Enzyme Regulation II
Blood Clotting

Dr. Kevin Ahern
Blood Clotting

Blood coagulation *in vivo*

- **initiation phase**
  - TF (tissue factor) → TF-VIIa → IXa
  - VII → IX

- **amplification phase**
  - (αTHR) Xa → X → XIa → XI
  - (APC) VIIIa → VIII
  - (αTHR) Va → V
  - prothrombin → THROMBIN

- Stabilised, cross-linked fibrin clot
- Fibrinogen → fibrin → XIIIa → XIII
Blood Clotting

Cellular Response

Blood coagulation in vivo

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  - IXa

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  - (APC) Vlla → (APC) VIII
  - Va → V
  - (αTHR) XIIIa → (αTHR) XIII

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Blood Clotting - Cellular Response
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5. Amplification begins with release of platelet factor 4 (inhibits heparin) and thromboxane A₂ (increases platelet stickiness).
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(Throughout this lecture, the ‘a’ subscript, such as TF VIIₐ, indicate the activated form of a factor)
Blood Clotting - Molecular Response

The three pathways that makeup the classical blood coagulation pathway

**Intrinsic**
- surface contact
- XII → XII$_{a}$
- XI → XI$_{a}$
- IX → IX$_{a}$

**Extrinsic**
- TF:VII$_{a}$ → tissue damage

**Common**
- prothrombin → thrombin (serine protease)
- fibrinogen → fibrin → stable fibrin clot

**Factors and Proteases**
- XII – Hageman factor, a serine protease
- XI – Plasma thromboplastin, antecedent serine protease
- IX – Christmas factor, serine protease
- VII – Stable factor, serine protease
- XIII – Fibrin stabilising factor, a transglutaminase
- PL – Platelet membrane phospholipid
- Ca$^{++}$ – Calcium ions
- TF – Tissue Factor (a = active form)
Blood Clotting - Molecular Response

The three pathways that makeup the classical blood coagulation pathway

**Intrinsic**
- XII → XIIa
- XI → XIa
- IX → IXa
- (VIII, PL, Ca++) → X → Xa → Xa

**Extrinsic**
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Blood Clotting - Molecular Response
Molecular response converges on polymerization of fibrin (resulting from intrinsic and extrinsic pathways) to make the blood clot.
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The intrinsic pathway is also known as the contact activation pathway and the extrinsic pathway is known as the tissue factor pathway (more important).
Blood Clotting - Molecular Response - Initiation Phase
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Blood Clotting - Molecular Response - Initiation Phase

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2. TF-FVIIa, FIXa, Platelet Membrane Phospholipid (PL) and calcium (from the cellular response) inefficiently convert FX to FXa
Blood Clotting - Molecular Response - Initiation Phase

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3. FXₐ, FV, PL, and calcium inefficiently convert prothrombin (zymogen) to a tiny amount of thrombin.
Blood Clotting - Molecular Response - Initiation Phase

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3. FXa, FV, PL, and calcium inefficiently convert prothrombin (zymogen) to a tiny amount of thrombin.
4. Thrombin is key to the amplification phase of the molecular response.
Blood Clotting - Molecular Response - Amplification Phase
The amplification phase of the molecular response requires factors from the intrinsic and extrinsic response.
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Blood Clotting - Hardening of Clot
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Transglutaminase (FXIII<sub>a</sub>)
Blood Clotting - Hardening of Clot

Transglutamininase (FXIII\textsubscript{a})
Blood Clotting - Hardening of Clot

Transglutamininase (FXIII$_a$)
Blood Clotting - Hardening of Clot

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4. Carboxylation of glutamate side chains requires vitamin K
5. Carboxylated glutamate side chains bind calcium
6. Blocking vitamin K action reduces clotting (blood thinner)
Blood Clotting - Summary
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6. Thrombin activates fibrinogen to make fibrin and form the clot.
Hemophilia
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2. Deficiency of FIX produces Hemophilia B (about 1 in 20,000 to 35,000 male births).

3. In 1960, the life expectancy of a hemophiliac was about 11 years. Today, it is over 60.
von Willebrand’s disease
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5. Binds to heparin and helps moderate its action.
6. Binds to collagen
7. Binds to FVIII in the molecular response, playing a protective role for it. In the absence of the von Willebrand factor, FVIII is destroyed.
Vitamin K

Phylloquinone (K$_1$)
Vitamin K
Fat Soluble Vitamin With Roles in Blood Clotting and Bone Health

Phylloquinone (K<sub>1</sub>)
Vitamin K
Fat Soluble Vitamin With Roles in Blood Clotting and Bone Health
Stored in Fat Tissue

Phylloquinone (K₁)
Vitamin K
Fat Soluble Vitamin With Roles in Blood Clotting and Bone Health
Stored in Fat Tissue
Most Abundant in Green Leafy Vegetables - Kale, Spinach, Collards

Phylloquinone (K₁)
**Vitamin K**

Fat Soluble Vitamin With Roles in Blood Clotting and Bone Health

Stored in Fat Tissue

Most Abundant in Green Leafy Vegetables - Kale, Spinach, Collards

Stable in Air. Decomposes in Sunlight

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Multiple Forms

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Multiple Forms
Vitamin K-related Modifications Facilitate Calcium Binding by Target Proteins

[Chemical structure of Phylloquinone (K₁)]
**Vitamin K**

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Absence of Vitamin K Leads to Uncontrolled Bleeding

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Vitamin K-related Modifications Facilitate Calcium Binding by Target Proteins
Absence of Vitamin K Leads to Uncontrolled Bleeding
Deficiency Rare in Healthy Adults
Required for Bone Formation

Phylloquinone (K₁)
Vitamin K
Vitamin K

Vitamin K is a Group of Molecules
Vitamin K

Vitamin K is a Group of Molecules
Kₑ - Phylloquinone - Electron Acceptor in Plants (Photosystem I)
Vitamin K is a Group of Molecules

$K_1$ - Phylloquinone - Electron Acceptor in Plants (Photosystem I)
Vitamin K

Vitamin K is a Group of Molecules
K₁ - Phylloquinone - Electron Acceptor in Plants (Photosystem I)
Found in Leaves of Green Plants

K₁
MK-4
MK-
Vitamin K

Vitamin K is a Group of Molecules
K₁ - Phylloquinone - Electron Acceptor in Plants (Photosystem I)
Found in Leaves of Green Plants
Involved in Carboxylation of Glutamates of Blood Clotting Factors II, VII, IX, X
Vitamin K

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\[ \text{K1} \]
\[ \text{MK-4} \]
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Vitamin K

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K₂ - Menaquinone-n - A Group of Compounds Differing in Number of Isoprenes

\[
\text{Menaquinone-n (K}_2\text{)}
\]
Vitamin K

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K₂ - Menaquinone-n - A Group of Compounds Differing in Number of Isoprenes
  MK-4 and MK-7 are Subtypes of K₂

![Menaquinone-n (K₂)](image-url)
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  MK-4 and MK-7 are Subtypes of K₂
  As Involved in Glutamate Carboxylations as K₁

Menaquinone-n (K₂)
Vitamin K
Vitamin K

Needed for Carboxylation of Proteins

Vitamin K

\[
\text{O}_2 + \text{CO}_2 \rightarrow \text{H}_2\text{O} + \text{H}^+ \]

Glutamate Carboxylase

\[
\text{Ca}^{++} \quad \text{COO}^- - \text{OOC} \quad \text{H}^+ \quad \text{R}_2 \quad \text{N} \quad \text{H} \quad \text{R}_1
\]

γ-carboxyglutamate

Vitamin K

Vitamin K Epoxide
Vitamin K

Warfarin Blocks Vitamin K Recycling
Warfarin blocks vitamin K recycling, which must be recycled.
Vitamin K Epoxide

Vitamin K Epoxide Reductase

H₂O

Vitamin K

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Vitamin K is Important for Bone Health
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  Periostin - Involved in Cell Migration, Bone Development,
Blood Thinning - Aspirin
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Inhibits synthesis of prostaglandins
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Prostaglandins are precursors of thromboxane A2
Blood Thinning - Aspirin

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Prostaglandins are precursors of thromboxane A2

Thromboxane A₂ helps make platelets “sticky” in cellular response
Clot Dissolving - Plasmin
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Blue arrows activate
Red arrows inhibit

- Tissue plasminogen activator (tPA)
- Plasminogen activator inhibitor 1 & 2
- Urokinase
- Factor Xla, XIIa Kallikrein
- α2-antiplasmin
- α2-macroglobulin
- Fibrin
- Plasmin
- Fibrin degradation products
- Thrombin

Thrombin-activatable fibrinolysis inhibitor
Clot Dissolving - Plasmin

Blue arrows activate
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Tissue plasminogen activator (tPA)

Plasminogen activator inhibitor 1 & 2

Urokinase

PLASMIN

PLASMINOGEN

Factor XIa, XIIa, Kallikrein

α2-antiplasmin

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FIBRIN

FIBRIN DEGRADATION PRODUCTS

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FIBRIN DEGRADATION PRODUCTS

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Thrombin-activatable fibrinolysis inhibitor

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Red arrows inhibit
Plasmin
Plasmin

Serine protease
**Plasmin**

Serine protease

Cleaves fibrin clots, fibronectin, thrombospondin, laminin, and the von Willebrand factor
Plasmin

Serine protease
Cleaves fibrin clots, fibronectin, thrombospondin, laminin, and the von Willebrand factor
Activates collagenases by cleavage also
Metabolic Melody
Thank Goodness My Blood is Clotting
(to the tune of "Don't Sleep in the Subway Darling")
Copyright © Kevin Ahern

I’m feeling so sad
‘Cuz I cut . . . . myself bad
Now I’m all worried ‘bout . . . . consequences

It’s starting to bleed
There’s some clo . . . . sure I need
So the body kicks . . . . in its defenses

It’s happened all so many times before
The blood flows out and then it shuts the door

Thank goodness my blood is clotting
Enmeshing the fibrin chains
Thank goodness my blood is clotting
The zymogens
Are activating and all is well
So I’ll stop bleeding again

The vitamin K’s
Help to . . . . bind to cee-ays
Adding C-O-. . . . O-H to amend things
Um-m-um-um-um-um-um
Thank Goodness My Blood is Clotting
(to the tune of "Don't Sleep in the Subway Darling")
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It hardens and stays
When a glu. . . . taminase
Creates co. . . . valent bonds . . . . for cementing

In just a moment, things are good to go
The clot’s in place and it has stopped the flow

But what about clot dissolving?
Untangling fibrin chains?
This calls for some problem solving
There is a way
Just activate up some t-PA
Get plasmin active in veins

Oh, oh, oh.
And thanks to the dis-enclotting’
As part of repairin’ veins
It’s part of my body’s plotting
The wound is gone
I’m back where I started and
Nothing’s wrong
My blood flow is normal again.