Imperial College London

Haemostasis & thrombosis

Part 3

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Session Plan

Part 1 –Overview of Haemostasis

- Primary Haemostasis
- Secondary Haemostasis (Coagulation)
- Fibrinolysis

Part 2 –Primary Haemostasis

- Platelets
  - Adhesion
  - Release reaction
  - Thromboxane A2 synthesis
  - Platelet aggregation
- Antiplatelet drugs
- Von Willebrand factor

Part 3 – Coagulation (Secondary Haemostasis)

- Clotting factor synthesis
- Cellular base model of coagulation
  - Initiation
  - Amplification
  - Propagation
- Coagulation inhibitory mechanisms
  - - Anticoagulant Pathway
  - Anticoagulant Drugs

Part 4: Fibrinolytic system

- Fibrinolysis
- Antifibrinolytic drugs

Part 5: Tests of Coagulation

- Prothrombin time (PT)
- Activated Partial Thromboplastin Time (APTT)

Part 6 – Bleeding and Thrombosis

- The Balance Model of Coagulation and its Application

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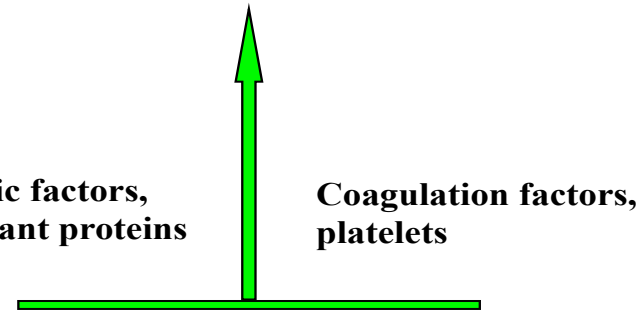
Coagulation (Secondary Haemostasis)

Functions of Haemostasis
1. Prevention of blood loss from intact vessels
2. Arrest of bleeding from injured vessels

Normal haemostasis: a state of equilibrium



Vessel constriction

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Formation of an unstable platelet plug
- -platelet adhesion
- -platelet aggregation

↓

Stabilisation of the plug with fibrin
- -blood coagulation

↓

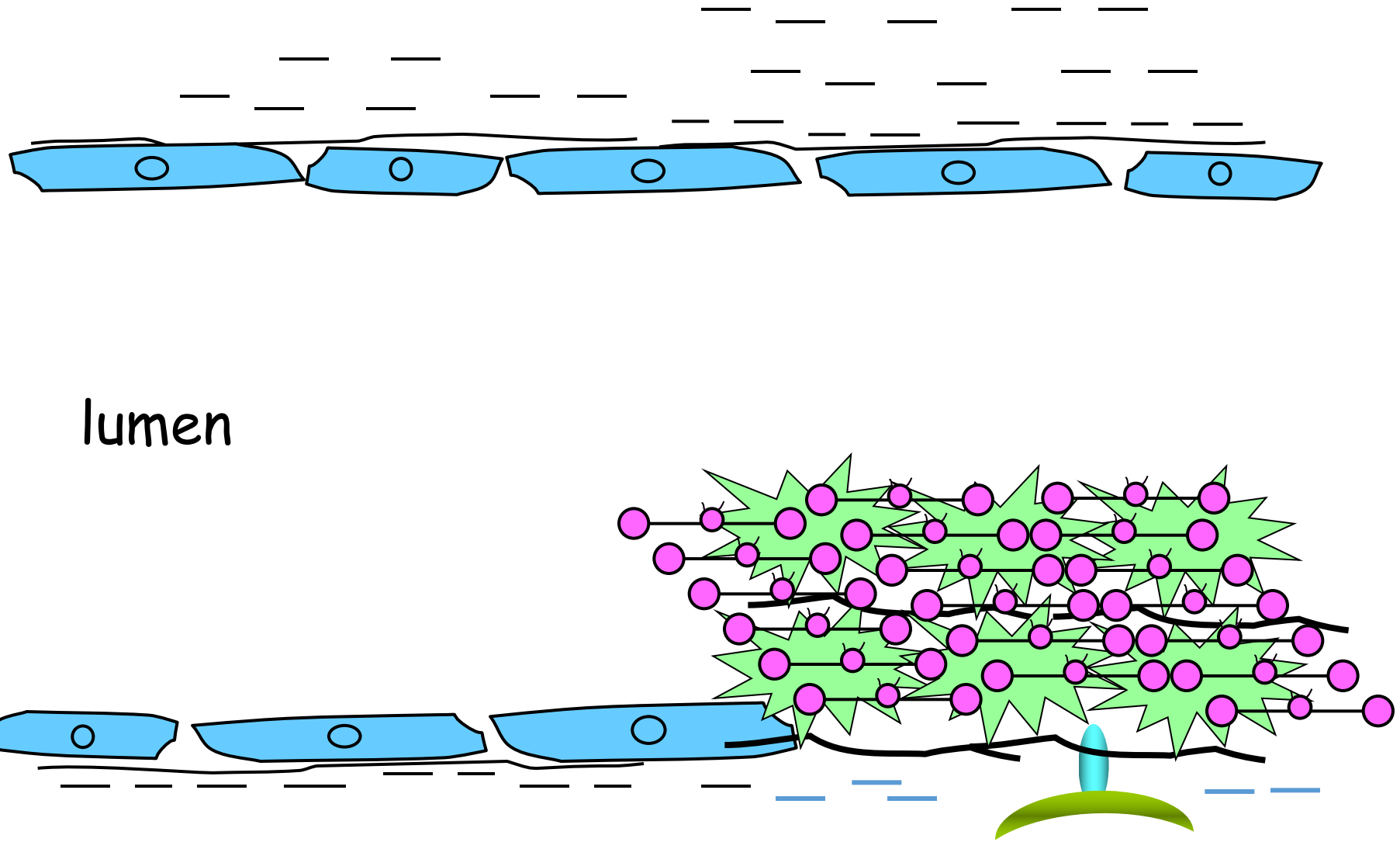
Dissolution of clot and vessel repair
- -fibrinolysis

The role of coagulation is to generate thrombin (IIa), which will convert fibrinogen to fibrin

Coagulation and secondary haemostasis

- The primary platelet plug is sufficient for small vessel injury
- In larger vessels it will fall apart
- Fibrin formation stabilises the platelet plug

So -



Haemostasis: fibrin clot stabilising platelet plug

Sites of Synthesis of Clotting Factors, Fibrinolytic Factors and Inhibitors

1. The liver

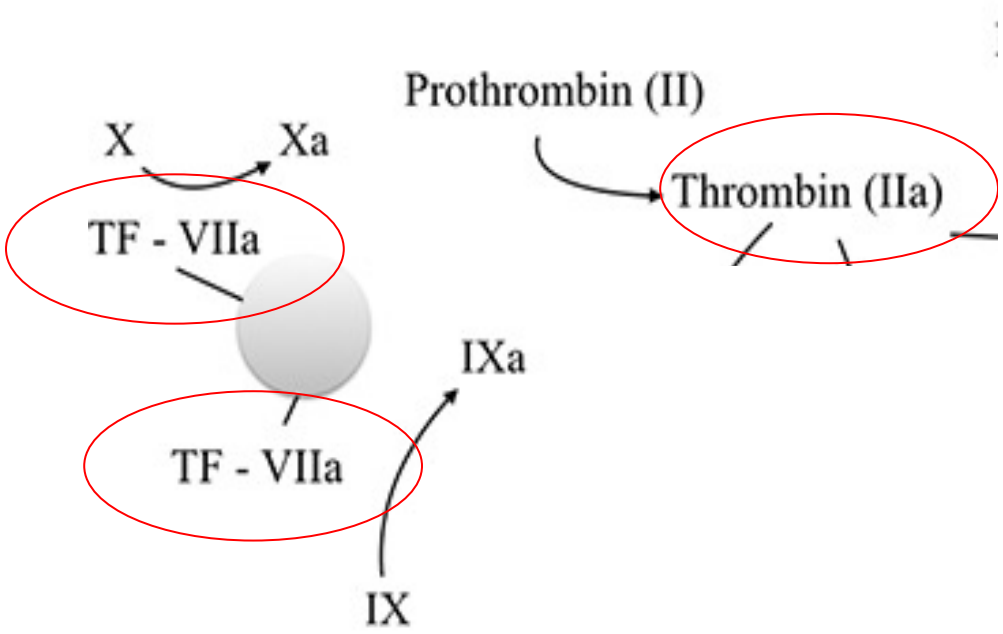
2. Endothelial cells

3. Megakaryocytes (platelets)

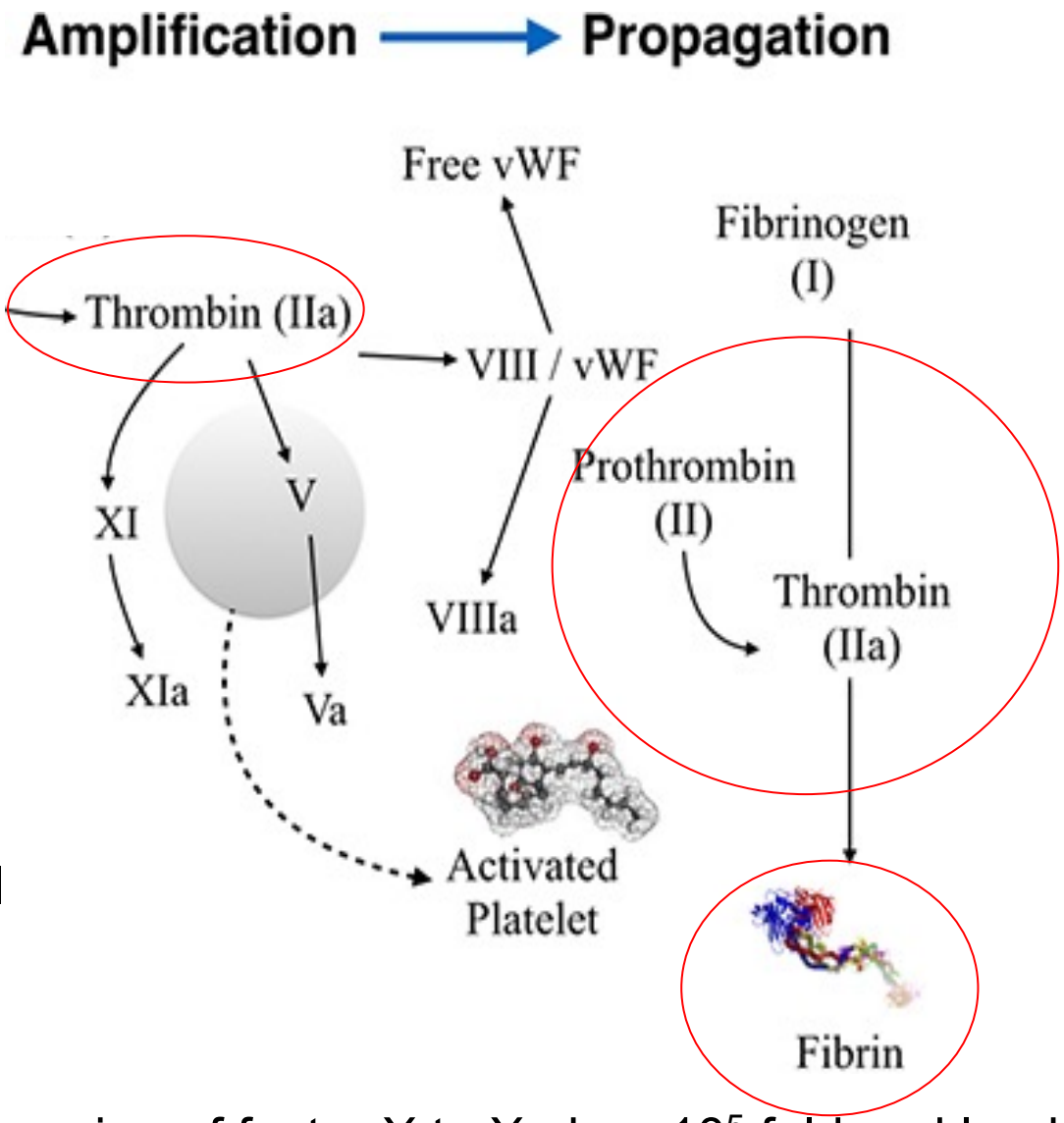
Most synthesis is in the liver but some proteins produced in high local concentration in endothelium (eg vWF) and in megakaryocyte (eg factor V)

Factors II (prothrombin), VII, IX and X are dependent on Vitamin K for carboxylation of their glutamic acid residues, which is essential for the function of these clotting factors.

Initiation



- Coagulation is INITIATED by Tissue Factor
- This results in the generation of a small amount of Thrombin

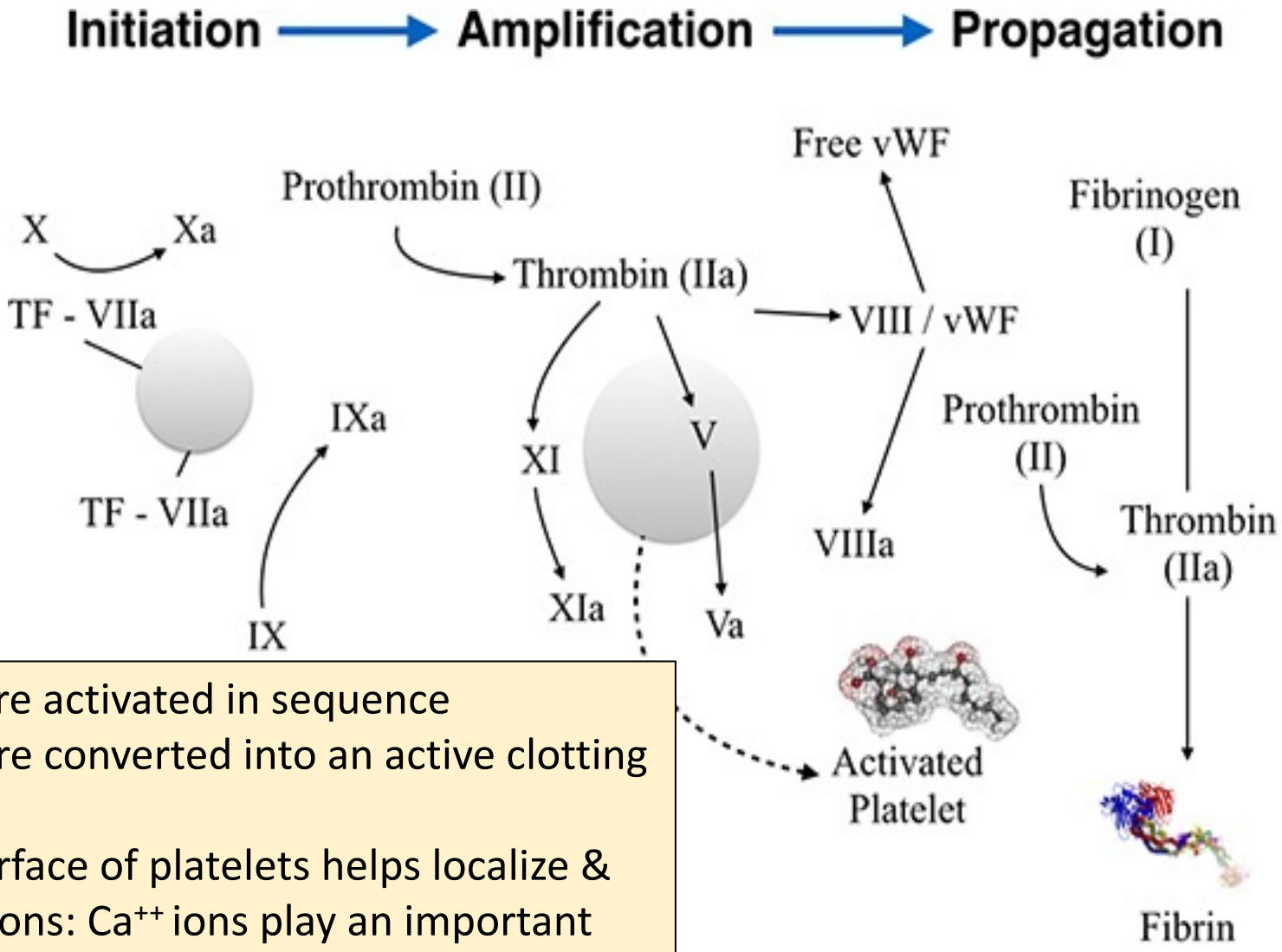


Thrombin then activates:

1. Co-factors V and VIII
2. Factor XI
3. Platelets

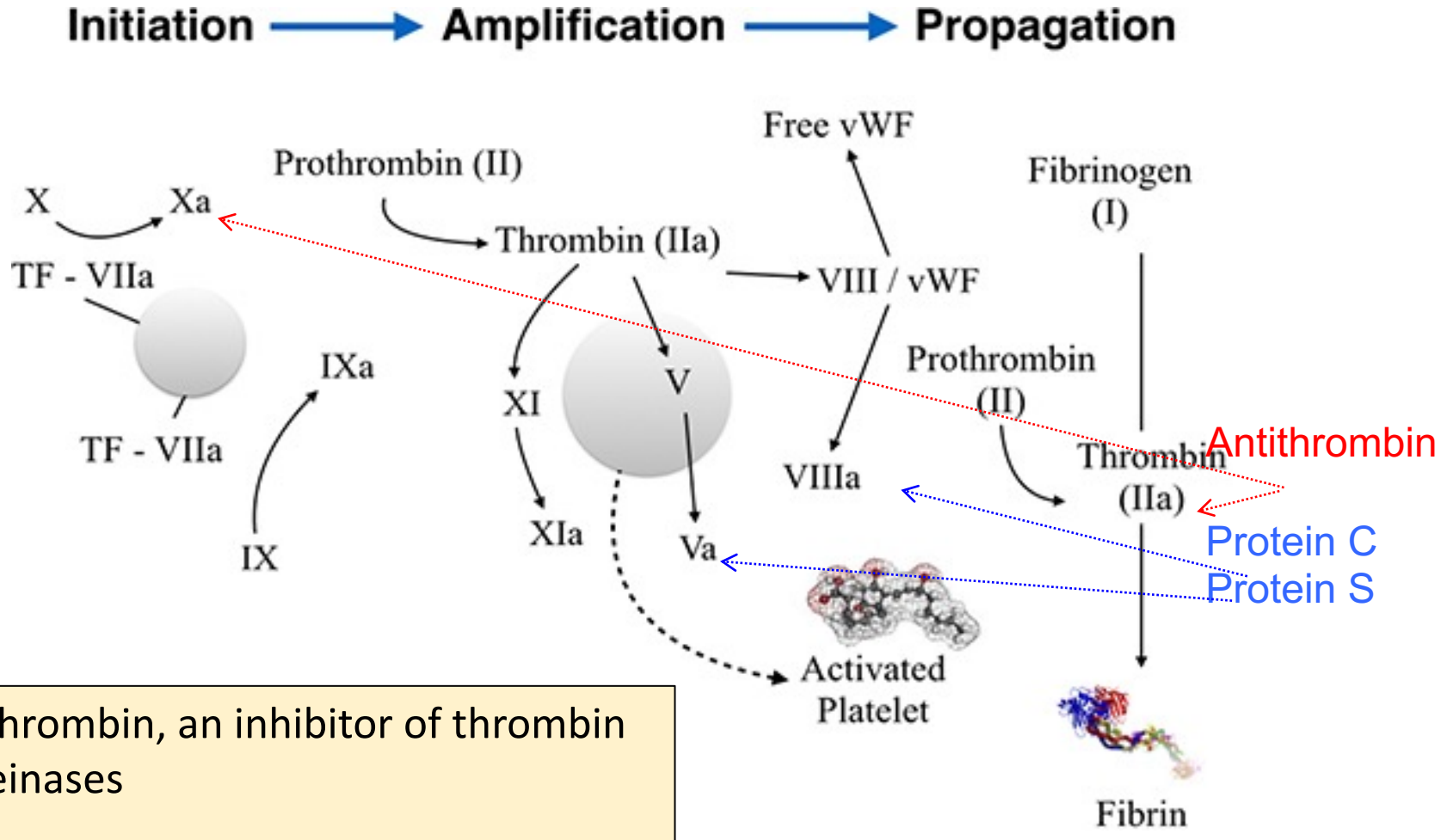
This AMPLIFIES the conversion of factor X to Xa by ~10^5 fold and leads to a rapid burst in thrombin generation that cleaves soluble fibrinogen to form the insoluble fibrin clot

Putting all this together….



1. A number of steps are activated in sequence
2. Inactive zymogens are converted into an active clotting factor
3. The phospholipid surface of platelets helps localize & accelerate these reactions: Ca^{++} ions play an important role in binding clotting factors to the platelet surface

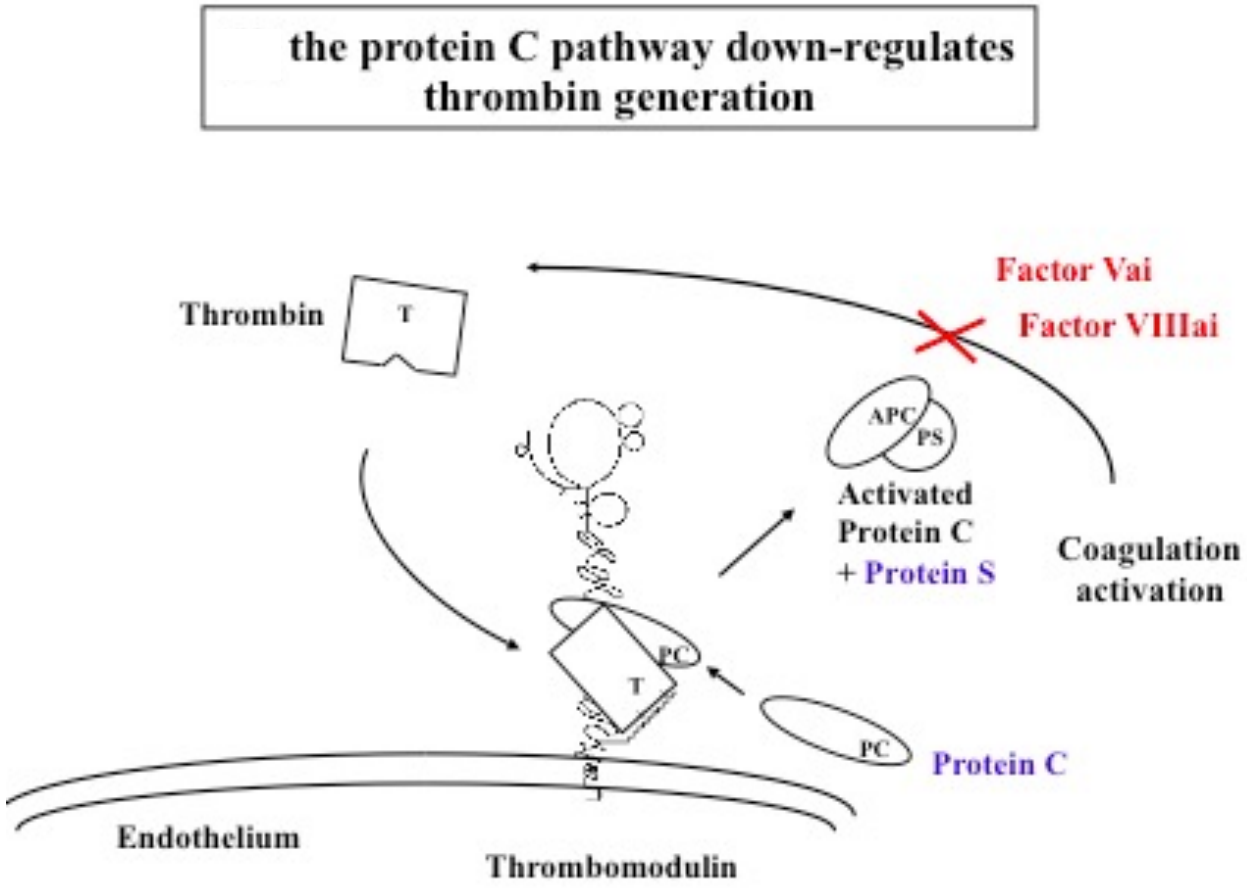
Coagulation Inhibitory Mechanisms



Direct Inhibition: Antithrombin, an inhibitor of thrombin and other clotting proteinases

Indirect inhibition e.g. Inhibition of thrombin generation by the protein C and protein S anticoagulant pathways

Coagulation Inhibitory Mechanisms

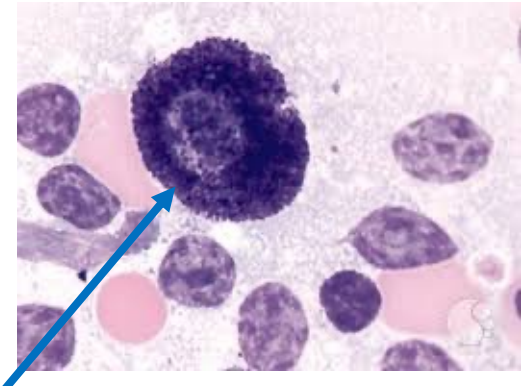


Approaches to therapeutic anticoagulation

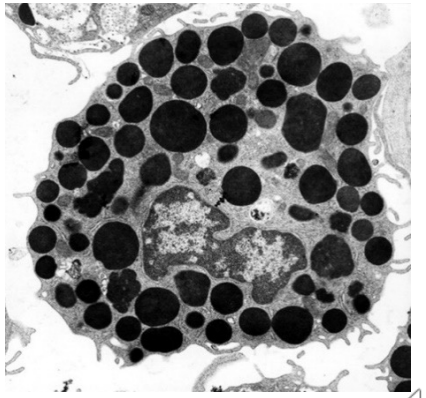
- Reduce procoagulant factors
  - Vitamin K antagonists
- Inhibit procoagulant factors
  - Direct oral anticoagulants
- Enhance natural anticoagulant pathways
  - Heparins and derivatives

Anticoagulant Drugs: Heparin

- Heparin is a mixture of glycosaminylglycan chains extracted from porcine mucosa
- Heparin works **indirectly** by potentiating the action of antithrombin leading to the inactivation of factors Xa and IIa (thrombin).
- Inactivation of thrombin requires longer chains of heparin, which are able to wrap around both the antithrombin and thrombin
- Heparin is administered intravenously or by subcutaneous injection



Light micrograph and electron micrograph of mast cells packed with granules containing heparin



Prabhani Nanoscale 2015 7: 11420
Chappell Shock 2010 34: 133

Anticoagulant Drugs: Warfarin

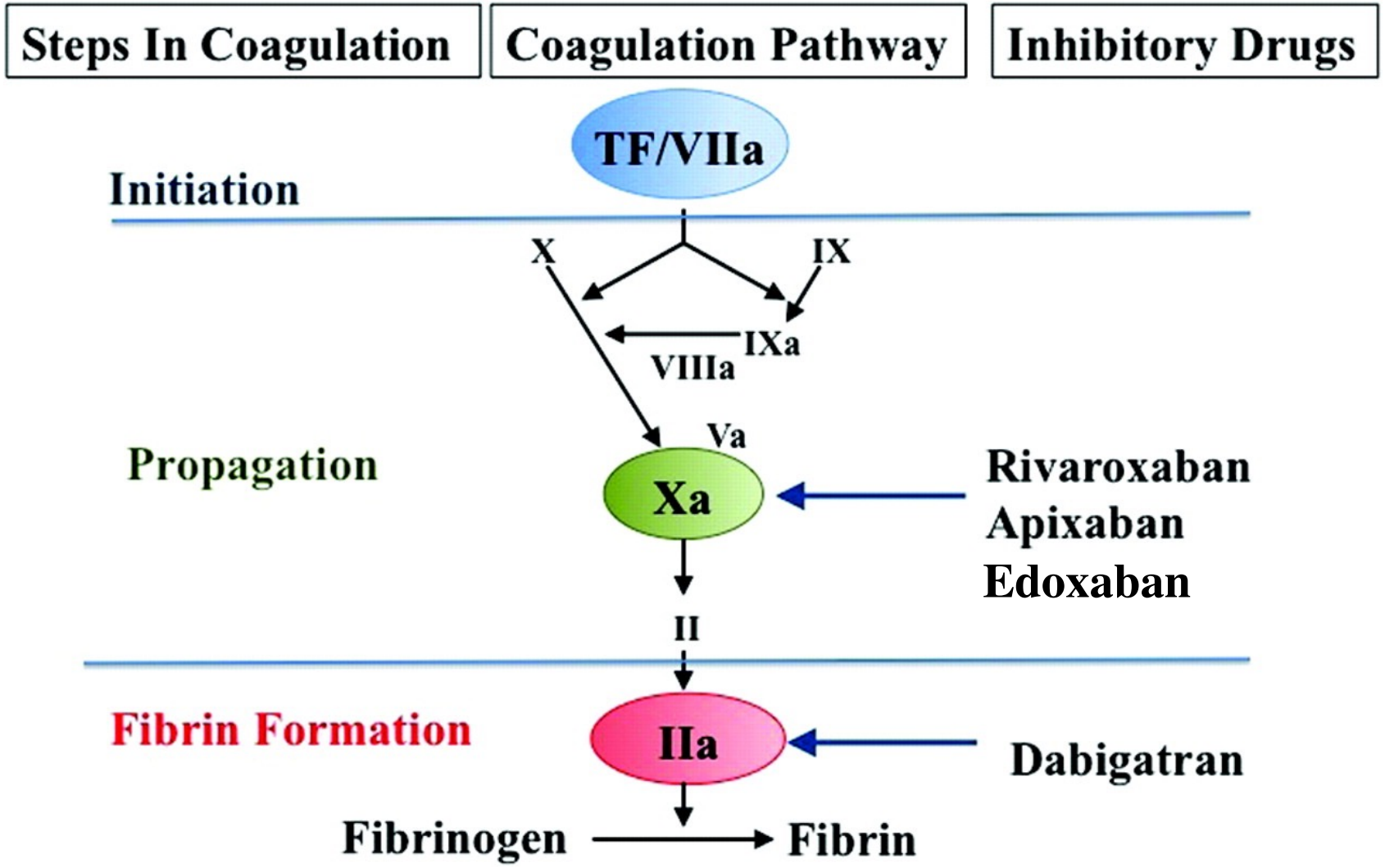
- Warfarin, derived from coumarin, is a vitamin K antagonist that works by interfering with protein carboxylation.
- It therefore reduces synthesis of functional factors II, VII, IX and X by the liver
- Warfarin competes with Vitamin K – complicated mechanism that prevents recycling of Vitamin K
- Warfarin is given as an oral tablet and its anticoagulant effect needs to be monitored by regular blood testing
- Because it reduces synthesis of coagulation factors rather than inhibiting existing factor molecules, it takes several days to take effect.

Anticoagulant Drugs: Direct Oral Anticoagulants (DOACs)

- Orally available drugs that **directly** inhibit either thrombin or factor Xa (i.e. without the involvement of antithrombin)

- These do not usually require monitoring

Direct Oral Anticoagulants (DOACs) - targets



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