Current Concepts of the Coagulation System

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Professor Harold R. Roberts

- Charter member and first Executive Director of ISTH [Roberts Medal]
- First plasma-derived FVIII concentrate (glycine precipitation)
- First description of a FIX molecular mutation
- Cell-based model of coagulation
- Recipient of:
  - French International Prize for Research in Hemophilia,
  - Kenneth Brinkhous Award (National Hemophilia Foundation),
  - Stratton Medal and Clinical Mentor Award (American Society of Hematology),
  - Distinguished Career Award and Grant Medal (ISTH)
## Disclosures

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<th>Category</th>
<th>Details</th>
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Presentation includes discussion of the following off-label use of a drug or medical device: None
FIGURE 3–12. Scanning electron micrograph of human coronary artery plaque. This photograph shows a denuded area of intima where, apparently, a single endothelial cell has been lost. The raw surface is covered by a small mass of adherent and aggregated platelets which have clearly undergone shape change (× 3,570).
Sub-endothelial von Willebrand Factor Provides Initial Tethering of Platelets under Shear
And... Other Mechanisms Consolidate Platelet Adhesion to Collagen

Platelet Aggregation is Mediated by GPIIb-IIIa in its Activated Conformation
Secondary Hemostasis
Morawitz’s Four-Factor Model of Coagulation

Paul Morawitz
(1879-1936)

Tissue Factor ("Thrombokinase"; "Thromboplastin"; "Factor III")

- Cell-bound glycoprotein
- Principal initiator of coagulation in vivo
- Mostly in extravascular location where it is not normally in contact with blood/clotting factors
- Exposed to blood when the endothelial barrier is breached
Blood Contacts Peri-Vascular TF Following Vascular Injury.

Coagulation Cascade

**Intrinsic Pathway**

- factor XII
- HMK
- PK

- factor XI → factor Xla

- factor IX → factor IXa
- factor VIIIa
- PL, Ca\(^{+2}\)

- factor X → factor Xa
- factor Va
- PL, Ca\(^{+2}\)

- prothrombin → thrombin

**Extrinsic Pathway**

- factor VIIa
- Tissue Factor
- PL, Ca\(^{+2}\)

- factor X → factor Xa
- factor Va
- PL, Ca\(^{+2}\)

- fibrinogen → fibrin
Coagulation Cascade

**Intrinsic Pathway**

- factor XII
- HMK
- PK

Glass, powdered clay (kaolin), Ellagic acid, sulfatides, dextran sulfate

- factor XI → factor Xla
- factor IX → factor IXa

factor IXa → factor VIIIa

PL, Ca$^{+2}$

- factor X → factor Xa

factor Xa → factor Va

PL, Ca$^{+2}$

- prothrombin → thrombin

**Extrinsic Pathway**

- factor VIIa
- Tissue Factor

PL, Ca$^{+2}$

- factor X → factor Xa

factor Xa → factor Va

PL, Ca$^{+2}$

- prothrombin → thrombin

- fibrinogen → fibrin
The Coagulation Cascade

- Consistent with the identification of each clotting factor being a zymogen, converted to an enzyme in the sequence observed by *in vitro* experiments.

- Nicely accounted for the roles of the clotting factors in the aPTT (factors XII, XI, IX, VIII) and PT (factor VII), and in both tests (factors V, X, prothrombin and fibrinogen).
However, the Cascade Model Failed to....

- Account for the fact that inherited deficiency of any contact factor (FXII, prekallikrein or high molecular weight kininogen) is not associated with bleeding, although deficiency of other factors in the intrinsic pathway (factors XI, IX, VIII) is associated with bleeding.

- Identify the biologic molecules analogous to the inorganic negatively charged contact activators.
The First Evidence Refuting The Cascade Model

 Proc. Natl. Acad. Sci. USA
 Vol. 74, No. 12, pp. 5260–5264, December 1977
 Biochemistry

 Activation of Factor IX by the reaction product of tissue factor and Factor VII: Additional pathway for initiating blood coagulation

 (bypass of activated Factor XI/assay for activated Factor IX)

 Bjarne Østerud and Samuel I. Rapaport

 Department of Medicine, University of California, San Diego, California 92103, and the San Diego Veterans Administration Hospital, San Diego, California 92161
TF-Initiated Coagulation Leads to Both Direct and Indirect Activation of Factor X
Tissue Factor Pathway Inhibitor (TFPI): Inhibits Coagulation in a FXa-Dependent Mechanism

Crawley, J. et al. 
ATVB 2008;28:233-242
How Can the Hemostatic Role of Factor XI be Explained?
Factor XI Activation in a Revised Model of Blood Coagulation

David Gailani and George J. Broze, Jr.*

Coagulation factor XI is activated in vitro by factor XIIa in the presence of high molecular weight kininogen (HMWK) and a negatively charged surface. Factor XII deficiency is not associated with bleeding, which suggests that another mechanism for factor XI activation exists in vivo. A revised model of coagulation is proposed in which factor XI is activated by thrombin. In the absence of cofactors, thrombin is more effective ($k_{cat}/K_m = 1.6 \times 10^5$) than factor XIIa ($1.7 \times 10^4$) in activating factor XI. Dextran sulfate enhances activation of factor XI by thrombin 2000-fold; part of this effect is due to autoactivation of factor XI by activated factor XI.
FXIIa Stabilizes Clot Structure Independently of Thrombin Generation

Konings, J. *Blood* 2011:118(14);3942
Find out what happens during an HAE attack.
‘Multi-tasking’ FXII(a)
The Majority of Thrombin is Generated After Whole Blood Clots

Clotting initiated by low conc. TF

Brummel KE. *Blood* 2002;100:148
Focusing on the Early Events in Blood Clotting...

A

Total Thrombin (nM)

Threshold of activation

Initiation

C.T. 4.7±0.2 min

Propagation

Time (min)

Brummel KE. Blood 2002;100:148
Early Coagulation Activation Events Mediated By Thrombin

Brummel KE. Blood 2002;100:148
Revised Coagulation Schematic

Anticoagulant Function of Thrombin
Accounting for the Role of Blood Cells in Coagulation
Cell-Based Model of Hemostasis
Cell-Based Model of Hemostasis

TF-Bearing Cell

TF
VIIa
Xa
Va
II

VIIIa/VWF
VIIa

V
Va

Platelet
Cell-Based Model of Hemostasis

TF-Bearing Cell

TF

VIIa

Xa

Va

II

IIa

VIII/vWF

VIIa

Platelet

V → Va

Activated Platelet

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Cell-Based Model of Hemostasis

TF-Bearing Cell

TF
VIIa
X

Xa
Va

II

VIIIa

VIII/vWF

IIa

VIIa

Activated Platelet

Platelet

IX

IXa

V

Va

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Cell-Based Model of Hemostasis

[Diagram showing the process of hemostasis involving TF-bearing cells, activated platelets, and interactions between clotting factors X, II, IXa, VIIIa, Va, and vWF.]
Formation of Cross-Linked Fibrin

Fibrinogen

Thrombin

FpA + FpB

Soluble Fibrin Polymer

Factor XIIIa
Fibrin Promotes Fibrinolysis

Activator

Plasminogen

Lysine-binding site

Fibrin
Fibrin Promotes Fibrinolysis

Activator

Plasminogen

Fibrin
Fibrin Promotes Fibrinolysis
Fibrin Promotes Fibrinolysis
Principal Inhibitors of Fibrinolysis

1. Plasminogen activator inhibitor-1 (PAI-1) inhibits t-Pa and urokinase

2. Alpha2-antiplasmin inhibits plasmin

3. Thrombin-Activatable Fibrinolysis Inhibitor (TAFI) inhibits binding of plasminogen and tPa
Fibrinolysis
Activated TAFI (TAFIa) Inhibits Fibrinolysis by Cleaving Essential Lysine Residues on Fibrin
Anti-fibrinolytic Lysine Analogs

Activation of Fibrinolysis

- Activator
- Plasminogen
- Lysine-binding site
- Fibrin-degradation products

Inhibition of Fibrinolysis

- Activator
- Plasminogen
- Aminocaproic acid or tranexamic acid
- Fibrin-degradation products
Procoagulant and Antifibrinolytic Roles of FXI

High Concentrations of Thrombin Needed to Activate Thrombin-Activatable Fibrinolysis Inhibitor (TAFI)

Conclusions

Thrombin generation is tightly regulated; it is both the product of and regulator of coagulation activation.