Coagulation and Anti-coagulation

√ Physical Process of Clotting
√ Chemical Process of Clotting
   Fibrin formation, Extrinsic and Intrinsic pathways, Amplification, Activation of Enzymes, Clot Localization
√ Inhibitors of Clotting
   Anti-platelets, anti-coagulants
√ Antithrombin
√ Heparin, Low molecular weight heparins, Heparin Pentasaccharide
   Structure, properties, biochemical mechanism
√ Heparin mimics
Scanning Electron Micrograph of a Clot
Physical Process of Clotting

1. injured tissue
2. exposure of subendothelial cells
3. vasoconstriction
4. blood
5. subendothelial cells
6. platelets
7. platelets adhere to exposed cells
8. platelets aggregate and form a "plug"
The Chemical Process of Clotting

Note:
- IXa and VIIIa work together to convert X into Xa.
- Xa and Va work together to convert II into IIa.
- IIa works on a number of steps.
- HMWK and TF are initiation points
- CLOT is the end point
Important Characteristics of Clotting Cascade

- Activation of Enzymes
- Amplification
- Clot Localization
Important Characteristics of Clotting Cascade

√ Activation of Enzymes

Prothrombin

fXa (Arg^{323}-Ile^{324})

Ser^{562}

fXa (Arg^{274}-Thr^{275})

PL, Ca^{2+}

fXa, Va

Thrombin

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Important Characteristics of Clotting Cascade

√ Amplification

A → E₁ → E₂ → C
D → E₃ → E₄ → F

A → E₁ → B
C → E₂
X

D → E₃ → Y
F → E₄ → G
Regulation of Clotting

√ Natural Anticoagulants
   Antithrombin, Tissue Factor Pathway Inhibitor, Protein C

√ Natural Products as Anticoagulant Drugs
   Heparin-based anticoagulants
   Coumarin-based anticoagulants
   Tick anticoagulant peptide
Heparin and Low molecular weight heparins

Structure and sequence

polymeric structure of heparin

β-D-glucosamine

α-L-iduronic acid

β-D-glucuronic acid

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Pentasaccharide

\[ \text{Pentasaccharide} \]

\[
\begin{align*}
\text{CH}_2\text{OSO}_3^- & \quad \text{COO}^- & \quad \text{CH}_2\text{OSO}_3^- & \quad \text{CH}_2\text{OSO}_3^- \\
\text{OH} & \quad \text{O} & \quad \text{OH} & \quad \text{OH} & \quad \text{O} & \quad \text{OH} & \quad \text{OH} & \quad \text{O} & \quad \text{OH}
\end{align*}
\]
Structure of Antithrombin - Pentasaccharide Complex

A)

B)

helix D

helix A

helix P

RCL
Biochemical Mechanism of Heparin Action

\[ \text{AT} + \text{H} \rightleftharpoons \text{AT:H} \]

\[ \text{AT-E} + \text{H} \]

Accelerated Inactivation of Factor Xa and Thrombin

Rate Constant (M\(^{-1}\)s\(^{-1}\))

- Thrombin
- Factor Xa

Antithrombin alone
Antithrombin + Heparin
Antithrombin alone
Antithrombin + Heparin
Designing Heparin Mimics

√ Binding in the Pentasaccharide Binding Site

√ Binding in the Extended Heparin Binding Site

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