

# Current Concepts of the Coagulation System

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of NORTH CAROLINA  
at CHAPEL HILL

ISTH Bangkok  
November, 2017



# Professor Harold R. Roberts

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- 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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Employee	No relevant conflicts of interest to declare
Consultant	CSL Behring; Baxalta/Shire; Genentech/Roche; Novo Nordisk
Major Stockholder	No relevant conflicts of interest to declare
Speakers Bureau	No relevant conflicts of interest to declare
Honoraria	No relevant conflicts of interest to declare
Scientific Advisory Board	RTI International

Presentation includes discussion of the following off-label use of a drug or medical device:

None



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# Primary Hemostasis

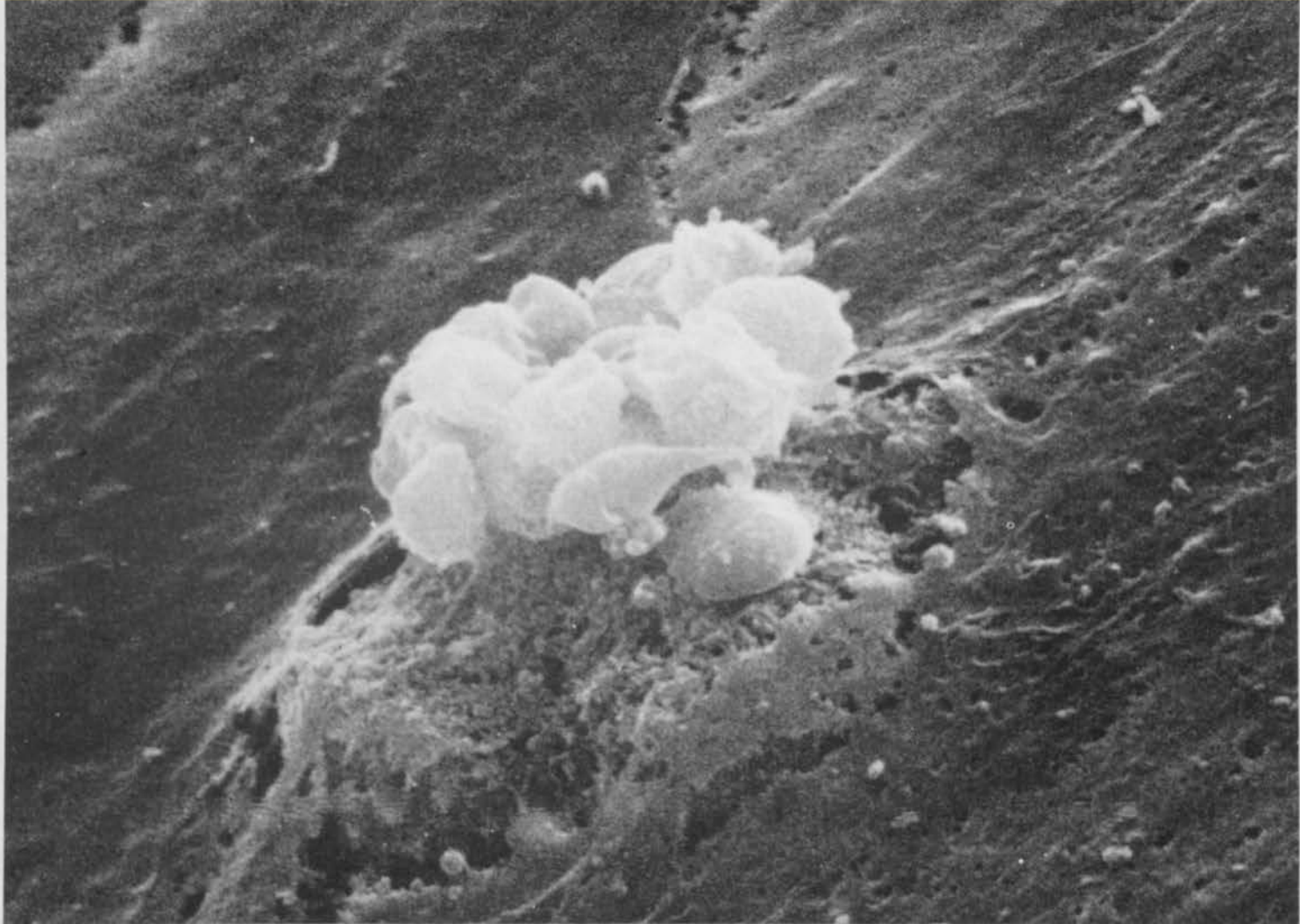
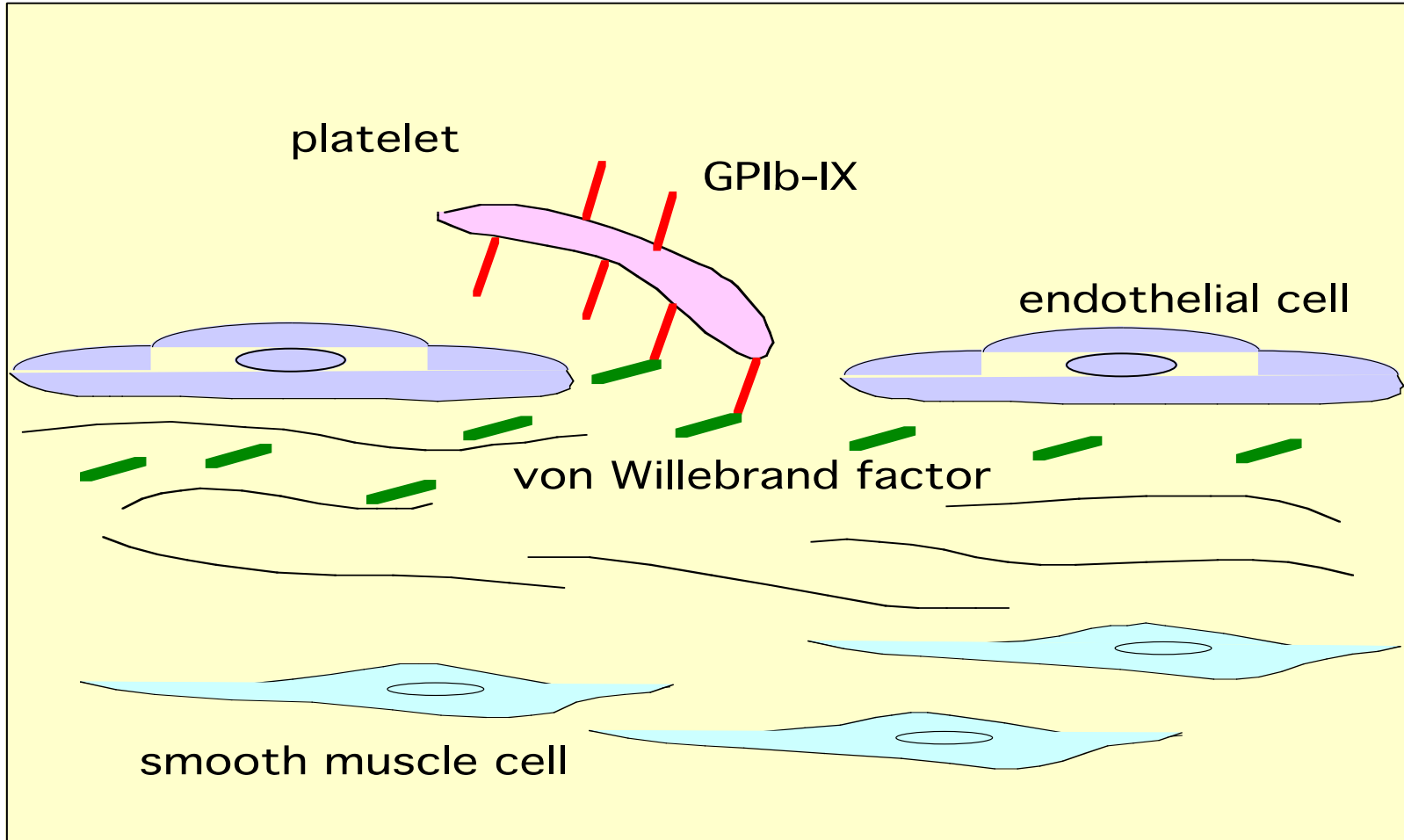
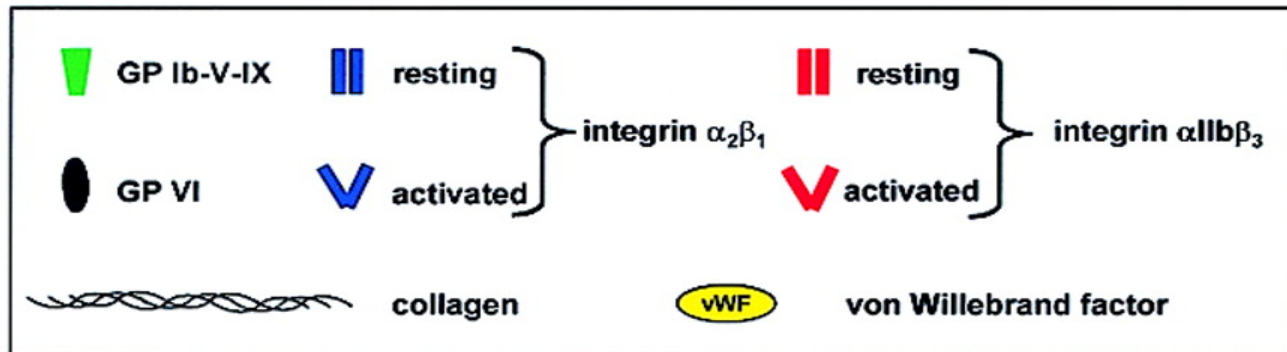
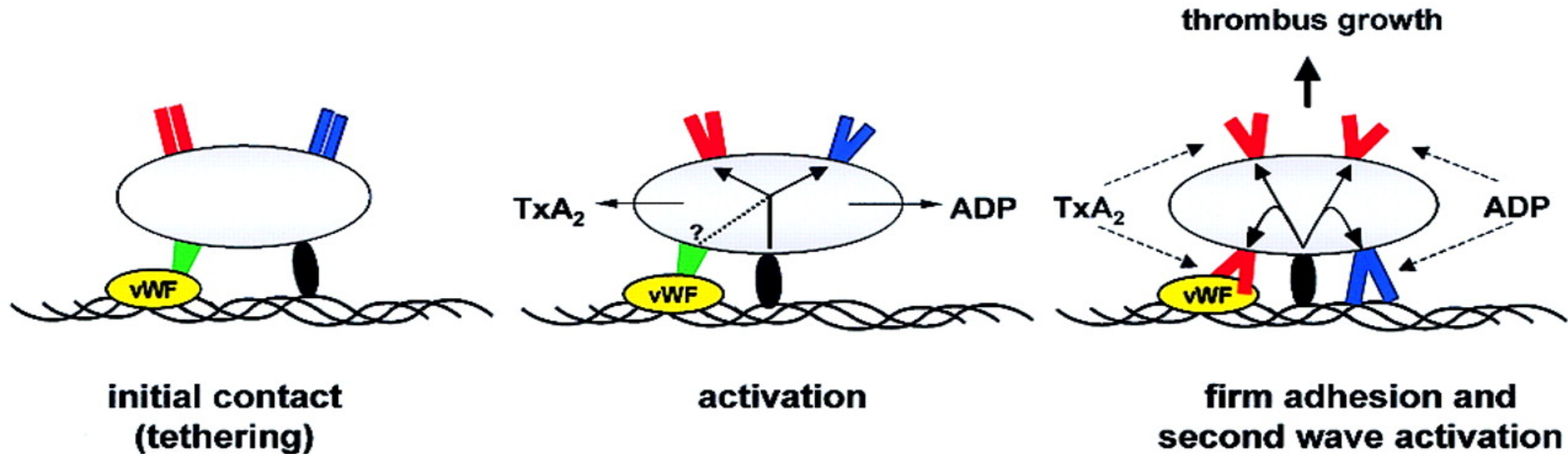


FIGURE 3-12. Scanning electron micrograph of human coronary artery plaque. This photograph shows a denuded area of intima where, apparently, a single endothelial cell has been lost. The raw surface is covered by a small mass of adherent and aggregated platelets which have clearly undergone shape change ( $\times 3,570$ ).

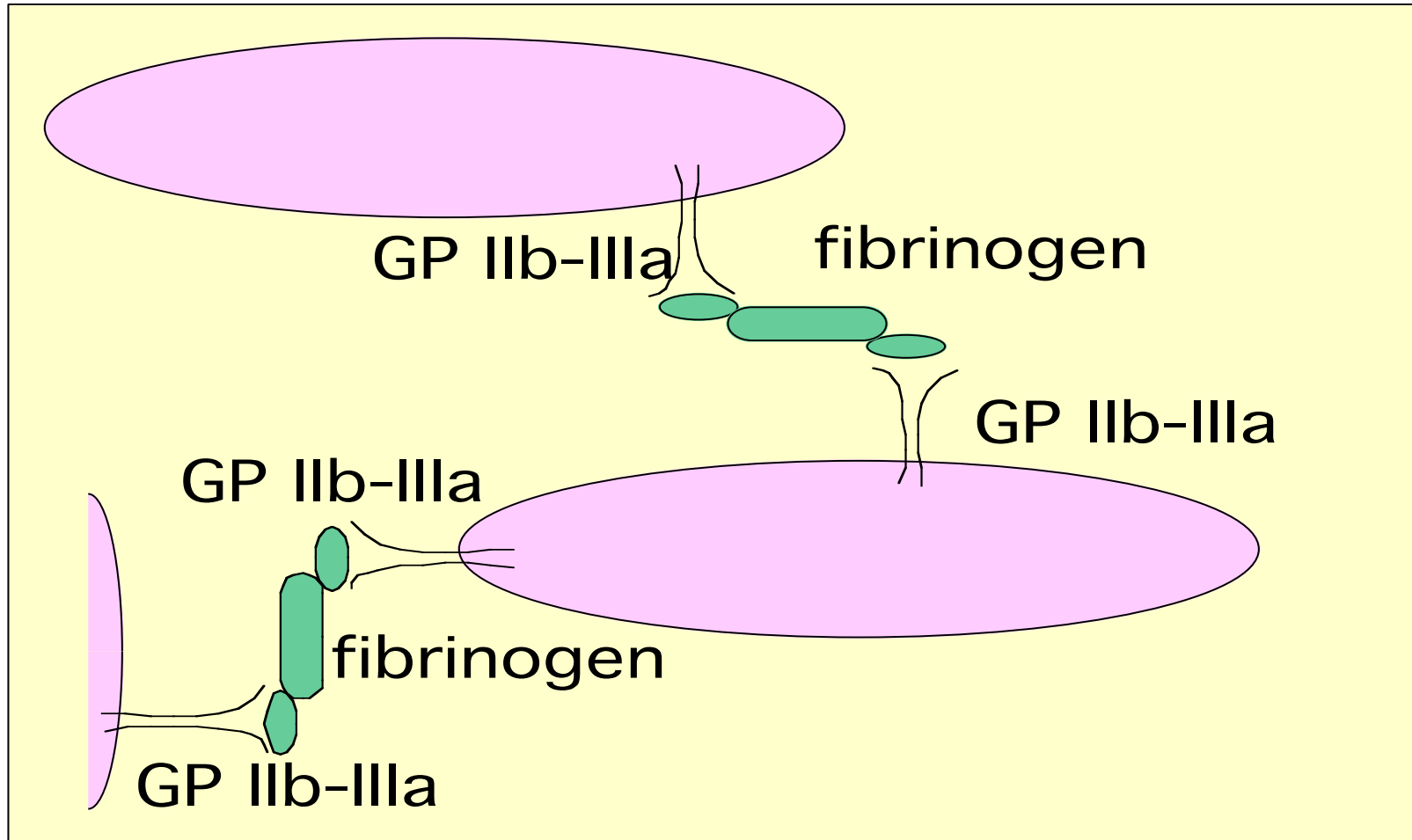
# Sub-endothelial von Willebrand Factor Provides Initial Tethering of Platelets under Shear



# And...Other Mechanisms Consolidate Platelet Adhesion to Collagen

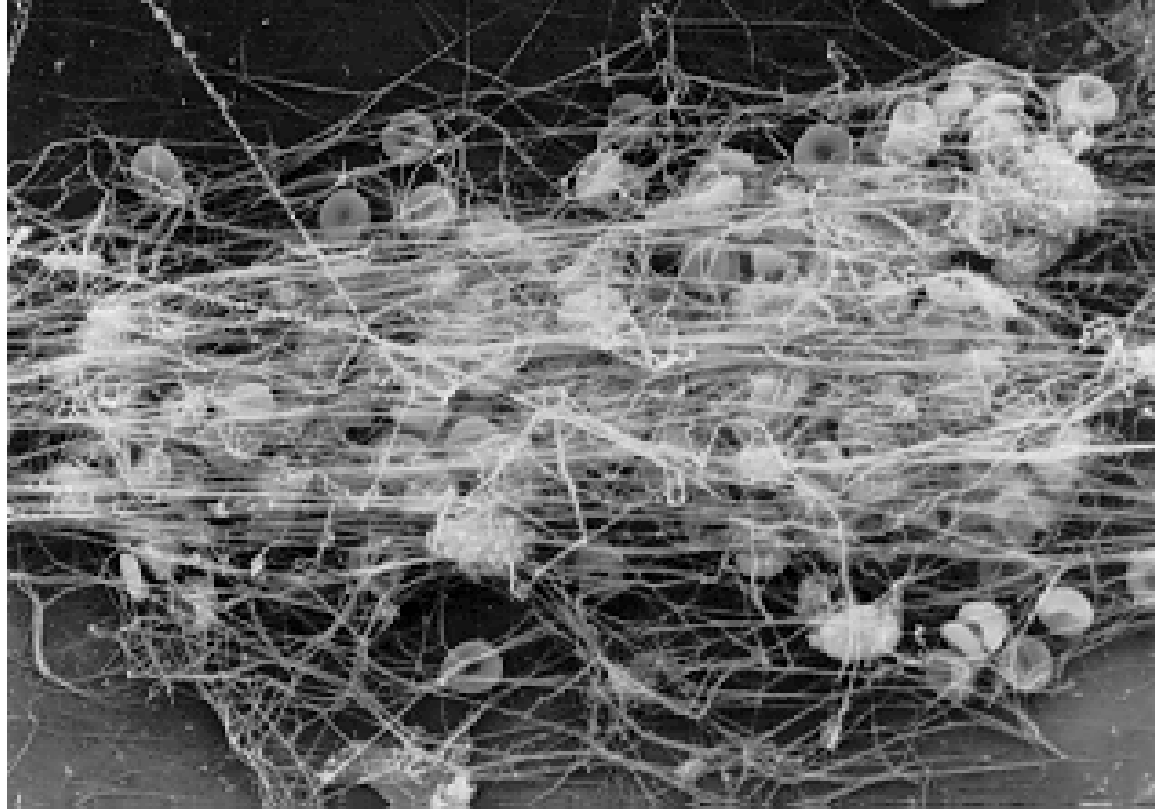


# Platelet Aggregation is Mediated by GPIIb-IIIa in its Activated Conformation



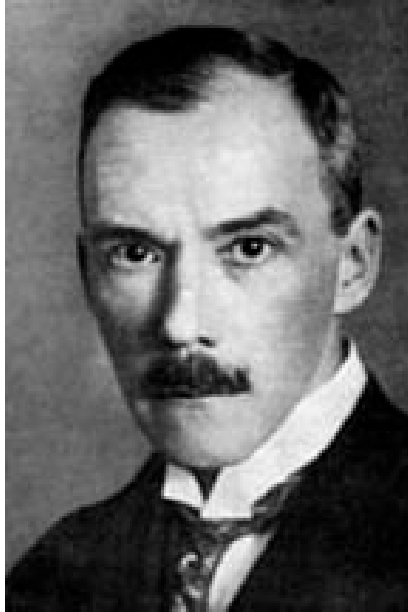
# Secondary Hemostasis

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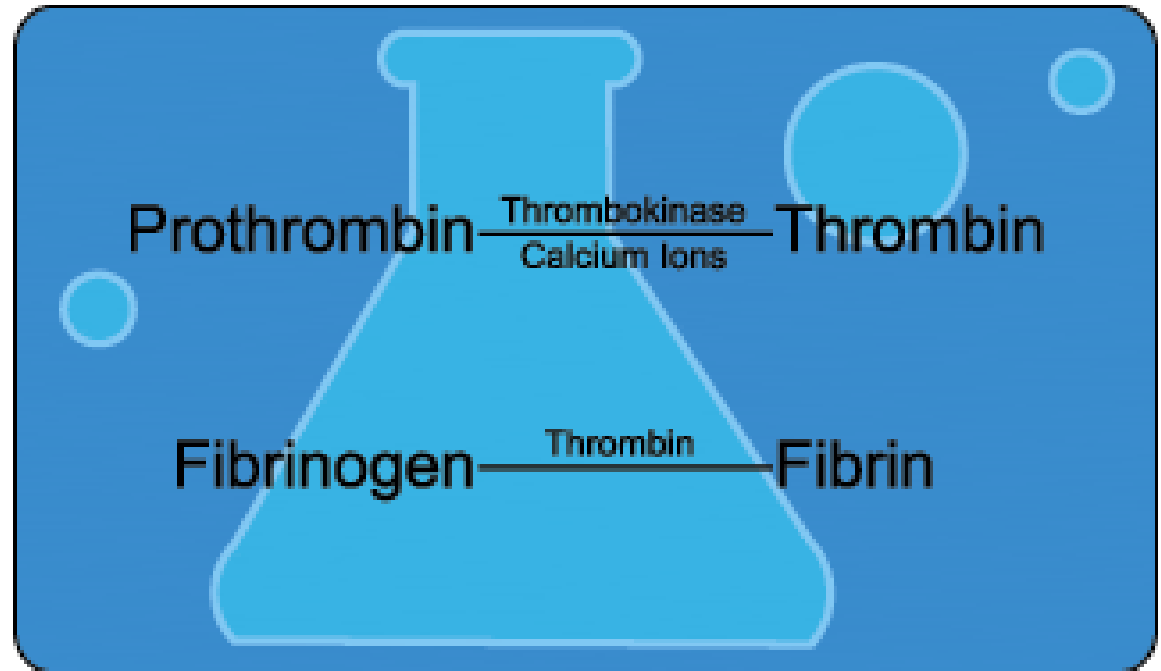




# Morawitz's Four-Factor Model of Coagulation



Paul Morawitz  
(1879-1936)



# Tissue Factor

(“Thrombokinase”; “Thromboplastin”; “Factor III”)

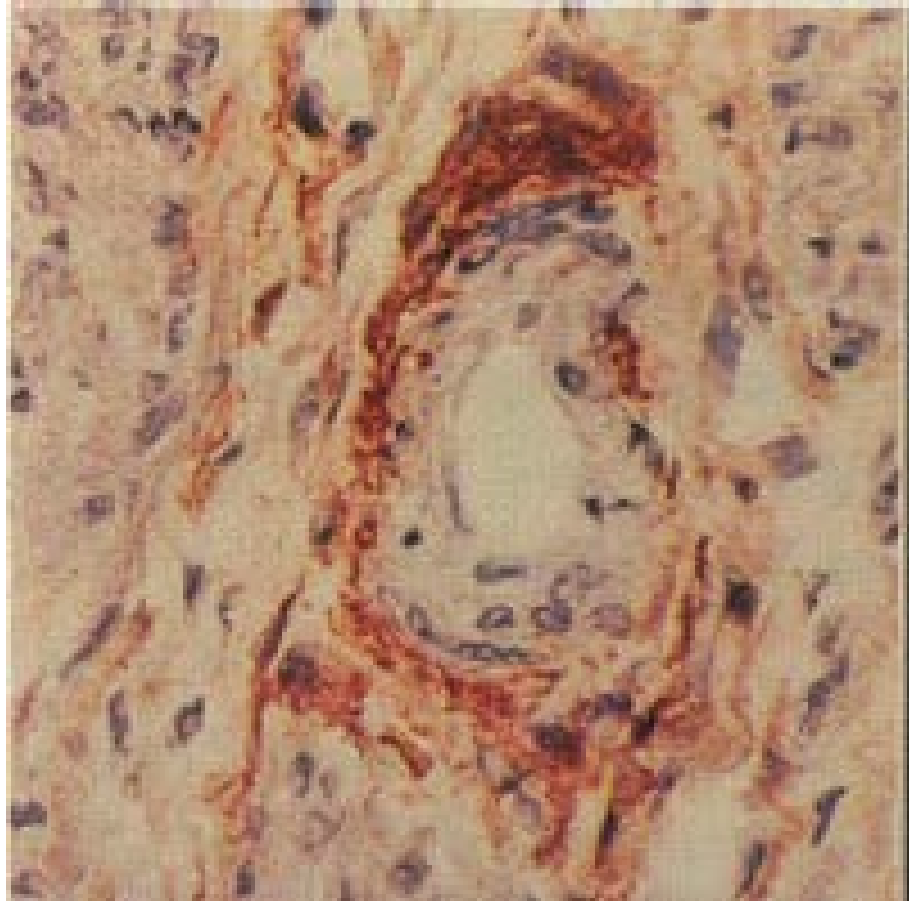
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- Cell-bound glycoprotein
- Principal initiator of coagulation *in vivo*
- Mostly in extravascular location where it is not normally in contact with blood/clotting factors
- Exposed to blood when the endothelial barrier is breached



# Blood Contacts Peri-Vascular TF Following Vascular Injury.

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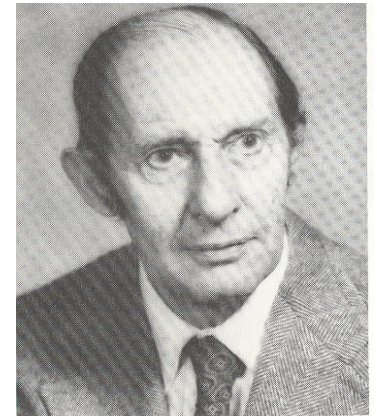


R. G. Macfarlane

Macfarlane RG. An enzyme **cascade** in the blood clotting mechanism, and its function as a biochemical amplifier. *Nature* 202: 498-9, 1964.



Davie EW, Ratnoff OD: **Waterfall** sequence for intrinsic blood clotting. *Science* 145:1310-11, 1964



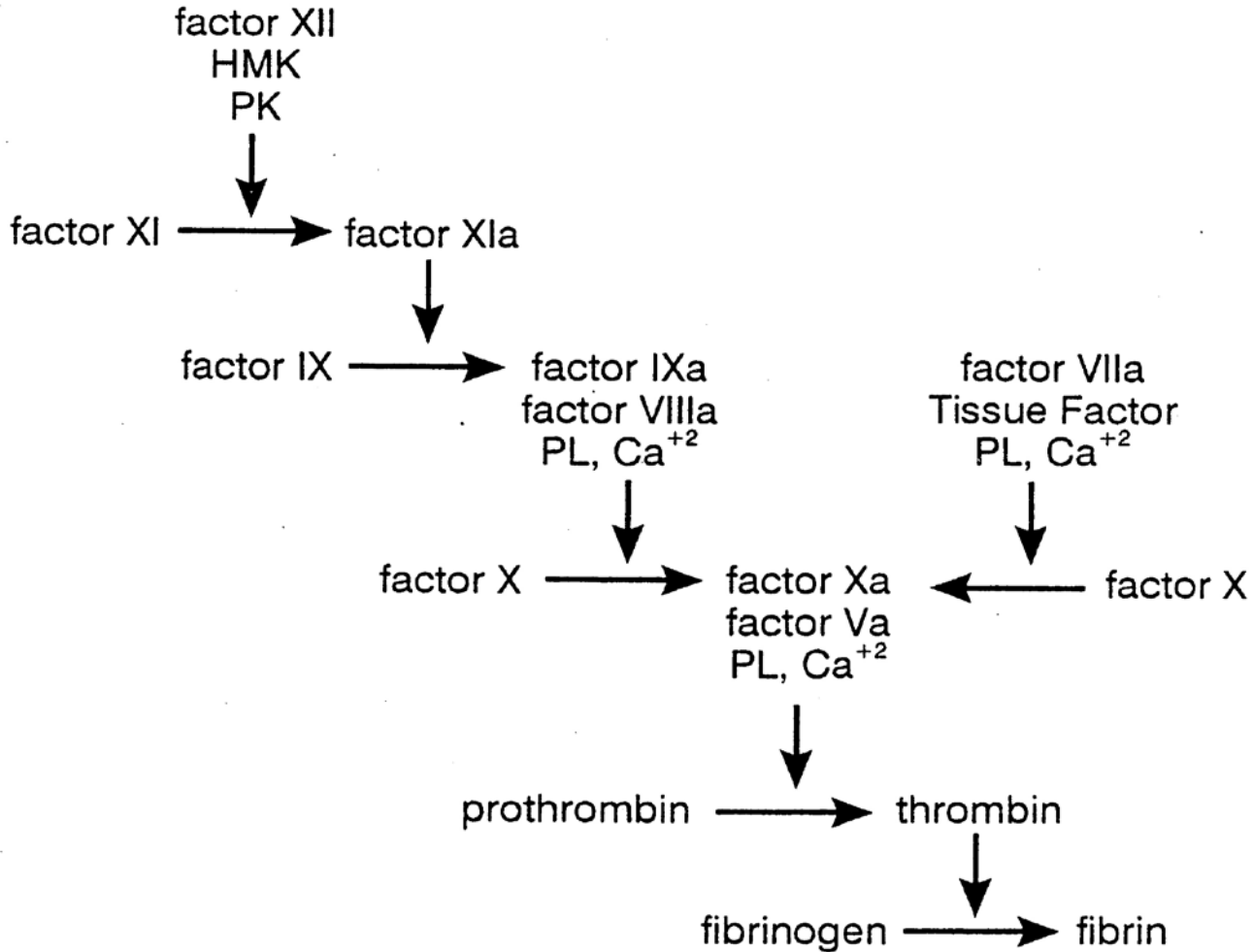
Oscar D. Ratnoff



# Coagulation Cascade

## Intrinsic Pathway

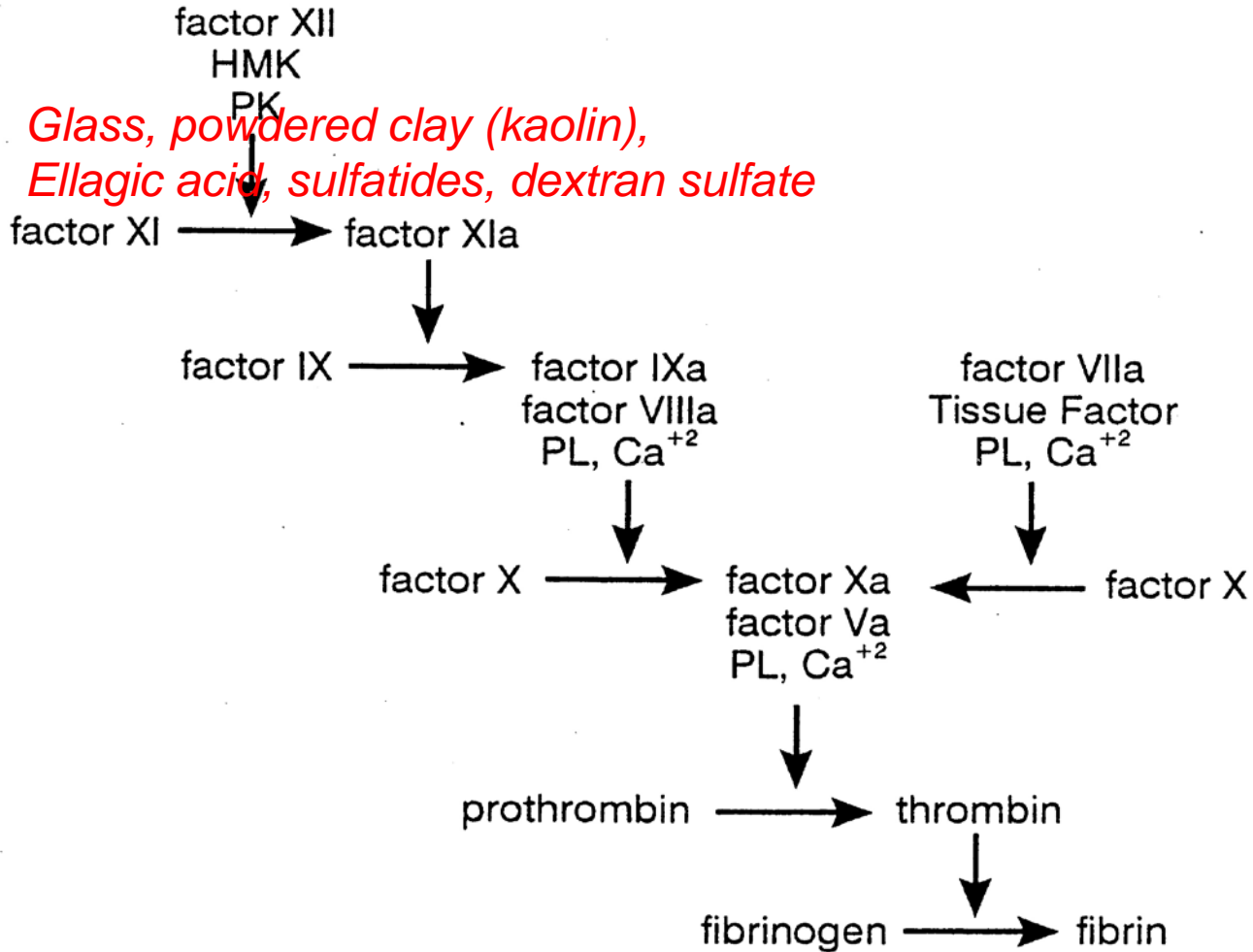
## Extrinsic Pathway



# Coagulation Cascade

## Intrinsic Pathway

## Extrinsic Pathway



# The Coagulation Cascade

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- 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....

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- 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

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*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)*

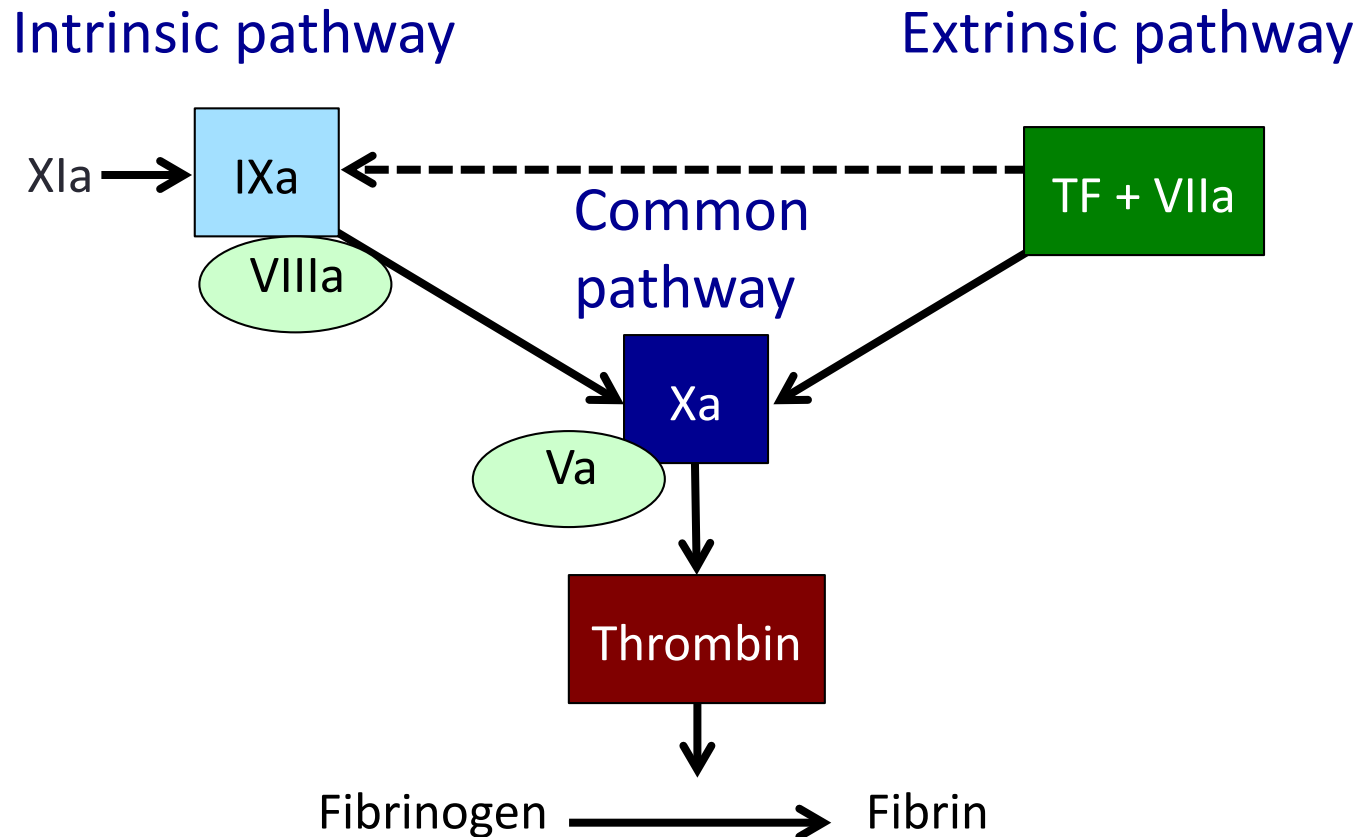
**BJARNE ØSTERUD AND SAMUEL I. RAPAPORT**

Department of Medicine, University of California, San Diego, California 92103, and the San Diego Veterans Administration Hospital, San Diego, California 92161



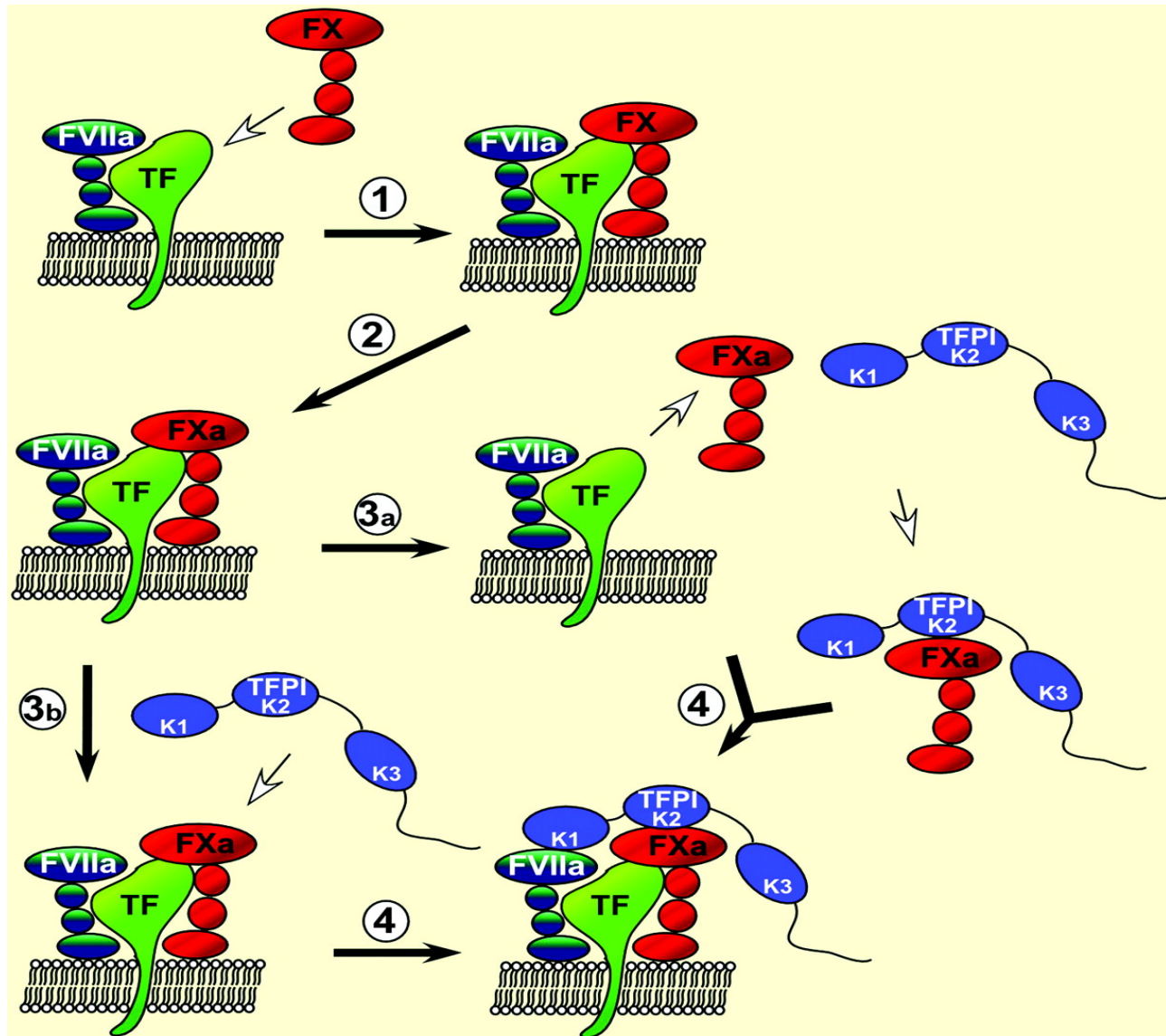
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# TF-Initiated Coagulation Leads to Both Direct and Indirect Activation of Factor X



# 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?

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# Activation of FXI by Thrombin

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## Factor XI Activation in a Revised Model of Blood Coagulation

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DAVID GAILANI AND GEORGE J. BROZE, JR. \*

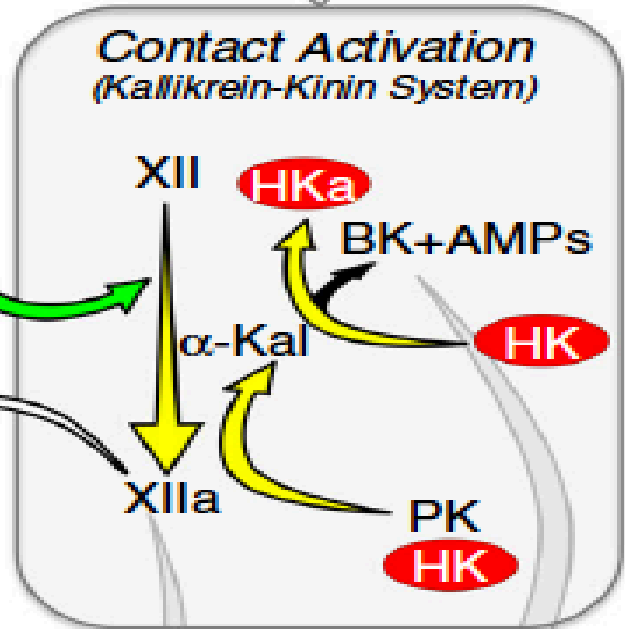
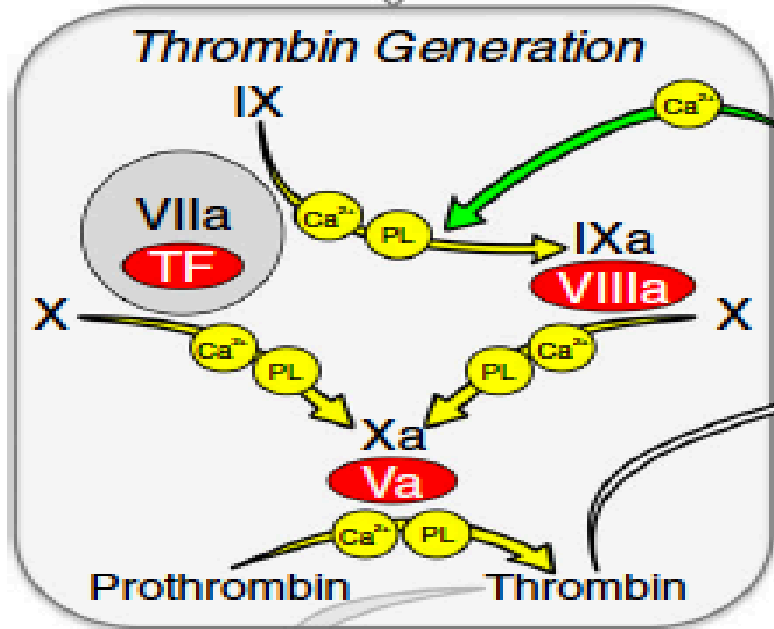
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Coagulation factor XI is activated in vitro by factor XIIa in the presence of high molecular weight kininogen (HMWK) and a negatively charged surface. Factor XII deficiency is not associated with bleeding, which suggests that another mechanism for 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.



1  
Tissue Injury  
Platelet Activation  
Inflammation  
Stasis  
Hypoxia

2  
Polyphosphate  
Nucleic Acid Polymers  
Basement Membranes  
Artificial Surfaces

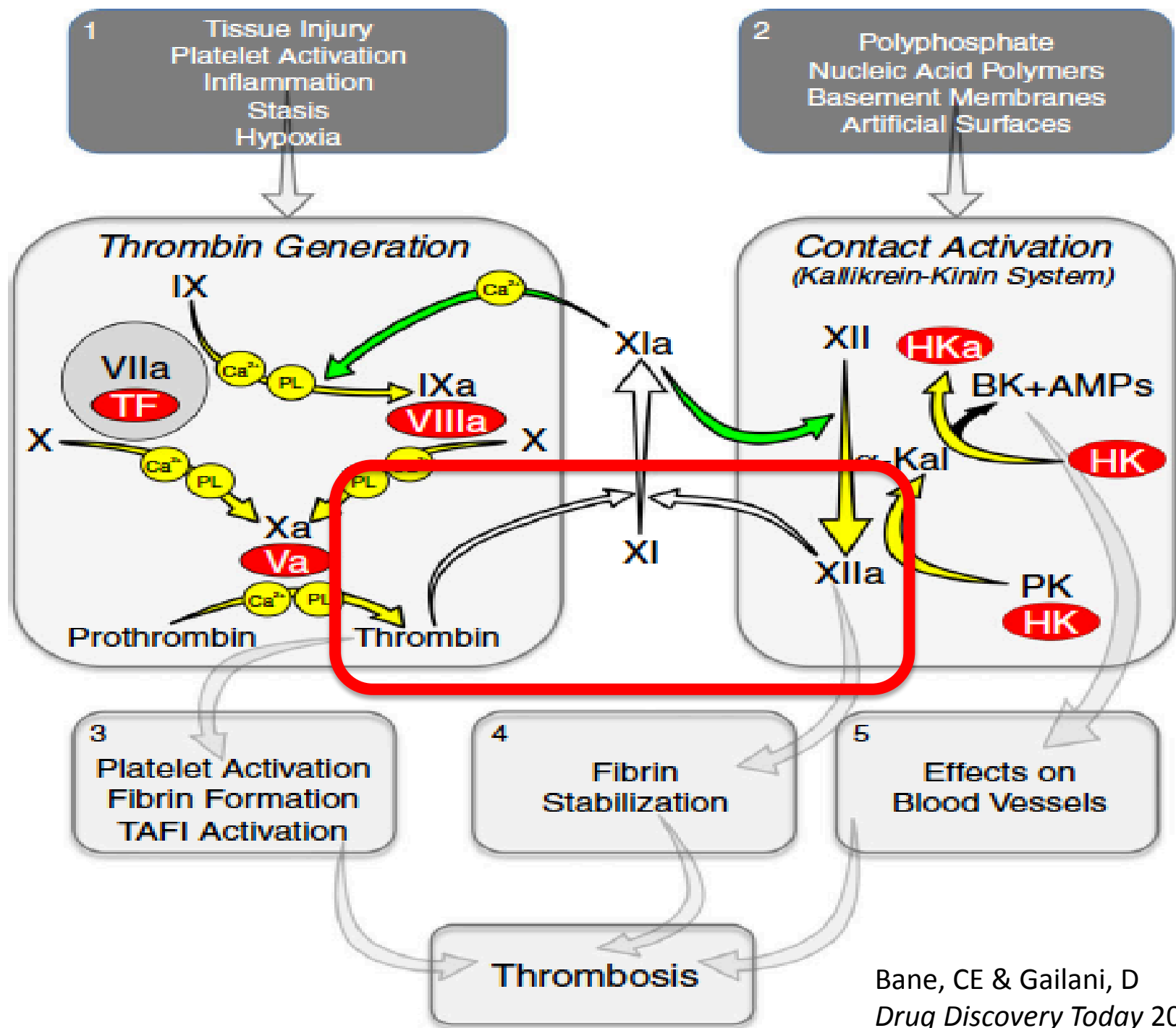


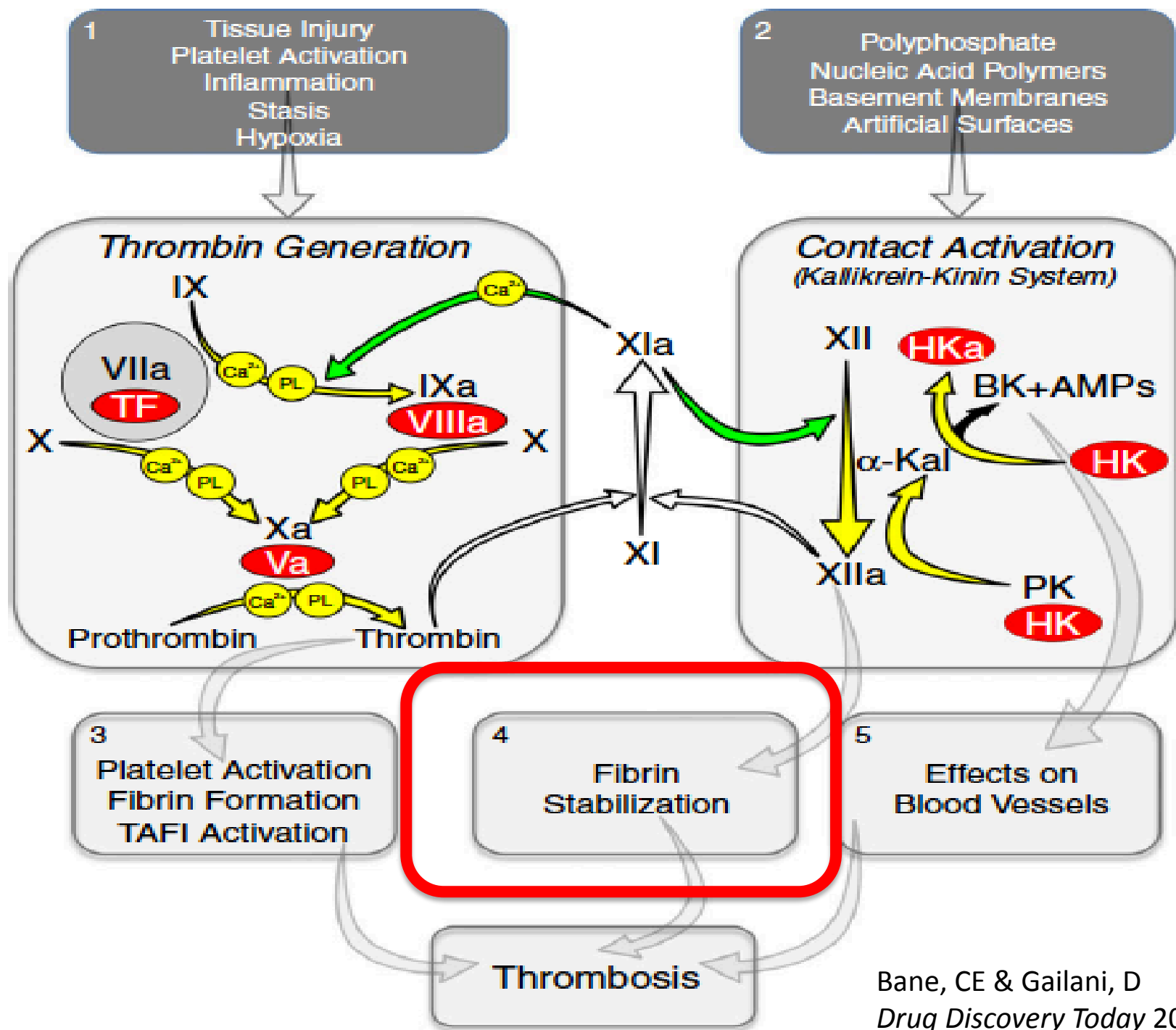
3  
Platelet Activation  
Fibrin Formation  
TAFI Activation

4  
Fibrin Stabilization

5  
Effects on Blood Vessels

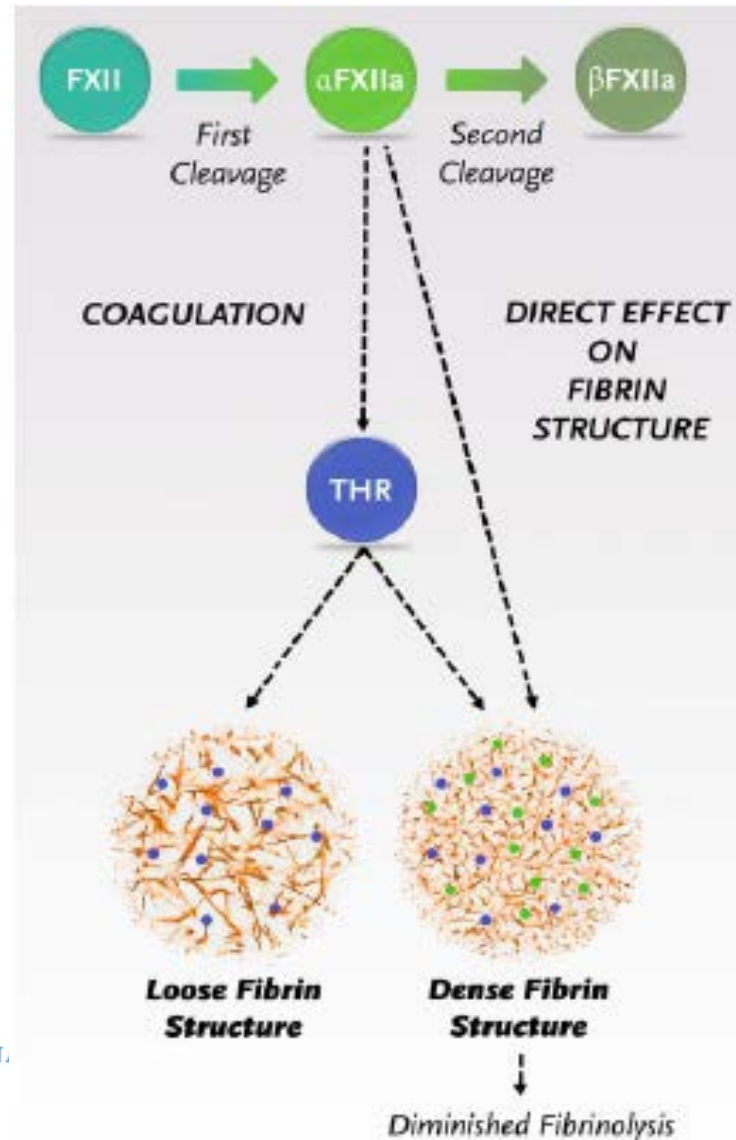
Thrombosis





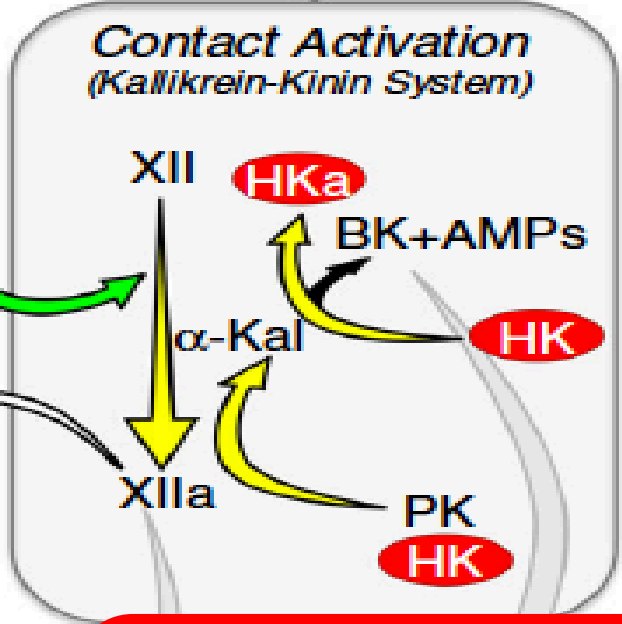
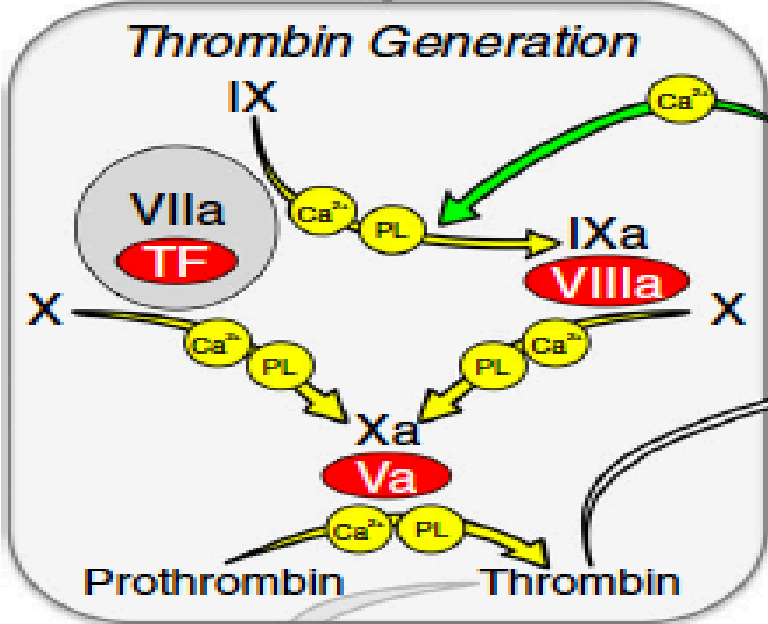


# FXIIa Stabilizes Clot Structure Independently of Thrombin Generation



1  
Tissue Injury  
Platelet Activation  
Inflammation  
Stasis  
Hypoxia

2  
Polyphosphate  
Nucleic Acid Polymers  
Basement Membranes  
Artificial Surfaces



3  
Platelet Activation  
Fibrin Formation  
TAFI Activation

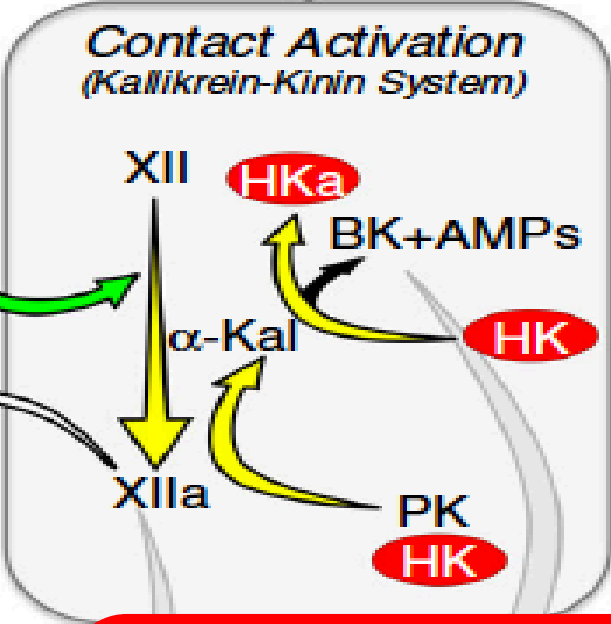
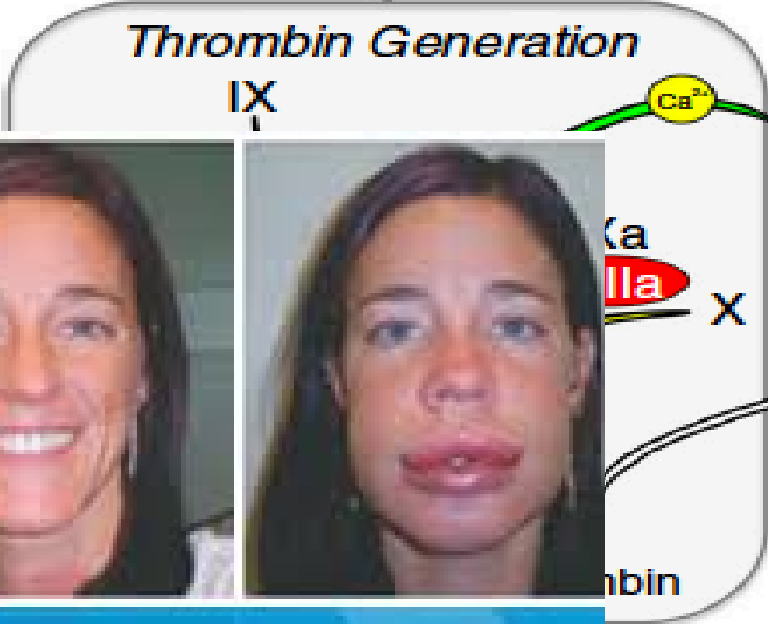
4  
Fibrin Stabilization

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Effects on Blood Vessels

Thrombosis

1  
Tissue Injury  
Platelet Activation  
Inflammation  
Stasis  
Hypoxia

2  
Polyphosphate  
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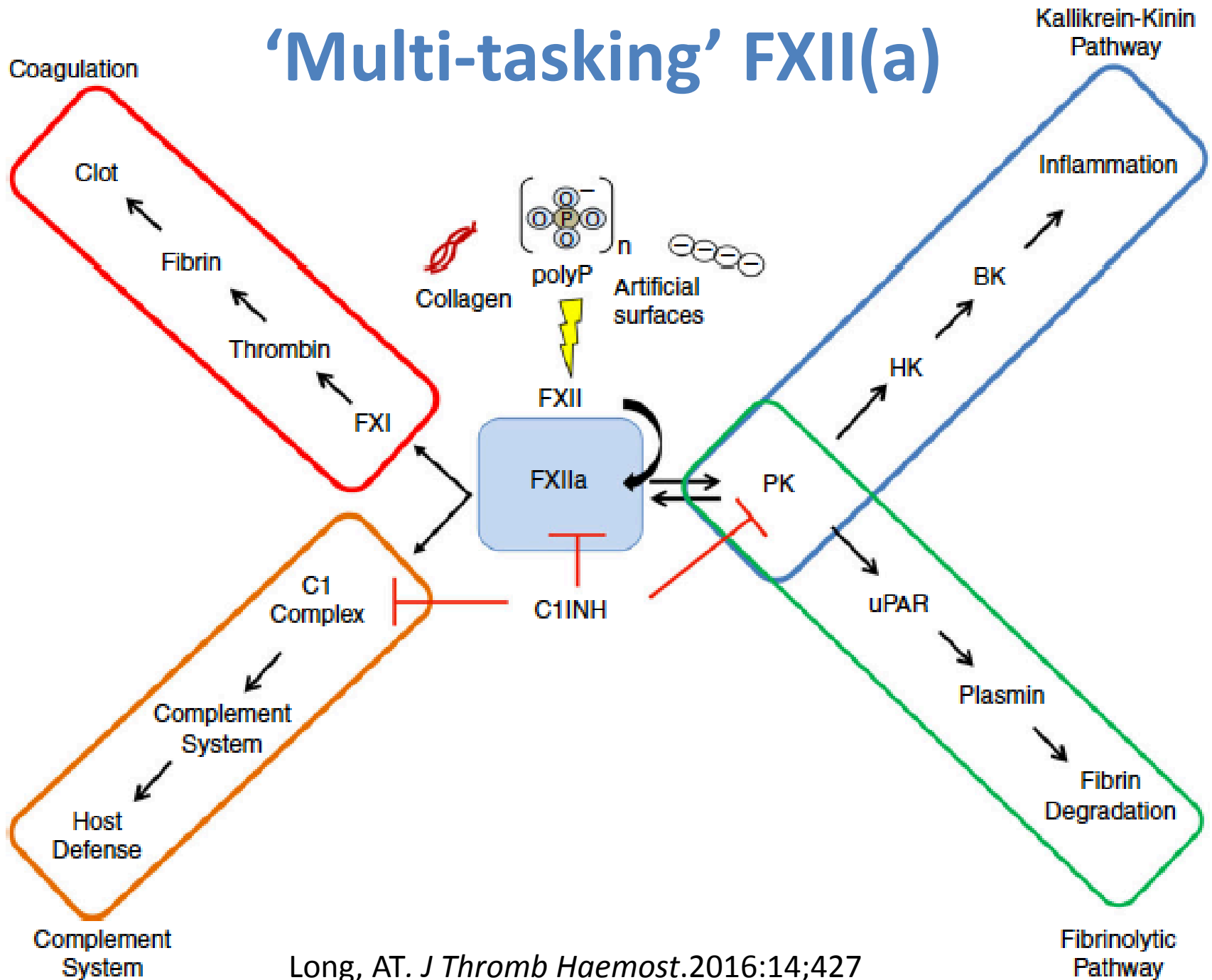
Find out what happens during an HAE attack.

4  
Fibrin Stabilization

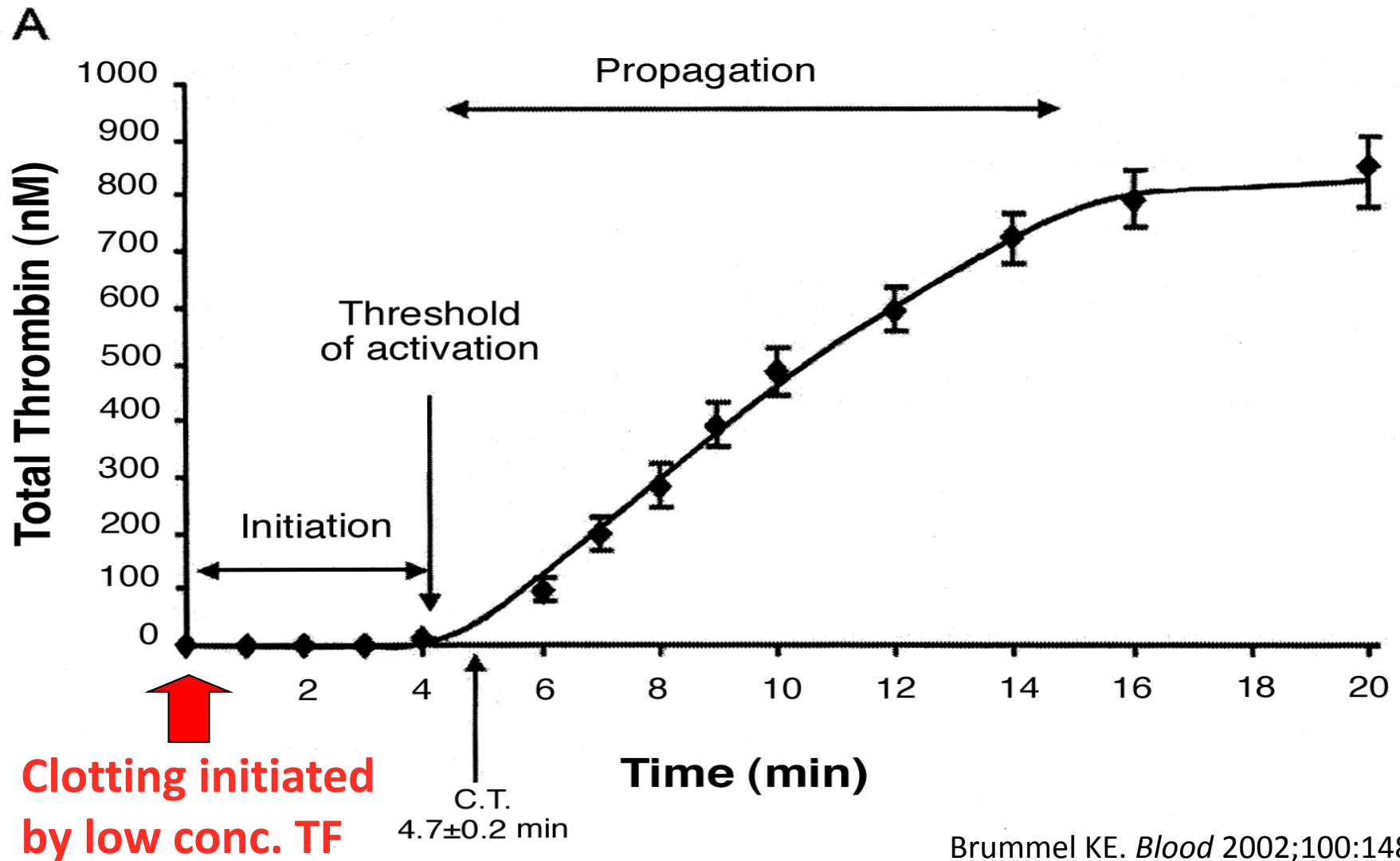
5  
Effects on Blood Vessels

Thrombosis

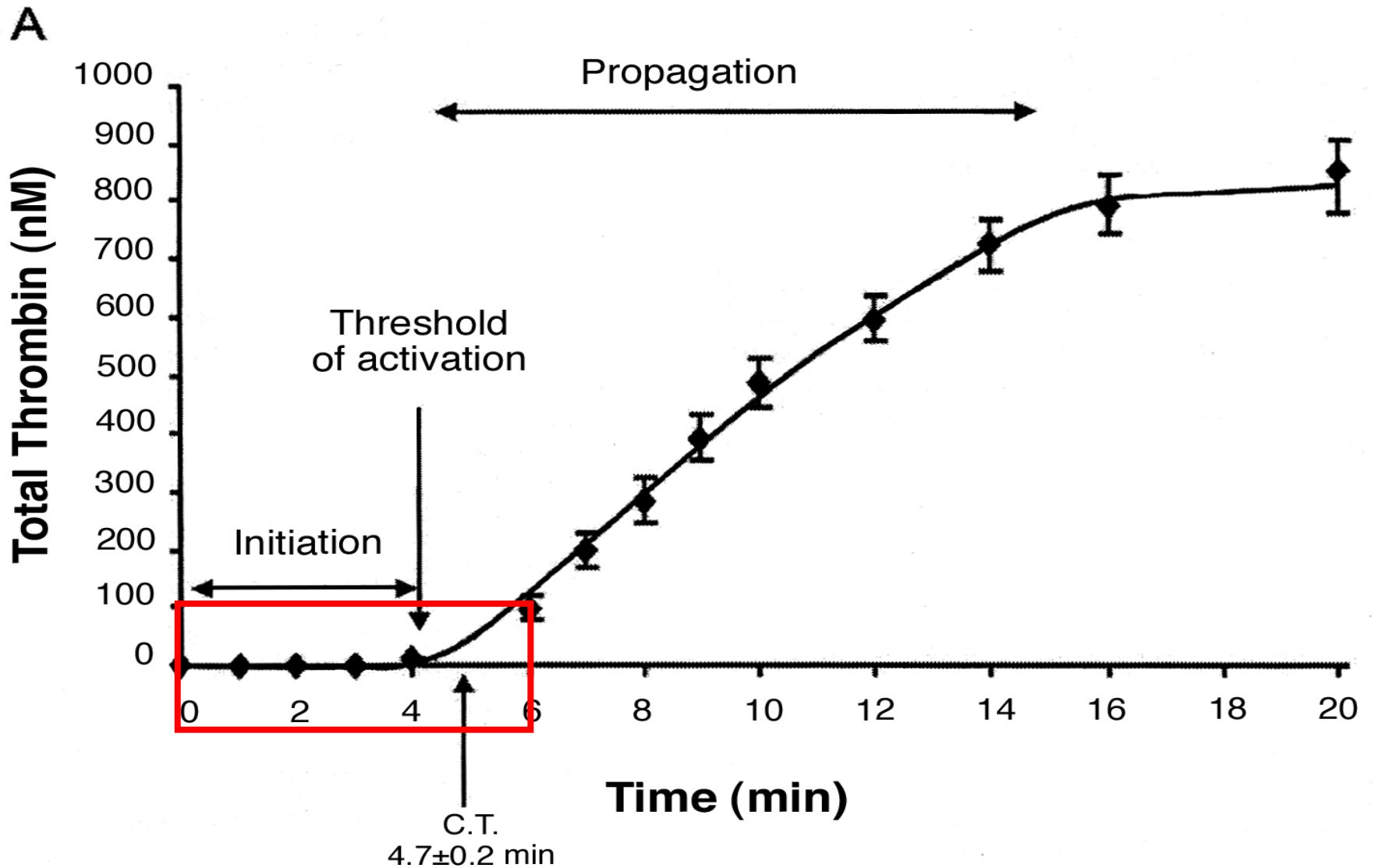
# 'Multi-tasking' FXII(a)



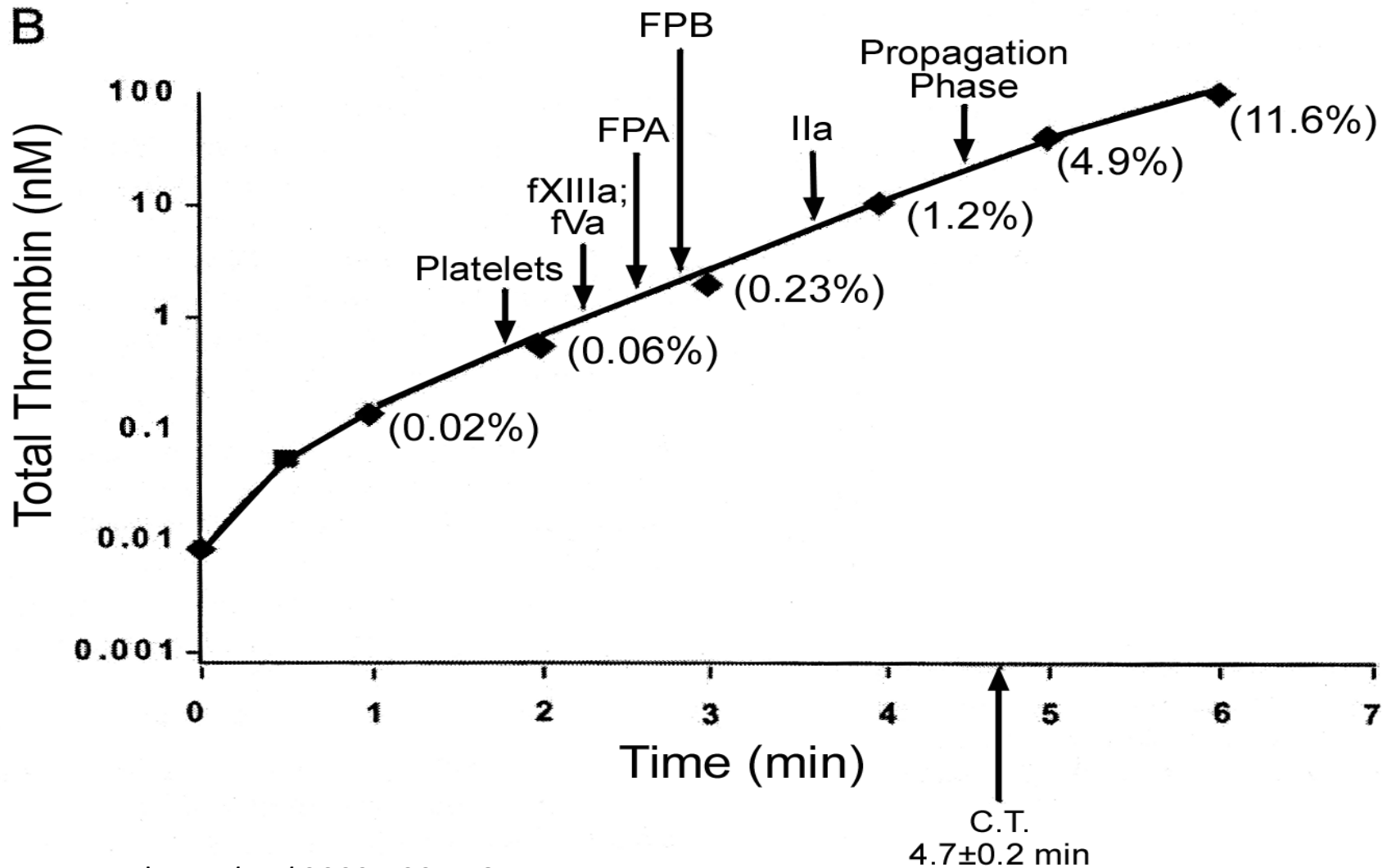
# The Majority of Thrombin is Generated After Whole Blood Clots



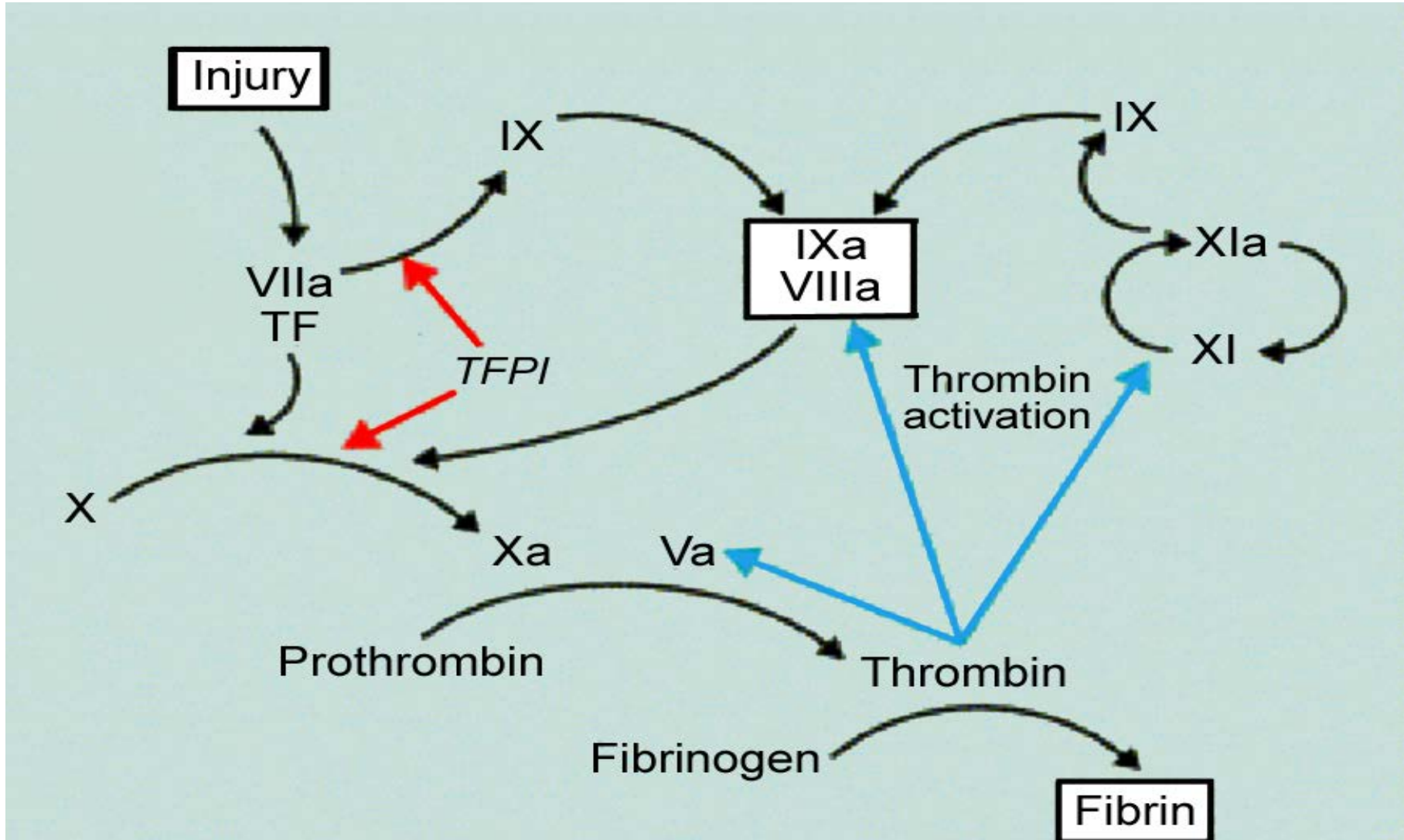
# Focusing on the Early Events in Blood Clotting...



# Early Coagulation Activation Events Mediated By Thrombin

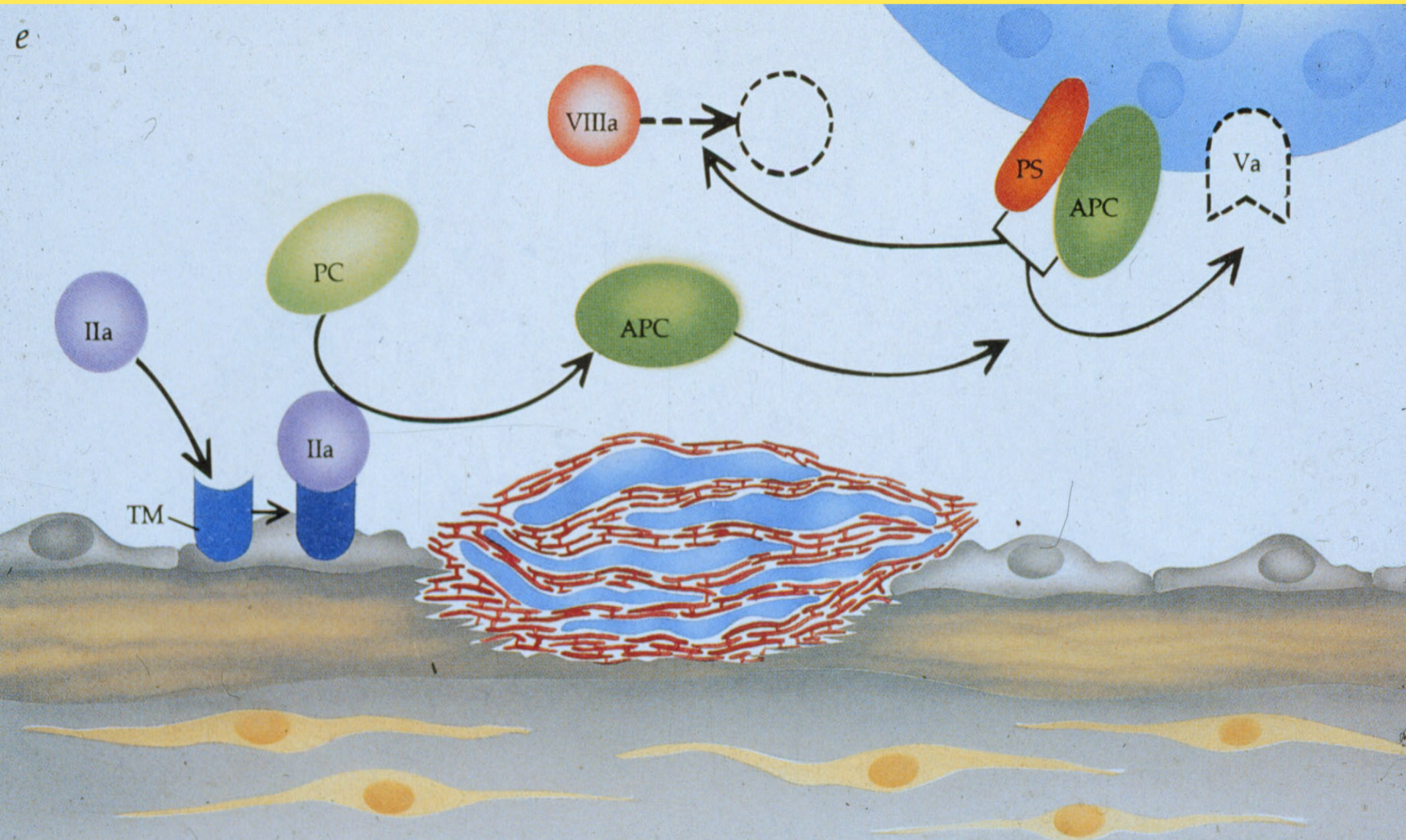


# Revised Coagulation Schematic





# Anticoagulant Function of Thrombin



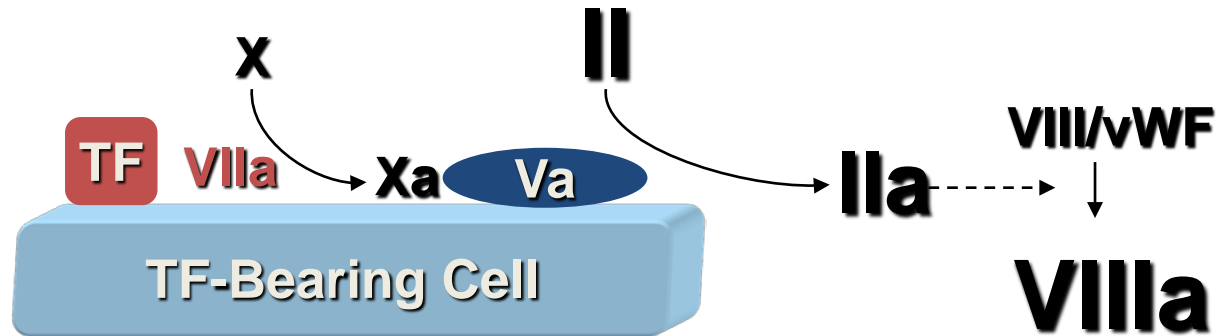
# Accounting for the Role of Blood Cells in Coagulation

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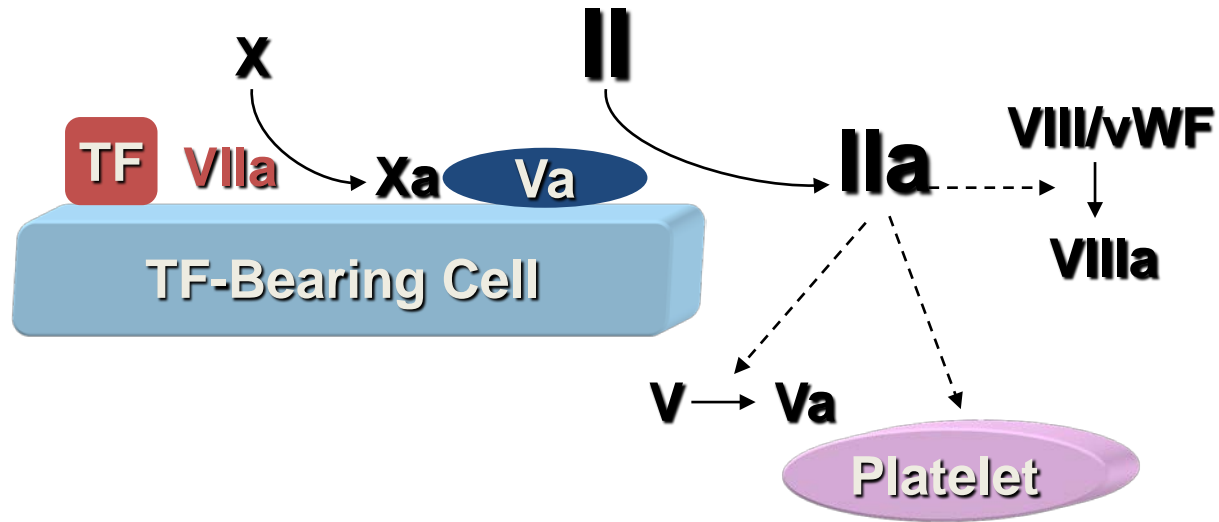


# Cell-Based Model of Hemostasis

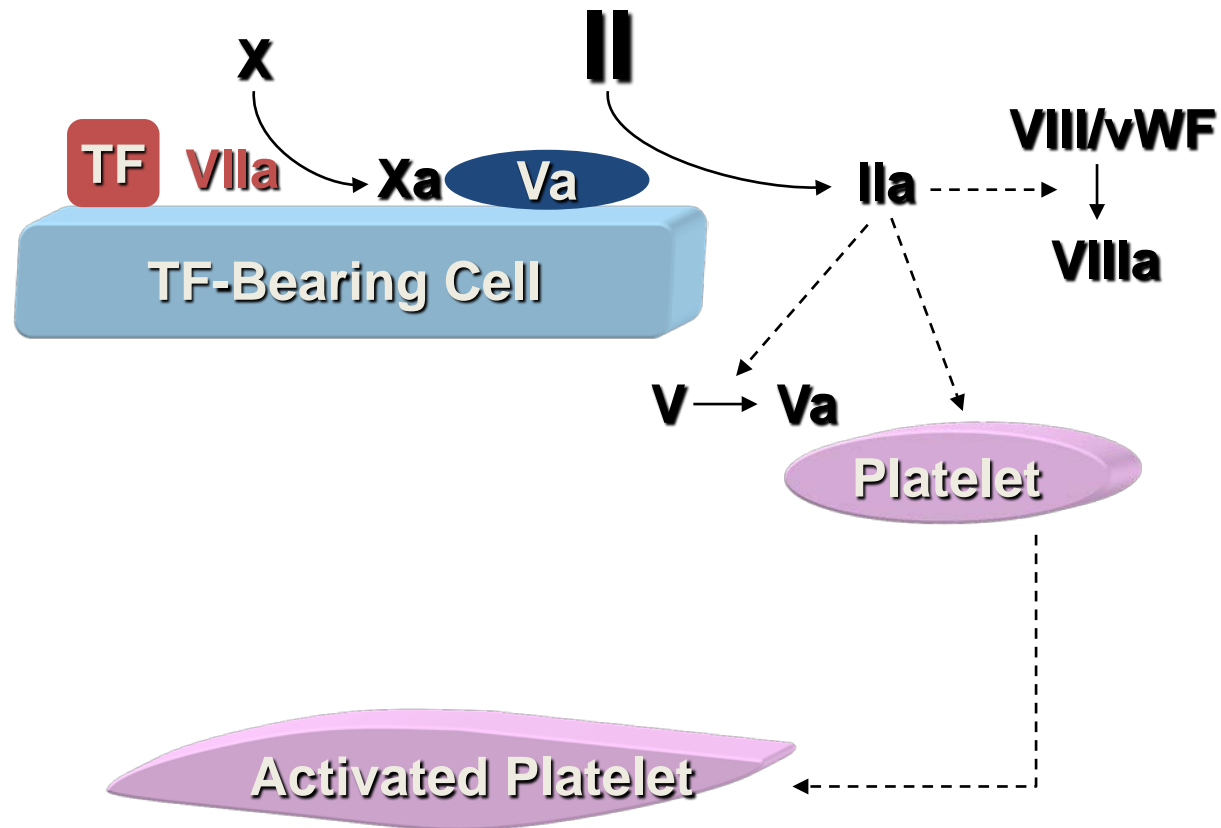
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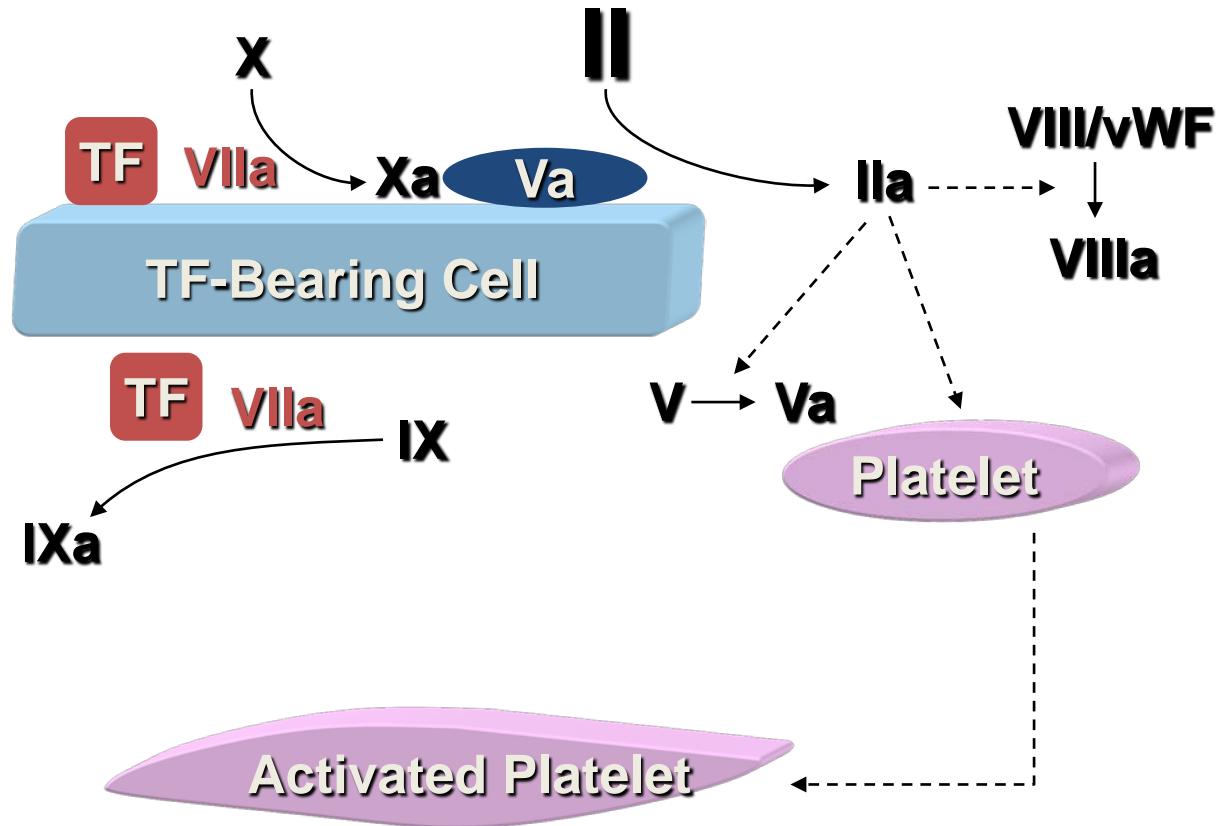
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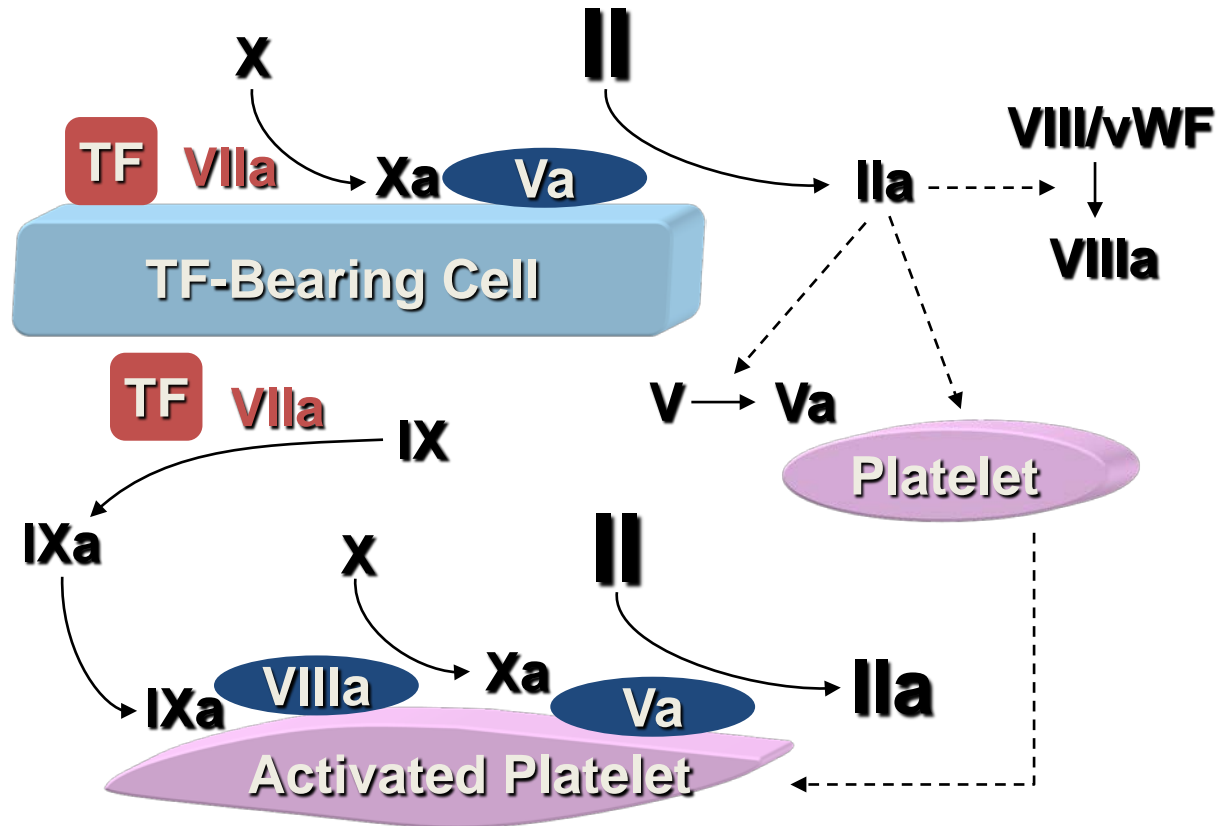
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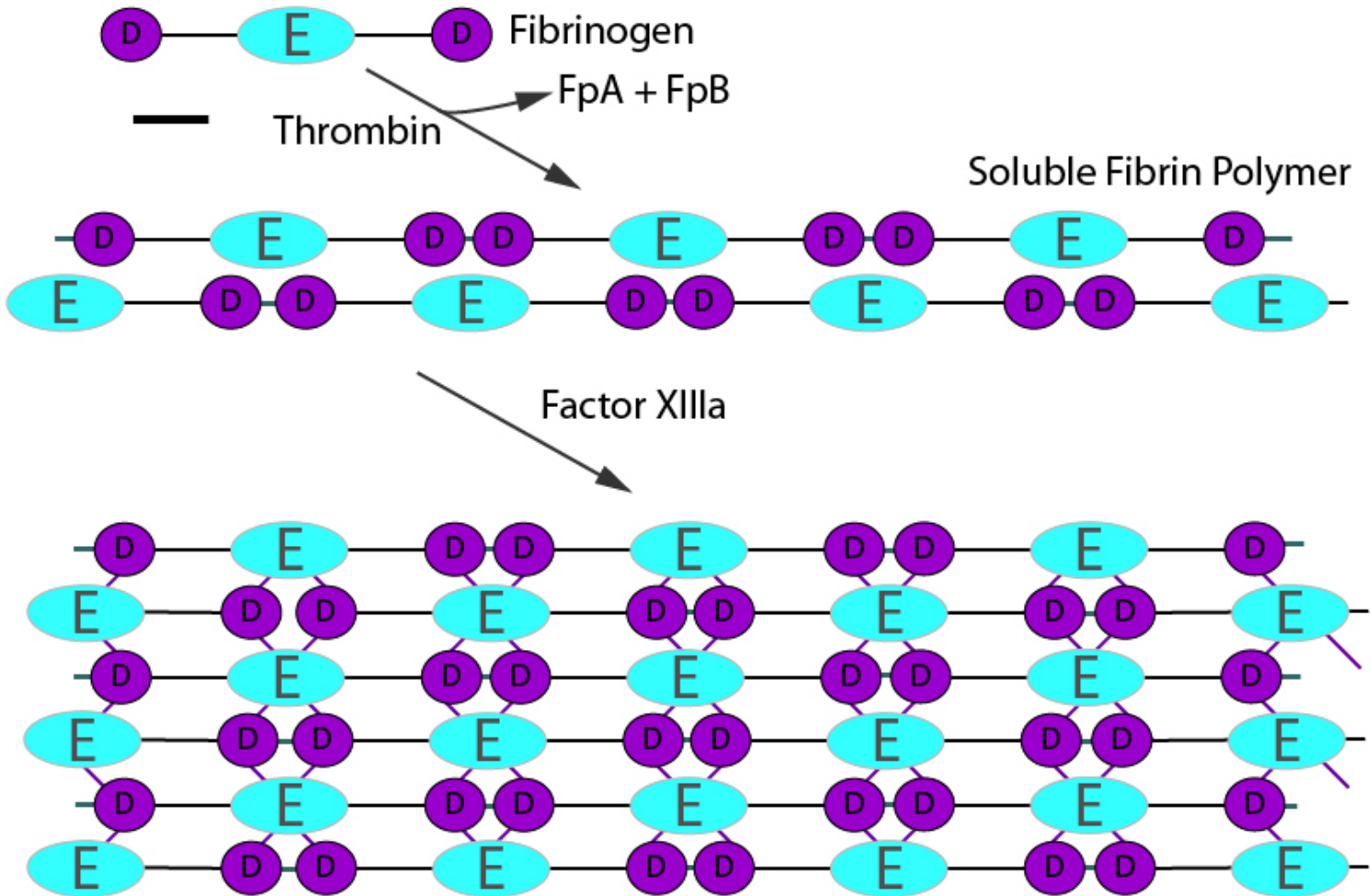
# Cell-Based Model of Hemostasis



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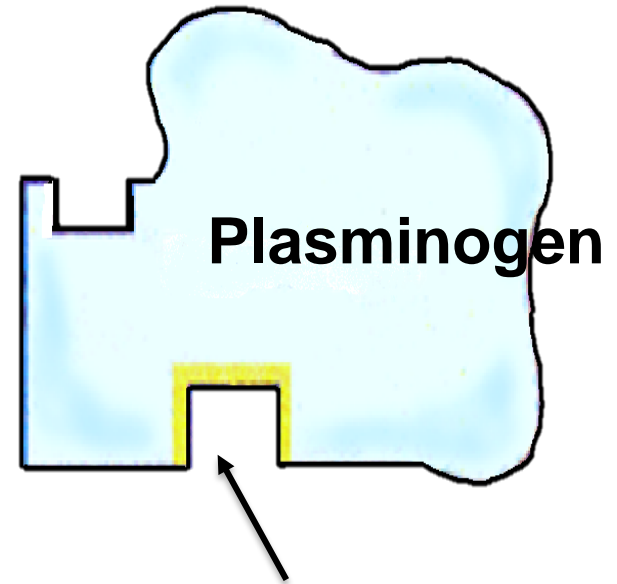


# Formation of Cross-Linked Fibrin

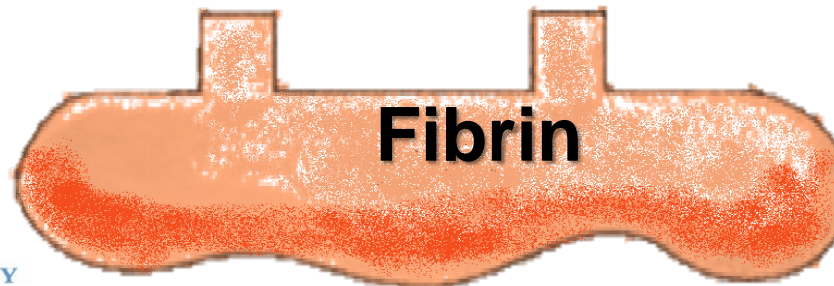




# Fibrin Promotes Fibrinolysis

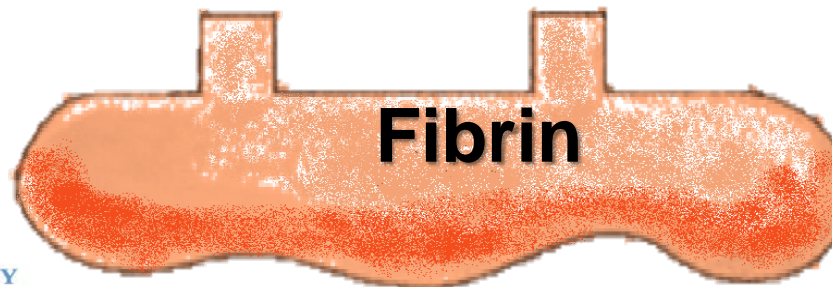
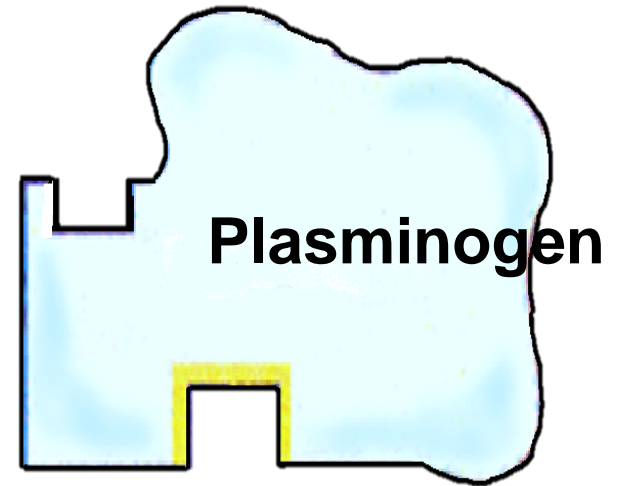


Lysine-binding site



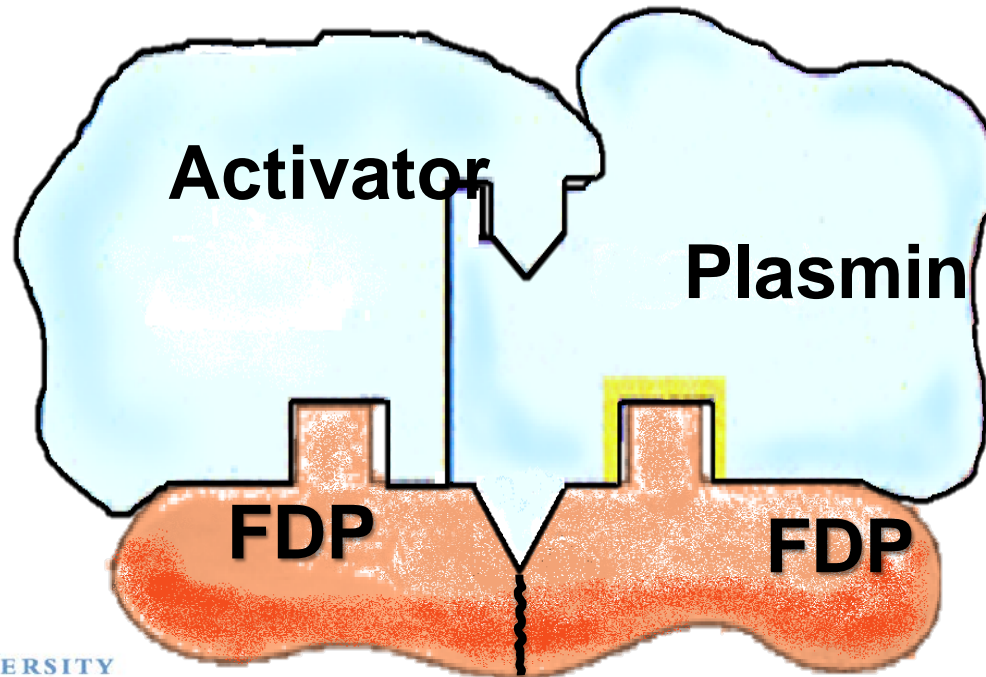
# Fibrin Promotes Fibrinolysis

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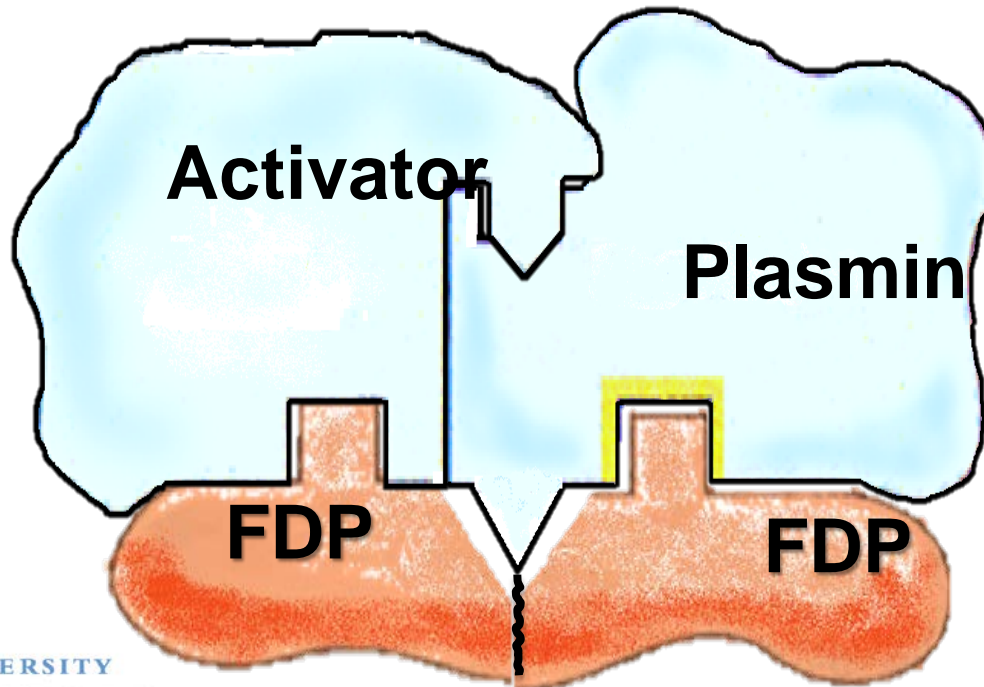
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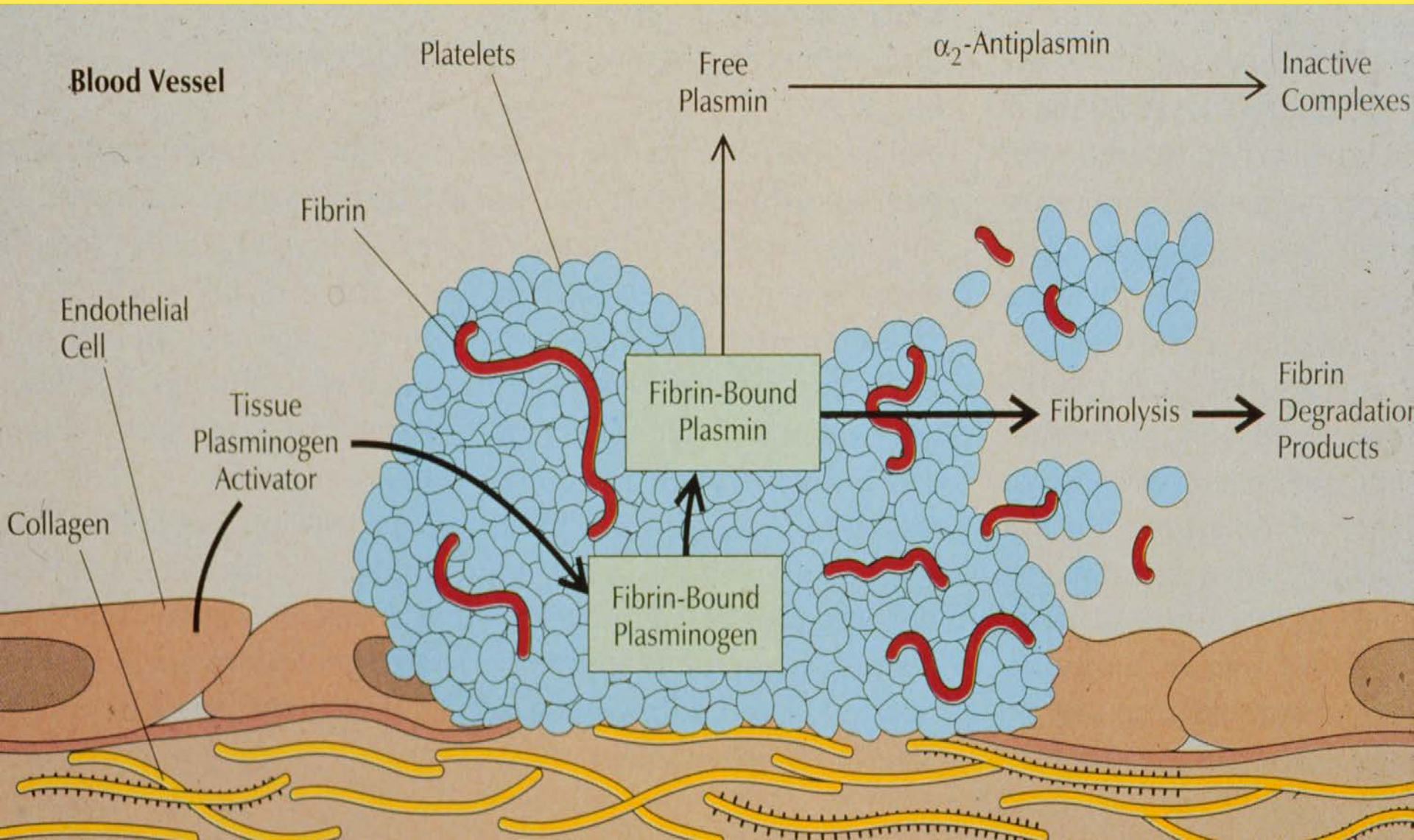
# Principal Inhibitors of Fibrinolysis

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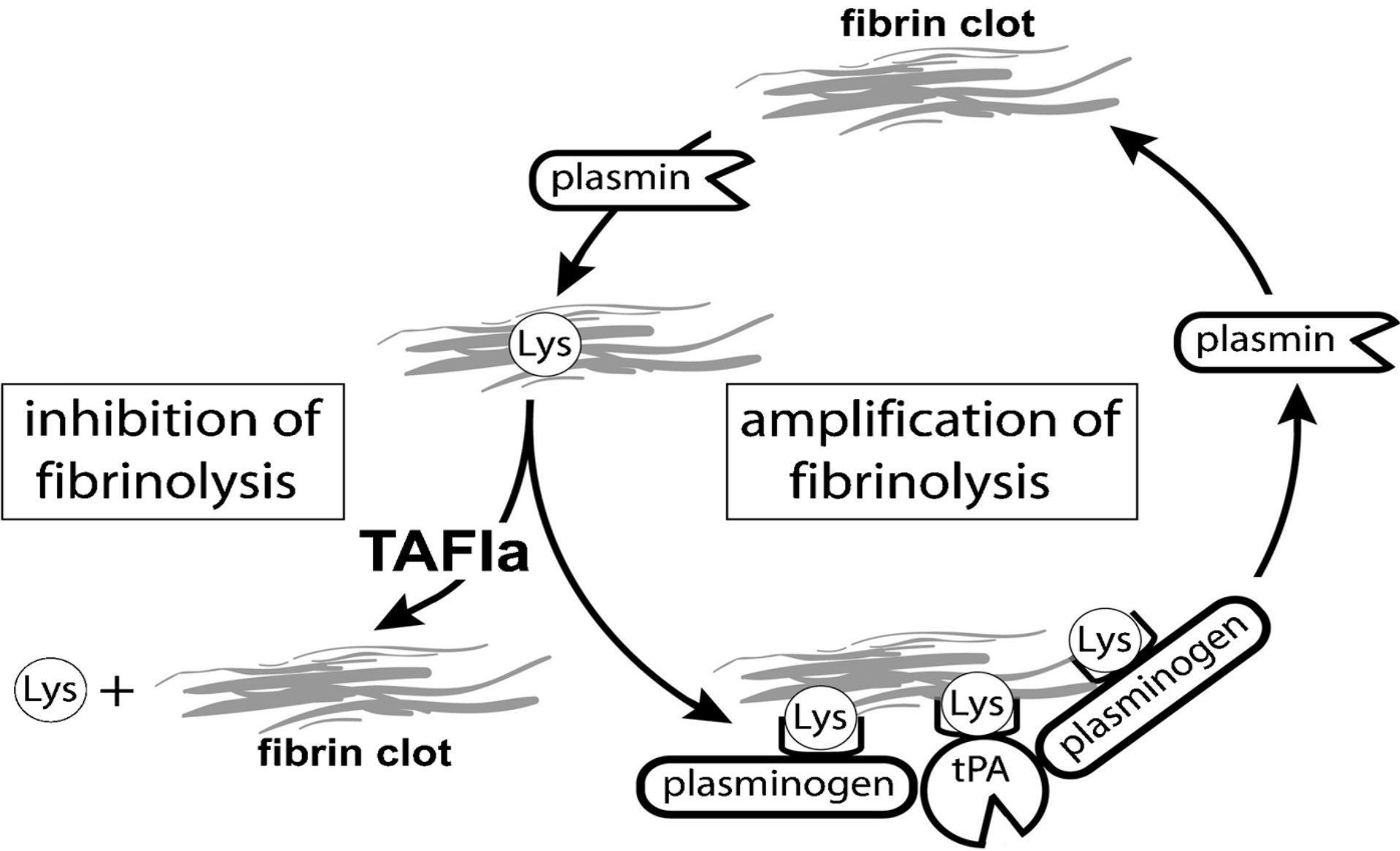
1. Plasminogen activator inhibitor-1 (**PAI-1**)  
...inhibits t-Pa and urokinase
2. **Alpha<sub>2</sub>-antiplasmin**.....inhibits plasmin
3. Thrombin-Activatable Fibrinolysis Inhibitor (**TAFI**).....inhibits binding of plasminogen and tPa



# Fibrinolysis

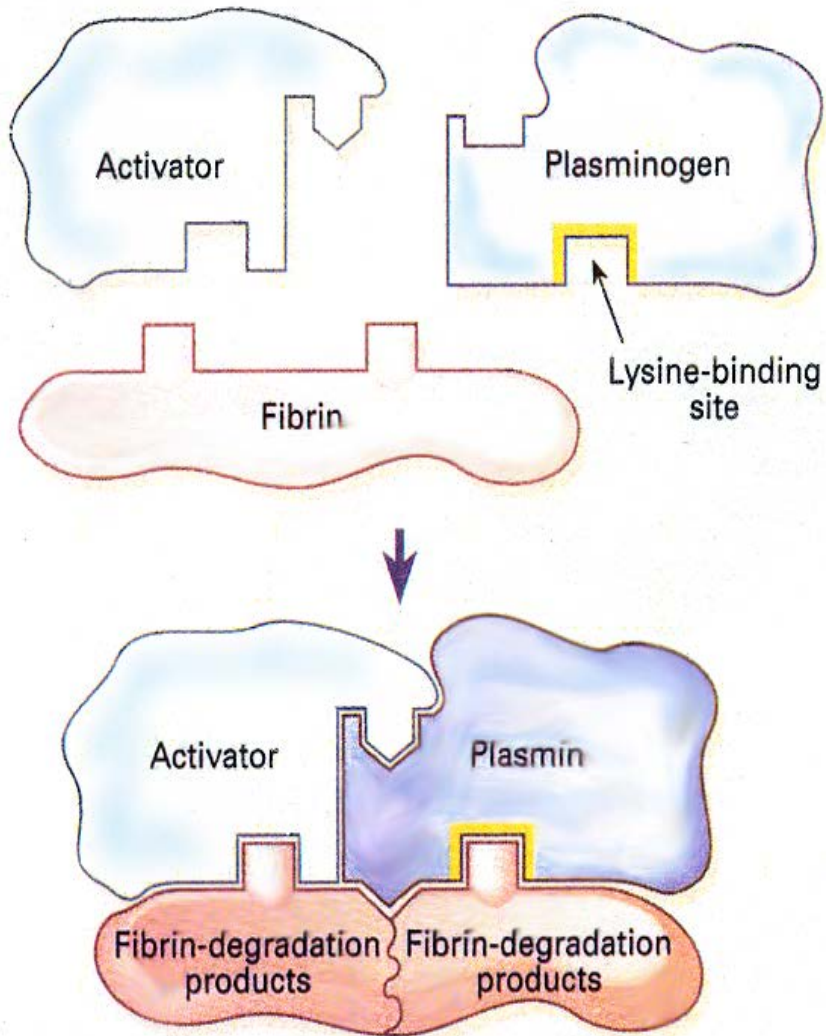


# Activated TAFI (TAFIa) Inhibits Fibrinolysis by Cleaving Essential Lysine Residues on Fibrin

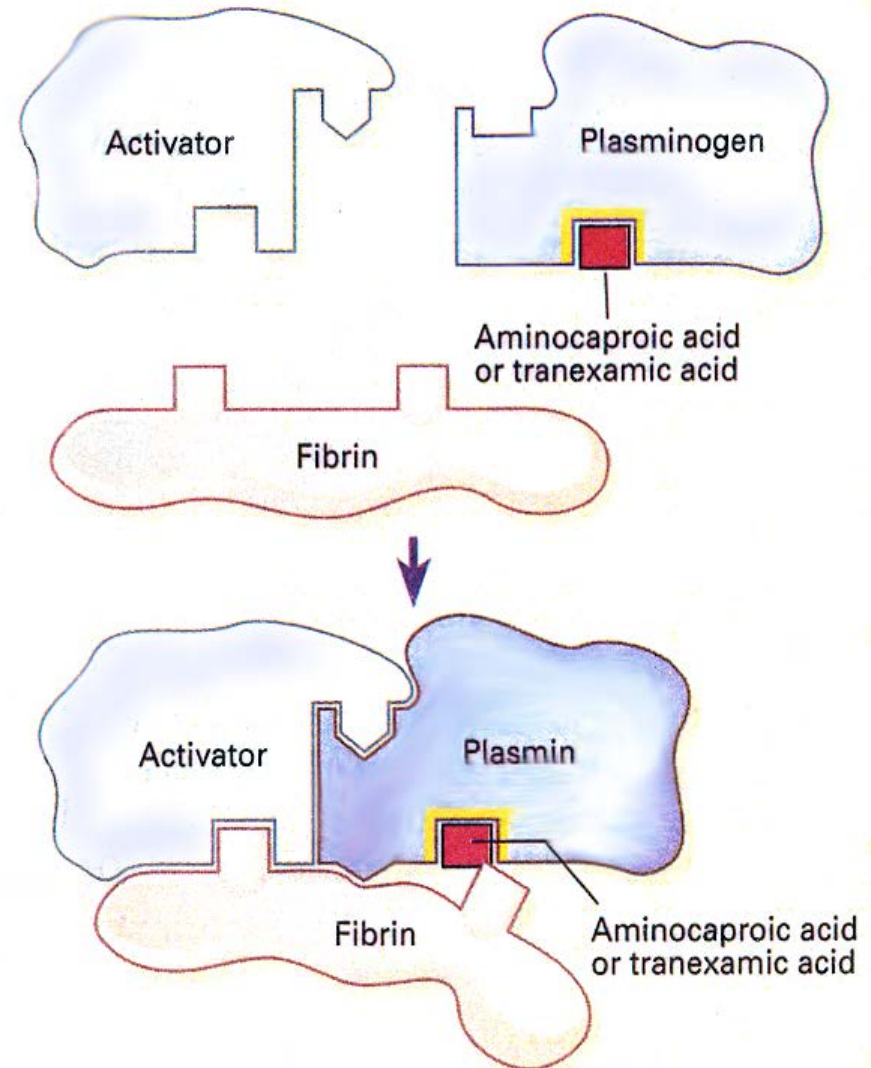


# Anti-fibrinolytic Lysine Analogs

## Activation of Fibrinolysis

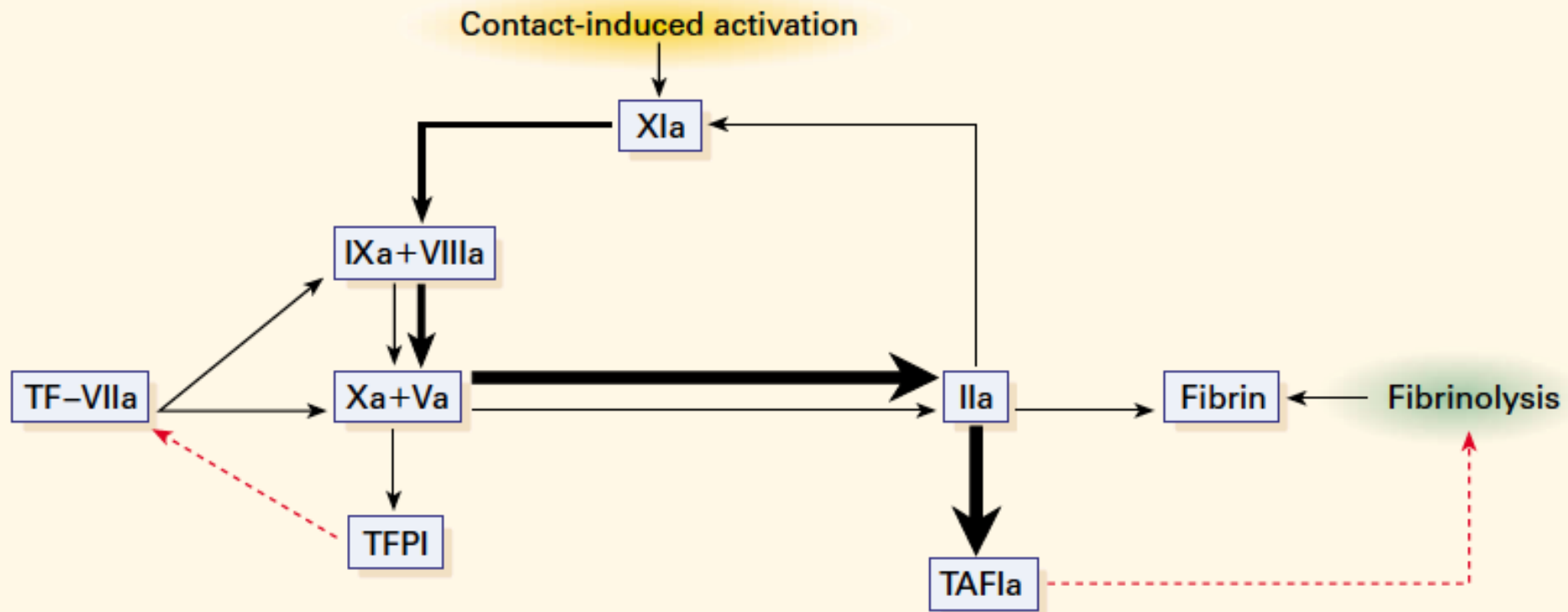


## Inhibition of Fibrinolysis

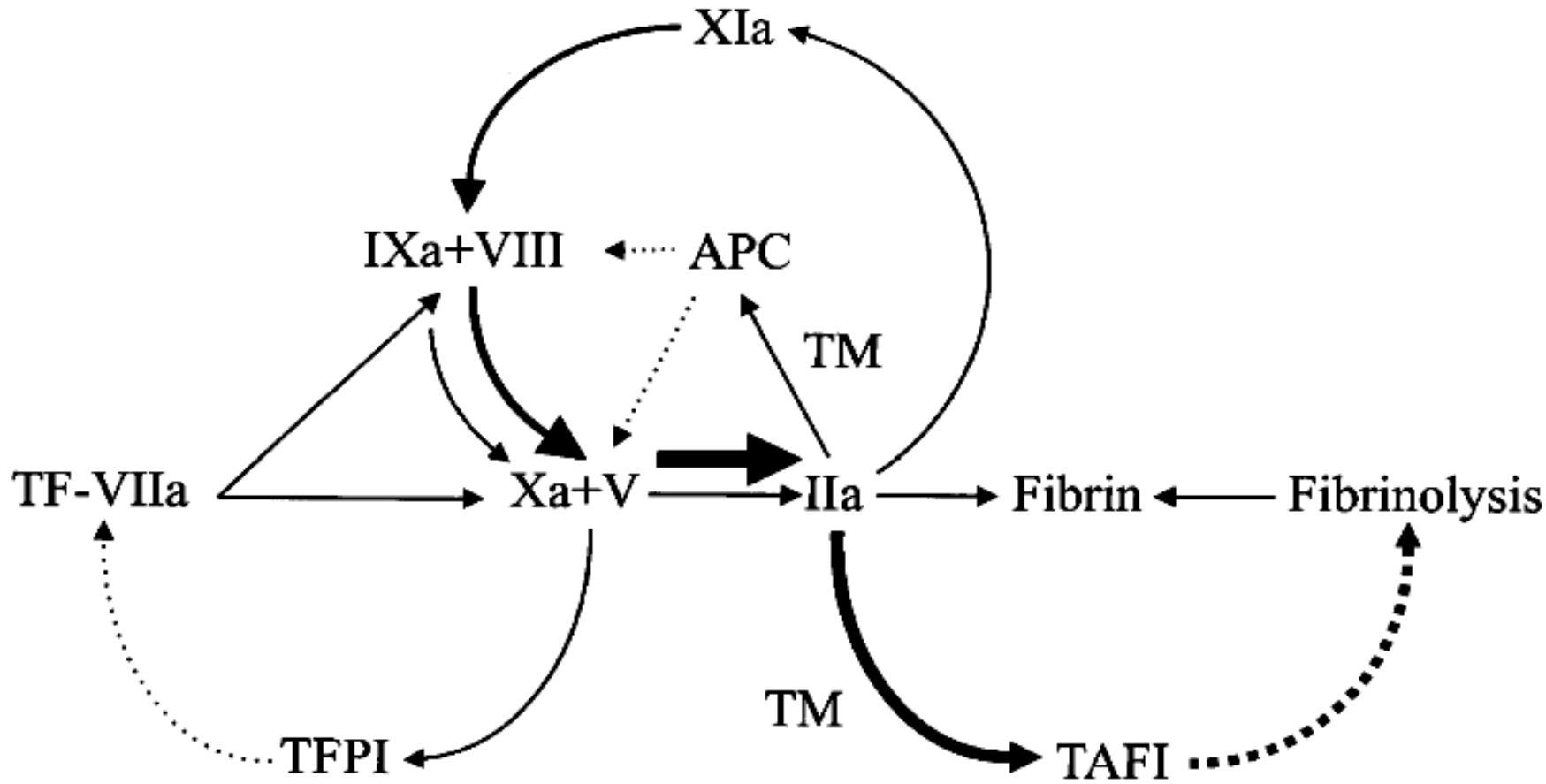




# Procoagulant and Antifibrinolytic Roles of FXI



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



# Conclusions

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

