Advanced Course in
Thrombosis & Hemostasis
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Current concepts of
the coagulation system

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The human body
(Vascular system)
PRIMARY HEMOSTASIS

BLOOD COAGULATION
Vessel wall damage
activation of primary hemostasis and blood coagulation
Scanning electron microscopy of platelets

Shape change associated with activation
PRIMARY HEMOSTASIS

PLATELET FUNCTIONS

ADHESION (TO SUBENDOTHELIIUM)
  GPIb-V-IX – von Willebrand faktorn (VWF)
  GPIa-IIa, GPVI – collagen

AGGREGATION (PLATELET-PLATELET)
  GPIIbIIIa (α\text{IIb}β_3) – fibrinogen, fibronectin, thrombospondin, VWF

RELEASE OF PLATELET GRANULES
  dense granules – Ca^{2+}, ADP, serotonin, polyphosphate
  α-granules – coagulation factors, VWF, PF4, P-selectin

Thromboxane A_2 (TXA_2), Platelet Activating Factor (PAF)
Platelet adhesion - role of von Willebrand’s factor
Platelet aggregation
receptor fibrinogen/VWF interaction

Activated platelet

\( \alpha \text{IIb}\beta 3 \)

\[ \longleftrightarrow \]

Fibrinogen
VWF

Activated platelet

\( \alpha \text{IIb}\beta 3 \)

Modified from McEver in Platelets, Elsevier
Thrombosis under laminar flow

- Discoid platelets
- Shape changed and degranulated platelets
- ADP
- Thrombin
- TxA2
- Laminar flow
- Platelet tethering
- Stable adhesion secretion
- Aggregate formation

Jackson SP et al J Thromb Haemost 2009, suppl 1, 17-20
Thrombosis under disturbed flow

- Stenotic flow
- Soluble agonist accumulation
- TxA2
- Thrombin
- ADP

Flow deceleration
Flow acceleration
Vortex formation flow recirculation

Jackson SP et al J Thromb Haemost 2009, suppl 1, 17-20
Pathogenesis of idiopathic TTP caused by ADAMTS13 deficiency.

Sadler J E Blood 2008;112:11-18

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Jackson, Nature Med 2011, 17; 1423
PRIMARY HEMOSTASIS - ANALYSES

ANAMNESIS

B-PLATELETS

PLATELET FUNCTIONS
Platelet aggregation
Vessel wall damage
activation of primary hemostasis and blood coagulation
Activation of Blood Coagulation

Tissue factor (TF) exposed at sites of vascular injury
FVIIa binds to Tissue Factor
TF-FVIIa complex activates FIX and FX

Rapid turnover
Activation and Propagation of Coagulation

Modified from Dahlbäck, Blood 2008
Enzyme-cofactor complex on negatively charged phospholipids
Blood coagulation is localized to surfaces

Extra vascular cell

Activated platelets
Vitamin K-dependent Coagulation factors

**Procoagulant**
- Factor VII
- Factor IX
- Factor X
- Prothrombin

**Anticoagulant**
- Protein C
- Protein S

Vitamin K needed for the formation of GLA
GLA=\gamma\text{-carboxyglutamic acid residue}
FVII, FIX, FX and PT are vitamin K-dependent and contain γ-carboxy glutamic acid residues.

Gla domain needed for binding to phospholipid surface.
Factor V and Factor VIII

two similar proteins
Activation of factor V by thrombin or factor Xa

R709  R1018  R1545

FVα
FV activation

gradual B domain release exposes FXa-binding site

FV

\[\text{R709 R1018}\]

FVa’

\[\text{R1545}\]

FVa

\[\text{K}_d \approx 10 \text{ nM}\]

\[\text{K}_d \approx 1 \text{ nM}\]

\[\text{K}_d \approx 0.2 \text{ nM}\]
Prothrombinase complex

Autin et al, Proteins 2006
Factor VIII - von Willebrand factor complex

Activation by thrombin

Factor VIIIa
Principles of Blood Coagulation Amplification

1. multiple linked enzymatic reactions
2. enzyme-cofactor complexes
3. surface localization
4. feed-back activation
5. coagulation factor concentrations increasing in pathway

Modified from Dahlbäck, Blood 2008
Explosive thrombin generation after initial lag phase

Thrombin generation

- Peak
- Inhibition

Lag phase
Fibrinogen cleavage by thrombin results in fibrin polymerisation

Thrombin cleaves fibrinogen and fibrinopeptides are released

erythrocyte trapped in fibrin clot
Fibrinolytic System Degrades the Fibrin Clot

[Diagram showing plasminogen activation by TPA (tissue plasminogen activator) leading to plasmin, which degrades crosslinked fibrin into D-dimers.]
Blood Coagulation

"contact phase"

intrinsic

XII → XIIa

XII → XI → Xa

Ca²⁺

extrinsic

XII → XI → Xa

Ca²⁺

IX → IXa

Pl → Ca²⁺

VIII → VIIIa

Ca²⁺

V → Va

Thrombin

Prothrombin → Thrombin

FXIII → FXIIIa

Crosslinks fibrin

Activates platelets

Fibrinogen → Fibrin
Polyphosphate: an ancient molecule that links platelets, coagulation, and inflammation

Morrissey et al, Blood 2012, 19;5972
Intrinsic pathway of blood coagulation

APTT (activated partial thromboplastin time)
Prothrombin complex analysis
Testing FVII, FX, and PT

**EXTRINSIC**

INR=International Normalized Ratio
Patient plasma
Control plasma
1 is normal
Activation and Propagation of Coagulation

Modified from Dahlbäck, Blood 2008
Current concepts of the coagulation system

Thank you!