Evolution of the Clotting Cascade

Kalyan Banda MD
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Who am I?

- Born in St. Petersburg, Russia
- Trivial injuries led to life threatening bleeds all of my life
- Usually bleeding from nose, joints, muscle hematomas
- *Nineteen of my great-grandmother’s descendants had the same bleeding abnormality*
- Supposedly revived from near death by an orthodox priest who then became a powerful figure
- Executed by firing squad at age thirteen

Alexei Nikolaevich
The last of the Romanovs
Who am I?

• Born in Mexico City, Mexico
• Serious street car accident ended my dream of becoming a physician
• Began my legendary painting career as an medical illustrator
• Best known for a series of self portraits
• Famously volatile relationship with a fellow painter
• Bedridden from chronic illness, died of a pulmonary embolism
Hemostasis – “stopping the blood”

Phases of hemostasis

• Endothelial injury/formation of the platelet plug
• Propagation of a clot
• Clot termination
• Clot Removal
What Is A Clot?

- Temporary, gelatinous, structural seal, composed of fibrin polymers and blood cells
- Acts as a scaffold for more permanent tissue repair

Key properties of the cascade:
- Fast
- Localized
- Highly regulated
Extrinsic System

Tissue factor

exposure

Factor VII

Factor VIIa

Factor X

Factor V

Factor Xa

Prothrombin

Thrombin

Fibrinogen

thrombin

Fibrin

transglutaminase

Cross-linked fibrin
Intrinsic System

Hæmatology
An Enzyme Cascade in the Blood Clotting Mechanism, and its Function as a Biochemical Amplifier

Surface contact
(1) XII→XIIa  ↓
(2) XI→XIa     ↓
(3) IX→IXa     ↓
(4) VIII→VIIIa ↓
(5) X→Xa       ↓
(6) V→Va?      ↓
(7) II→IIa (Thrombin) ↓
(8) I→Ia (Fibrin)

Waterfall Sequence for Intrinsic Blood Clotting

R G Macfarlane

Earl W. Davie and Oscar D. Ratnoff
**Intrinsic System**

Contact Factors

- prekallikrein
  - HK
  - XIIa
- a-kallikrein
  - Factor XIIa
  - Factor XI
  - Factor IX
  - Factor VIII
  - Factor X
  - Factor V
  - Factor Xa
  - Prothrombin
  - Thrombin
Schematic representation of the coagulation cascade including our improved understanding of the role of the tissue factor (TF) pathway in initiating clotting; interactions between pathways; and the role of thrombin in sustaining the cascade by feedback activation of coagulation factors.

HK: high-molecular-weight kininogen; PK: prekallikrein; PL: phospholipid.

Modern View Of Coagulation

Role of multicomponent complexes

Extrinsic X-ase

Intrinsic X-ase

Prothrombinase

Slide courtesy: Barbara Konkle
A Fulminating Cascade!

http://imgur.com/gallery/cEKvA82
# Kinds Of Proteins Involved In Blood Clotting

<table>
<thead>
<tr>
<th>(Pro)Enzymes</th>
<th>Cofactors</th>
<th>Structural</th>
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<tbody>
<tr>
<td>Prothrombin</td>
<td>Thrombomdulin</td>
<td>Fibrinogen</td>
</tr>
<tr>
<td>Factor VII</td>
<td>Tissue factor</td>
<td></td>
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<tr>
<td>Factor IX</td>
<td>Factor VIII</td>
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<tr>
<td>Factor X</td>
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<td>Protein C</td>
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<td>Factor XI</td>
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<td>Factor XII</td>
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<td>Factor XIII</td>
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<tr>
<td>Prekallikrien</td>
<td>Kininogen</td>
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</tbody>
</table>
Common Domains In Vitamin K Dependent Factors

Factor VII

Remarkably similar tertiary structures
How Do Complex Systems With Interdependent Parts Evolve?
The ‘Irreducible Complexity’ Of The Clotting Cascade

“If it could be demonstrated that any complex organ existed, which could not possibly have been formed by numerous, successive, slight modifications, my theory would absolutely break down. But I can find no such case.”

- Charles Darwin, The Origin of Species
Milestones in Vertebrate evolution

Invertebrates

First vertebrates

Russell Doolittle, The Evolution of Vertebrate Blood Clotting
Clotting Cascade In Lampreys

Missing Factor VIII, IX, and contact factors

Russell Doolittle, The Evolution of Vertebrate Blood Clotting
Clotting Cascade in Bony Fish

No contact factors. VIII and IX invented – where did they come from?

Russell Doolittle, The Evolution of Vertebrate Blood Clotting
Evolution By Gene Duplication

https://commons.wikimedia.org/wiki/User:Veryhuman
Evolution By Gene Duplication
Introducing Complexity

- B → B*
- A → A*
- Fibrinogen → Fibrin
- Tissue factor

Introducing Complexity
Four Stages Of Evolution Of The Clotting Cascade

Russell Doolittle, The Evolution of Vertebrate Blood Clotting
Model Of Evolution Of Clotting Factors

Nature is a tinkerer, not an inventor
- Francois Jacob

Russell Doolittle, The Evolution of Vertebrate Blood Clotting
Fibrinogen Like Peptide Present in Protochordates

Russell Doolittle, The Evolution of Vertebrate Blood Clotting
Sequence Of Events

Russell Doolittle, The Evolution of Vertebrate Blood Clotting
Summary

• Clotting cascade has numerous components
• Mediated by multicomponent membrane complexes
• First seen in ‘jawless’ fish in vertebrates
• Increasingly complex with time
• Not ‘irreducibly’ complex
• New proteins come from old proteins
Acknowledgements

• Dr. Barbara Konkle
That’s all folks!