The Physiology and Pathology of Coagulation Factor XI

Dr. David Gailani

Discovery of Factor XI

- 1953 - Robert Rosenthal and coworkers characterized a bleeding disorder in two sisters and their uncle.
- As in hemophilia, the plasma clotting time (similar to the partial thromboplastin time [PTT]) was prolonged, while the prothrombin time and bleeding time were normal. There was no evidence of an inhibitory anticoagulant.
- Unlike hemophilia, bleeding was relatively mild, primarily occurring with tooth extraction, and males and females were affected.
- Mixing plasma from these patients with plasma from patients with "true" hemophilia (factor VIII deficiency), or the clinically similar disorder "Christmas disease" (factor IX deficiency), corrected the prolonged clotting time.
- Based on these observations, a third plasma factor, tentatively named plasma thromboplastin antecedent (PTA), was proposed that, when missing, could confer a "hemophilic-like" disorder.
- Congenital deficiency of PTA - Rosenthal syndrome or hemophilia C.
- The plasma factor missing in congenital PTA deficiency was designated factor XI.

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Thrombin Generation in Platelet Rich Plasma

Fibrin Clot Resistance to Fibrinolysis
Microtiter Plate Assay

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**Physiology of Factor XI**

- Classical intrinsic pathway (factor IX activation by factor XIa) is probably not a mechanism for initiation of fibrin formation in vivo.
- Factor XI is now thought to function in sustaining factor IX activation, and ultimately thrombin generation after initiation of fibrin clot formation.
- The physiologic mechanism for factor XI activation is uncertain, but thrombin-mediated activation on the platelet surface is a possibility.
- Sustained thrombin production through factor XIa and factor IX may be required in areas where tissue factor is limiting, or for maintaining fibrin integrity in tissues with high fibrinolytic activity.
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Bleeding in Factor XI Deficiency

- 54 families
- 249 individuals
- 128 partial deficiency
- 45/128 (35%) bleed

Bleeders vs. Non-bleeders

Type II and III Mutations

<table>
<thead>
<tr>
<th>Patient Genotype</th>
<th># of Subjects</th>
<th>Factor XIc (% normal)</th>
<th>aPTT (seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II / II</td>
<td>16</td>
<td>1.2 ± 0.5</td>
<td>108 ± 18</td>
</tr>
<tr>
<td>II / III</td>
<td>23</td>
<td>3.3 ± 1.6</td>
<td>85 ± 22</td>
</tr>
<tr>
<td>III / III</td>
<td>13</td>
<td>9.7 ± 3.8</td>
<td>67 ± 18</td>
</tr>
<tr>
<td>II / WT</td>
<td>25</td>
<td>52 ± 16</td>
<td>39 ± 7.4</td>
</tr>
<tr>
<td>III / WT</td>
<td>22</td>
<td>67 ± 24</td>
<td>36 ± 4.4</td>
</tr>
<tr>
<td>Controls</td>
<td>58</td>
<td>113 ± 30</td>
<td>ND</td>
</tr>
</tbody>
</table>

Genotype
- Type II
- Type III

Other surgical procedures:
- Tonsillectomy
- Nasopharynx
- Urinary tract

Surgical procedures:
- Tooth Extraction
- Circumcision

- 12/16 (75%)
- 8/38 (21%)
- 26/40 (65%)
- 1/22 (4.5%)

* procedures with bleeding/glutaraldehyde procedures (no. of patients)

After McMullen et al., Biochemistry 2056-2060; 1991

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Factor XI Deficiency Type II

<table>
<thead>
<tr>
<th></th>
<th>Wild type</th>
<th>Heterozygote</th>
<th>Homozygote</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity</td>
<td>100%</td>
<td>50%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Antigen</td>
<td>100%</td>
<td>50%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Factor XI A4 Domain Mutations

Factor XI Deficiency Types II and III Mutations

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Factor XI Deficiency

- 125 patients from 80 kindreds
- 96 Jewish patients (70 kindreds), 29 non-Jewish patients (10 kindreds)
- 78 homozygotes, 47 heterozygotes
- No CRM+ patients

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
<th>Factor XI:C %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homozygotes - Jewish</td>
<td>63</td>
<td>3.5 ± 3.3</td>
</tr>
<tr>
<td>Homozygotes - non-Jewish</td>
<td>15</td>
<td>1.1 ± 0.9</td>
</tr>
<tr>
<td>Heterozygotes - Jewish</td>
<td>33</td>
<td>55.5 ± 17.4</td>
</tr>
<tr>
<td>Heterozygotes - non-Jewish</td>
<td>14</td>
<td>43 ± 10.5</td>
</tr>
</tbody>
</table>


Autosomal Dominant Factor XI Deficiency?

Wild type allele → Wild type peptide

s
Mutant allele → Mutant peptide

s
→ s 25%

→ s 50%

→ s 25%
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Factor XI Deficiency
Dominant Mutations

Classification System for CRM-Factor XI Deficiency

Category 1: mutations that prevent synthesis of the fXI polypeptide (deletions; premature stop codons; splice variants; promoter defects)

Category 2: mutations that result in a defect in protein dimer formation (type II, Nagoya II)

Category 3: mutations that result in peptides that cannot be secreted, but that do form dimers

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Factor XI Deficiency

Summary

- Excessive bleeding in factor XI deficient patients may be influenced by:
  - Factor level
  - Site and type of injury
  - Other coagulation defects or procoagulant factors
- The type II and type III mutations probably follow an autosomal recessive inheritance pattern, with symptoms primarily in those with severe deficiency (homozygotes)
- The dimeric structure of factor XI predicts that dominant negative forms of factor XI deficiency should occur through heterodimer formation
- Dominant negative mutations are likely to be responsible for cases of families with apparent autosomal dominant factor XI deficiency

Factor XI Deficiency

Treatment

- Bleeding in factor XI deficiency is usually trauma or surgery induced and may occur immediately after injury or after several hours delay
- Bleeding, once it occurs, tends to persist in the absence of treatment
- It is recommended that all factor XI deficient patients undergoing surgery receive replacement therapy, regardless of past bleeding history
- The target level for replacement is 10-40% of the normal level prior to surgery, with the goal of maintaining this level for about one week
  - Fresh frozen plasma
  - Factor XI concentrates (thrombosis in 10%)
- Anti-fibrinolytic agents such as tranexamic acid may be used for tooth extraction without plasma replacement
- Replacement therapy is not routinely recommended prior to vaginal delivery or caesarean section (reserve for post-partum hemorrhage)

Factor XI Deficiency

Inhibitors

- Alloantibody factor XI inhibitors may complicate factor replacement in factor XI deficient patients
- A study by Solomon and coworkers in Israel demonstrated that 33% of homozygotes for the type II (Glu117Stop) mutation develop these inhibitors
- Inhibitors were associated with bleeding during surgery
- It may be prudent to identify these patients by DNA analysis, and avoid plasma replacement therapy where possible (anti-fibrinolytic therapy for tooth extraction, for example)
- In bleeding factor XI deficient patients who do not respond to replacement therapy because of inhibitors, recombinant factor VIIa has been used in several cases to stop bleeding
Factor XI and Thrombotic Disease

- Leiden thrombophilia study (Meijers et al., NEJM 2000; 342:696-701) - individuals in the upper 10% of the normal population for factor IX or factor XI levels have a ~2-fold increased risk of venous thromboembolic disease.

- Elevated factor XI levels may increase risk of arterial cerebrovascular thrombotic events (Yang et al., Blood 2005; 106:384a).


- Thrombus formation in tissue factor coated shunts in primates is inhibited by blocking factor XI (Gruber and Hansen, Blood 2003; 102:953-5).

- Factor XI deficiency allows mice with total deficiency of protein C to survive into adulthood (Chan et al., Am J. Pathol. 2001; 158:A797).

Factor IX and Factor XI Deficient Mice

Factor IX null mice - Lin et al., Blood 90:3962-3966; 1997
Factor XI null mice - Gailani et al., Blood Coag. Fibrinol. 8:134-144; 1997

<table>
<thead>
<tr>
<th>Assay</th>
<th>Wild Type</th>
<th>Factor IX</th>
<th>Factor XI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial Thromboplastin Time</td>
<td>25 - 37</td>
<td>55 - 185</td>
<td>55 - 185</td>
</tr>
<tr>
<td>Prothrombin Time (sec)</td>
<td>8 - 12</td>
<td>10 - 12</td>
<td>10 - 12</td>
</tr>
<tr>
<td>Tail Bleeding Time (sec)</td>
<td>265 ± ± ± ±</td>
<td>68 ± ± ± ±</td>
<td>1550 ± ± ± ±</td>
</tr>
</tbody>
</table>

Carotid Artery Occlusion

Ferric Chloride Model

Doppler flow probe

Ferric chloride → Blood flow
Factor XI and Thrombotic Disease

Summary

* Epidemiologic studies in humans indicate that factor XI may contribute to venous and arterial thrombotic disease.
* The procoagulant and anti-fibrinolytic activities of factor XI could contribute to thrombus formation.
* Factor IX deficient mice have a significant bleeding disorder while factor XI deficient mice have little excessive bleeding.
* In a carotid artery thrombosis model, factor XI and factor IX deficiency appear to have comparable protective effects.
* This suggests that the role of factor XI in pathologic thrombus formation differs substantially from its role in normal hemostasis.
* As factor XI deficient patients do not suffer from spontaneous bleeding, therapeutic inhibition of factor XI may be a safe and effective method for treating or preventing thromboembolic disease.