HEMOSTASIS AND THROMBOSIS FUNDAMENTALS

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Disclosures

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Hemostasis vs. Thrombosis

- Hemostasis is the spontaneous arrest of bleeding from a damaged blood vessel
- Hemostasis is a highly regulated process involving platelets, clotting factors, and the vasculature
- Bleeding/thrombotic disorders (acquired and hereditary)
  - Bleeding disorders: Defects or deficiencies in clotting factors or platelets that result in inappropriate bleeding and bruising
  - Thromboembolic disorders: Inappropriate coagulation that results in clots that can occlude blood vessels and ischemia
- Thrombosis is “hemostasis in the wrong place”
Overview

- Hemostasis is the arrest of bleeding following blood vessel damage
- Rapid formation of impermeable platelet and fibrin plug at site of injury
- Localized to site of injury
- Fibrin within clot triggers its own dissolution (fibrinolysis)
- Pathogenic thrombus = normal regulatory controls overwhelmed

A Clot is Formed

Red = platelets
Green = tissue factor
White = platelets + fibrin + tissue factor
Blue = fibrin
Role of Platelets in Hemostasis

Platelets play a key role in hemostasis and thrombosis

Platelets adhere to site of vascular injury
- Neutrophil
- Red blood cell
- Endothelial cell
- Platelet
- Basement membrane
- Smooth muscle cell

Platelet aggregation and activation
- Thromboxane A2
- AOP
- Thrombin
- Activation of coagulation cascade

Haemostatic plug formation
- Fibrin
Platelet Thrombus Formation

- Dynamic process influenced by shear, flow, turbulence and number of platelets in circulation
- Platelet activation (by collagen or tissue factor) results in the release of components critical for thrombus formation and platelet-platelet interaction

Coagulation Complexes

- Extrinsic Xase: Co-factor, Zymogen(s), Phosphatidylserine + surface
- Intrinsic Xase: Ca$^{2+}$ binds complexes to surface

**Tissue Factor**

- Membrane protein
- Present on many cells
  - In vessel wall
  - Can be expressed on inflammatory cells (monocytes, neutrophils)
  - In circulating blood (microparticles)
  - Can be expressed on endothelial cells following exposure to proinflammatory cytokines
  - Can be expressed on tumor cells
- **Key initiator of thrombus formation**

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**Retrieval Practice**

Coagulation protein reactions take place on _______________ surfaces.

Negatively charged coagulation factors are held in place on negatively charged cell surfaces by _______________ ions.

_______________ is a key initiator of thrombus formation.

A coagulation complex is composed of an enzyme, a zymogen, and a _______________.

The prothrombinase complex is responsible for converting _______________ to _______________.

Learning about coagulation physiology and pathophysiology is _______________!
The Coagulation Cascade

- **‘Intrinsic Pathway’**
  - XII
  - HMK
  - PK
  - XI
  - Xla
  - IX

- **‘Extrinsic Pathway’**
  - Xla
  - IXa
  - VIIIa
  - Xa
  - Va

- **‘Common Pathway’**
  - XI
  - Xla
  - IX
  - IXa
  - VIIIa
  - Xa
  - Va

- **Thrombin (IIa)**

Does NOT explain how blood clots *in vivo*

**Bleeding in Hemophilia**

- **‘Intrinsic Pathway’**
  - XII
  - HMK
  - PK
  - XI
  - Xla
  - IX

- **‘Extrinsic Pathway’**
  - IXa
  - VIIIa
  - Xa
  - Va

- **‘Common Pathway’**
  - XI
  - Xla
  - IX

Deficiency results in increased PTT but no bleeding tendency

Deficiency results in increased PTT and hemophilia

Unable to sustain hemostasis in hemophilia
Initiation Phase

- Activated tissue factor is the fuse
- TF/VIIa complex activates small amounts of IX and X
- Xa then associates with Va to form prothrombinase complex
- A small amount of thrombin is produced
- TFPI
  - Neutralizes Xa
  - Feedback inhibition on TF/VIIa in presence of Xa

Amplification Phase

- Low concentrations of thrombin activate platelets adhering to injury site
- Thrombin activates V, VIII, and XI
- Va, VIIIa, and XIa bind to surfaces of activated platelets
Propagating Phase

- Intrinsic tenase and prothrombinase assemble on surface of activated platelets
- XIa activates IX to form additional intrinsic tenase
- Burst of thrombin
- Fibrin generated and stabilized by XIIIa

Cellular Model of Clot Formation

- Extrinsic and intrinsic pathways not redundant
- Extrinsic pathway initiates thrombosis and takes place on tissue factor-bearing cells-can’t sustain thrombosis due to TFPI
- Intrinsic pathway propagates thrombosis and takes place on activated platelets
Endogenous Anticoagulant Mechanisms

- **Antithrombin**
  - Inhibits only free enzymes
  - Limits coagulation to site of injury

- **Thrombomodulin**
  - Activates protein C

- **Protein C**
  - Modulates activity of FVa & VIIIa (even when part of intrinsic tenase and prothrombinase complexes)
  - Limits coagulation to site of injury

- **Protein S**
  - Supports activity of protein C

- **Tissue Factor Pathway Inhibitor (TFPI)**
  - Inhibits FXa and TF/VIIa complex
Thrombolysis

Blood vessel endothelium

Fibrin clot

PAI
Plasminogen
Plasmin
Inhibition

Inhibition

Breakdown of clot

FDPs


Thank You for Watching!

GO TO BOOTCAMP THEY SAID

IT’LL BE FUN THEY SAID,