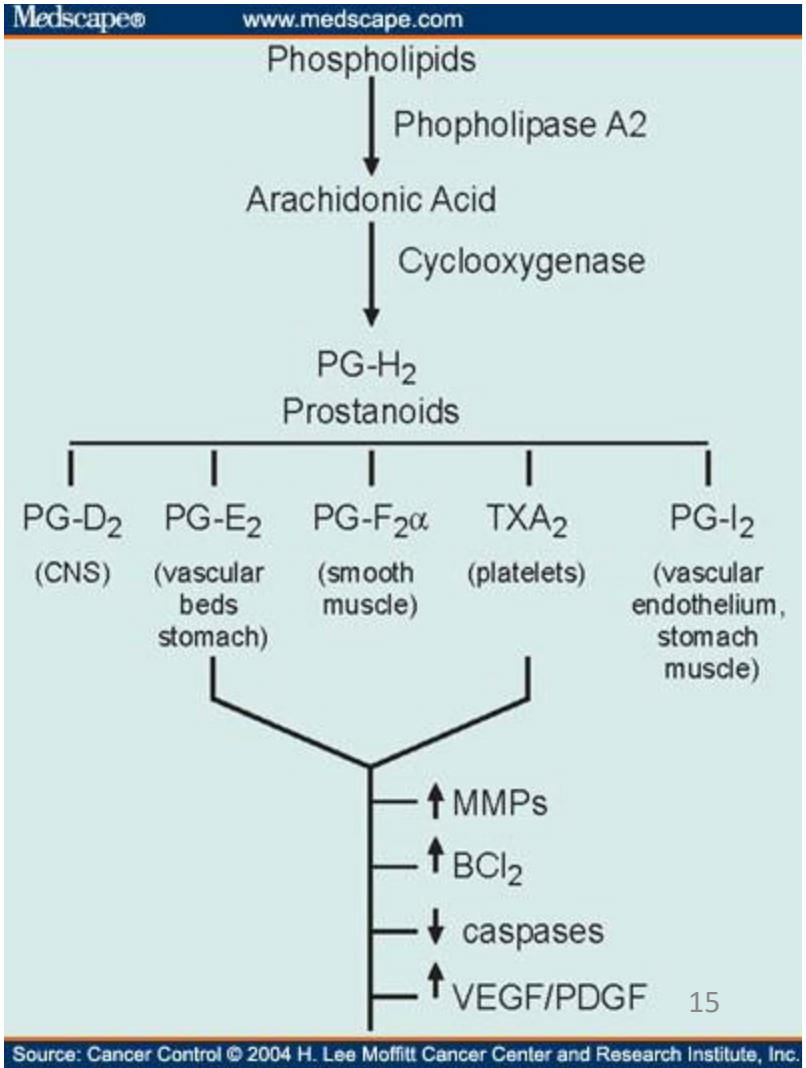
- Abnormalities of the **<u>arachinodate/ thromboxane A2</u>** pathway ® platelet function **<u>defects</u>**, mild **<u>bleeding</u>**.

● Impaired liberation of Arachidonic acid from membrane phospholipids

● Cyclooxygenase deficiency (aspirin like disease")

● Thromboxane synthetase deficiency

● Thromboxane A2 receptor abnormalities



Disorders of receptors and signal transduction:

- Cyclooxygenase inhibitors (TXA2 –e.g. Aspirin)
- Adenosine diphosphate inhibitors (ADP)
- GPIIb-IIIa receptor antagonists

Therapy

- Platelet **transfusion** should be used only in **severe bleeding** episodes
- **Recombinant factor VIIa**
- **Antifibrynolytic agents** (tranexamic acid)
- Desmopressin (DDAVP)

Thrombocytopenia

Abnormal bleeding due to thrombocytopenia or abnormal platelets function is also characterized by spontaneous skin purpura & hemorrhage & prolonged bleeding after trauma.

A. **Decreased** marrow **production** of megakariocytes

- ✓ **congenital** disorders
- ✓ **acquired** disorders

B. **Splenic sequestration** of circulating platelets

C. **Increased destruction** of circulating platelets (**congenital/acquired** disorders)

- **immune** destruction
- **nonimmune** destruction

Thrombocytopenia (A)

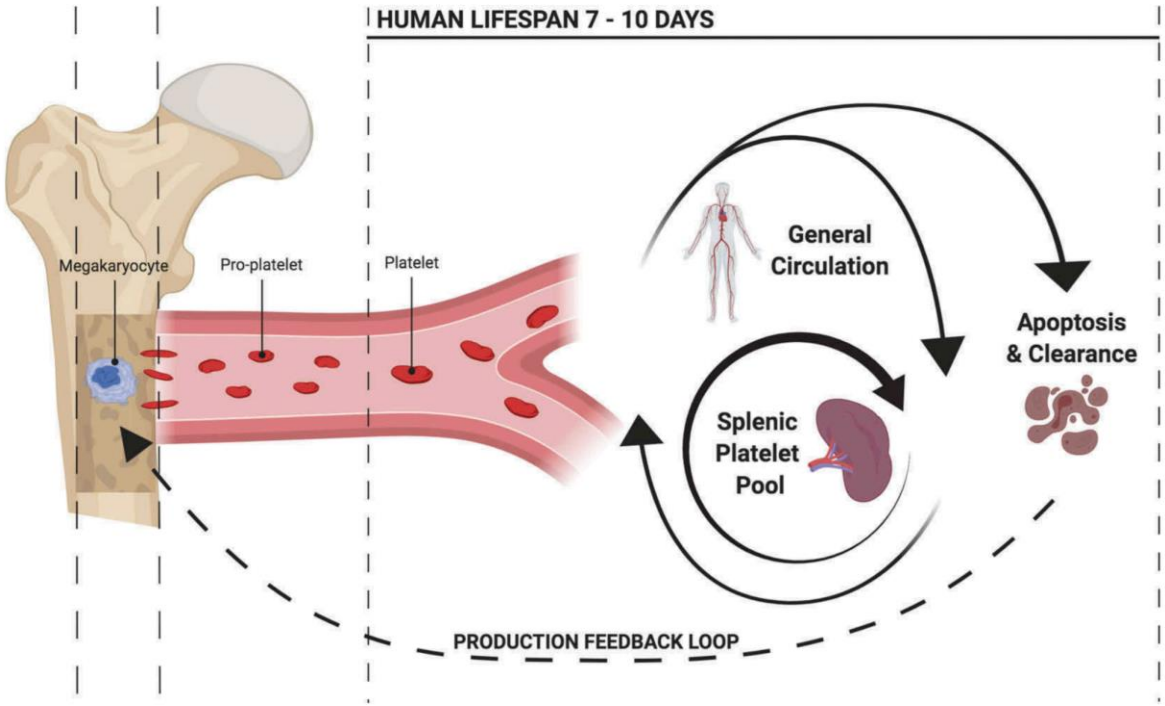
A. **Decreased** marrow production of **megakariocytes**

- **congenital** disorders
  - **Fanconi's** anemia→ **genetic defect** in a cluster of proteins responsible for **DNA repair**
  - thrombocytopenia with absent radii (**TAR**)→ absence of the radius bone in the forearm, and a dramatically reduced platelet count
- **acquired** disorders
  - marrow **infiltration** with malignant cells
  - marrow **fibrosis**
  - **aplastic** and **hypoplastic** anemias (idiopathic, drugs, toxins)
  - **deficiency** states (vitamin **B12**, **folate**, **iron**)

Thrombocytopenia (B)

B. Splenic **sequestration** of circulating platelets

- splenic enlargement due to **tumor infiltration**
- splenic enlargement due to **portal hypertension**



Thrombocytopenia (C)

C. **Increased destruction** of circulating platelets

- **congenital** disorder
  - **Wiscott-Aldrich** syndrome→ rare **X-linked** recessive disease →eczema, thrombocytopenia, immune deficiency, and bloody diarrhea (secondary to the thrombocytopenia).
  - **Bernard-Soulier** syndrome

Thrombocytopenia (C)

- **acquired** disorders
  - ❑ **nonimmune destruction**
    - Disseminated intravascular coagulation (DIC)→pathological activation of coagulation
    - hemolytic-uremic syndrome/thrombotic thrombocytopenic purpura
    - Sepsis
    - vascular prostheses, cardiac valves
  - ❑**immune destruction**
    - Primary immune thrombocytopenic (ITP)
    - drug-induced thrombocytopenia
    - chronic autoimmune disorders
    - infection (HIV)
    - malignancies

Thrombocytosis

- Thrombocytosis resulting from **myeloproliferation**
  - essential thrombocythemia
  - polycythemia vera
  - chronic myelogenous leukemia
  - myeloid metaplasia
- Secondary (reactive) thrombocytosis
  - systemic inflammation
  - malignancy
  - iron deficiency
  - hemorrhage
  - postsplenectomy

HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

- It is an immune complication caused by antibodies directed against heparin in complex with platelet factor 4→ activating the platelets and promoting a prothrombotic state
- 50% or more reduction in platelet count
- Beginning 5 or more days after first exposure to heparin
- Thrombotic complications
- Therapy – to discontinue all forms of heparin
- Direct IIa inhibitors (lepirudin, argatroban) and Xa (danaparoid)