Platelet Review
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Hemostasis

- Hemostasis is the process that leads to the stopping of bleeding
- Hemostasis involves blood vessels, platelets, plasma clotting proteins
- Primary Hemostasis is the initial response to injury to a blood vessel involving platelets
- Secondary Hemostasis occurs to fortify primary hemostasis thru the activation of clotting proteins to form an insoluble deposition of fibrin in and around platelets
Bleeding – Cut a Blood Vessel – What Happens?
What is Going on in the Blood Vessel – a lot!

PRIMARY HEMOSTASIS = PLATELET PLUG

SECONDARY HEMOSTASIS = CLOTTING CASCADE
Overview of Hemostasis

Hemostasis - 2 components - Platelets, Clotting Proteins
Both Occurring Simultaneously

Clotting Cascade Leads to Secondary Hemostasis

Platelets Lead to Primary Hemostasis

HEMOSTASIS
VWF
VESSEL INJURY
TISSUE FACTOR
SUBENDOTHELIAL COLLAGEN
PLATELET ADHESION
Epi ADP TXA2
PLATELET AGGREGATES
HEMOSTATIC PLUG
THROMBIN
FIBRINOGEN
FIBRIN
Hemostasis

• Intricate system maintaining blood in fluid state
  – Reacts to vascular injury to stop blood loss and seal vessel wall

• Involves platelets, clotting factors, endothelium, and inhibitory/control mechanisms
  – Highly developed system of checks and balances

Normal Hemostasis
Absence of overt bleeding/thrombosis
Platelets are typically 1-2 micron
The normal PLT count is 150-350,000/ul
One large one above shows how granular they appear.
A scanning electron micrograph of normal platelets
Really are fragments of megakaryocyte cytoplasm
Platelet- Number, Lifespan and Kinetics

• Normal platelet concentration is 150,000-350,000/ ul
• Platelets are produced in the bone marrow by megakaryocytes and released into the circulation
• They circulate in the blood for about 10 days after release from the marrow
• About 1/3 of all the body’s platelet mass is stored in the spleen
Megakaryocytes produce platelets in the marrow, stimulated by thrombopoietin.
Platelets are released from megakaryocytes, this shows this process in vitro culture.
Stages of platelet development

Stem cell

Commitment

BFU-Mk, CFU-Mk

Immature Mk

Terminal differentiation

Mature Mk

Platelet shedding

All stages are driven by thrombopoietin.
Thrombopoietin (TPO)

- Growth factor produced in liver
- Increases production of megakaryocytes
- Essential for stem cells
TPO Effect on Normal Mice

Platelets (x 10^6/mm^3)

Days

control  ---+TPO  ---
Mouse bone marrow
control + TPO
TPO regulation

- Constitutive (constant) production
- Level depends on binding sites on platelets and megakaryocytes
Thrombopoietin Regulation (Sponge theory)

As Platelet Count Increases, serve as a sponge, having less available to stimulate Megakaryocytes.
Primary Hemostasis

Adhesion
Aggregation
Secretion
Adhesion occurs within 1-3 seconds after injury
As adhesion occurs, platelets release ADP and Thromboxane (TxA2), these help recruit other platelets into the platelet plug and as secondary hemostasis gets started, thrombin is generated, causing more platelet stimulation and conversion of fibrinogen to fibrin.
3-7 minutes for entire process to occur—"The Bleeding Time"
Activated platelets

Note pseudopodia and how platelets aggregating to each other
A scanning EM of a clot with platelets, RBCs trapped in mesh of developing fibrin
Fibrinogen

Fibrin – polymerized remains of fibrinogen

Thrombin transforms fibrinogen to a mesh of fibrin strands

EM of fibrinogen that has been treated with Thrombin
Summary of Platelet Processes

ADP (P2Y12)

ADP (P2Y1)

Thrombin

Thromboxane

Collagen

Adhesion

Fibrinogen

Aggregation

Secretion

Platelet Coagulant Activities
Testing for Abnormal Platelet Function

Bleeding Time
Normal 3-7 minutes
Prolonged in platelet function abnormalities
**Bleeding Time**

A bleeding time that did not

normal < 7-8min

**Aggregometry**

An abnormal response to ADP
Bleeding – Cut a Blood Vessel – What Happens?
The endothelium is “antagonistic” to platelets under normal conditions.
Vascular Endothelium Function

- **Tissue factor pathway inhibitor**
  - Anticoagulant- Inhibits coagulation extrinsic pathway

- **Thrombomodulin**
  - Anticoagulant- Inhibits coagulation by activating protein C system

- **Tissue plasminogen activator**
  - Anticoagulant- Inhibits coagulation by activating fibrinolysis

- **Heparan sulfate proteoglycans**
  - Anticoagulant- Inhibits coagulation by activating antithrombin

- **Tissue factor**
  - Procoagulant- Inflammatory cytokines (IL-1, TNF) induce expression
Vascular Endothelium Function

- **Prostacyclin**: Vasodilation, inhibition of platelet aggregation
- **Thromboxane A₂**: From platelets, muscular arteries constrict
- **ELAMs, ICAMs**: Cytokines induce synthesis to promote leukocyte adhesion
- **von Willebrand factor**: Promote platelet-collagen adhesion to exposed sub-endothelium
Thombocytopenia

- > 100,000/ul no excessive bleeding, even with major surgery
- 50-100,000 may bleed longer than normal with severe trauma
- 20-50,000 bleed with minor trauma
- < 20,000 may have spontaneous hemorrhage
Petechiae- subcutaneous bleeding develops when the platelet counts falls below 20-50,000/ul
Adherens Junction at the Postcapillary Venular Bed

Bleeding in Patients with Thrombocytopenia through Disassembly of the Adherens Junction

Causes of Thrombocytopenia

- Decreased production: marrow hypoplasia, leukemia, toxins, chemotherapy
- Increased Destruction: antibodies to platelets, activation of coagulation cascade resulting in PLT consumption
- Platelet Sequestration: 1/3 of platelets are normally stored in the spleen, if enlarges more platelets are stored and patient becomes thrombocytopenic
Decreased Production

Decreased production: marrow hypoplasia, leukemia, toxins, chemotherapy

No straightforward method to assess platelet production, unlike RBCs & Retic Count
Severe thrombocytopenia in autoimmune thrombocytopenia

Blood smear shows no platelets

Isotope labeled platelets are destroyed in the spleen, in presence of antibody
An example of a common consumptive thrombocytopenia

Autoantibodies are formed against the platelet glycoprotein receptor IIb-IIIa, and are destroyed in the Reticuloendothelial system.

Pathophysiology of Autoimmune Thrombocytopenia
Panel A, patient without increased Megakaryocytes, versus patients with increased megakaryocytes
Overview of Immature Platelet Fraction Percentage (IPF%) Measurement & Some Examples

normal

ITP

Nadir after Chemo

Recovery from Chemo
Thrombocytosis

Seen in myeloproliferative disorders, chronic infection, iron deficiencies, malignant tumors
Platelets Role in Thrombosis

- Coronary or cerebrovascular thrombosis is multifactorial
- Genes – lipids
- Society – diet, exercise, smoking
Triggers of Thrombosis
Artery v Vein

**VEIN – CLOTTING PROTEINS ROLE CERTAIN**

**ARTERY – PLATELETS ROLE CERTAIN**
Summary

• Describe the major physiologic functions of platelets
• Describe the major platelet agonists
• Describe the ligands responsible for adhesion and aggregation
• Describe the pathophysiology of thrombocytopenia
Hemostasis - Summary

Gachet C. 2006.