Factor XIIa Cross-Linking of the Marburg Fibrin: Formation of \( \alpha_m\gamma_n \)-Heteromultimers and the \( \alpha \)-Chain–Linked Albumin–\( \gamma \) Complex, and Disturbed Protofibril Assembly Resulting in Acquisition of Plasmin Resistance Relevant to Thrombophilia

By Teruko Sugo, Chizuko Nakamikawa, Mikihiro Takebe, Isao Kohno, Rudorf Egbring, and Michio Matsuda

The truncated \( \alpha \)-chain of fibrinogen Marburg is partly linked with albumin by a disulfide bond. Based on the recovery of the first six amino acid residues assigned to the subunit polypeptides of fibrinogen (the \( \alpha \)- and \( \gamma \)-chains) and albumin, 0.33 mol of albumin was estimated to be linked to 1 mol of the Marburg fibrinogen. When the Marburg fibrinogen was clotted with thrombin-factor XIIa-Ca\(^{2+} \), various \( \alpha_m\gamma_n \) heteromultimers were produced, and part of the albumin was cross-linked to the \( \gamma \)-chain. Acid-solubilized Marburg fibrin monomer failed to form large aggregates that could be detected by monitoring turbidity at A350, but it was able to enhance tissue-type plasminogen-activator-catalyzed plasmin generation, though not as avidly as the normal control, indicating that the double-stranded protofibrils had, to some extent, been constructed. This idea seems to be supported by normal factor XIIa-catalyzed cross-linking of the fibrin \( \gamma \)-chains. However, the cross-linked Marburg fibrin, being apparently fragile and translucent, was highly resistant against plasmin, and its subunit components were considerably retained for 48 hours as noted by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Although the exact mechanisms are still unclear, the albumin-incorporated factor XIIa-cross-linked Marburg fibrin seems to have undergone a critical structural alteration(s) to acquire resistance against plasmin. This acquisition of plasmin resistance may be contributed to the postoperative pelvic vein thrombosis and recurrent pulmonary embolism in the patient after caesarian section for her first delivery at the age of 20 years.

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Osaka, Japan), plasminogen (1.0 µmol/mL), and a chromogenic substrate, S-2251 (H-D-valine-leucine-lysine-p-nitroanilide; 0.3 mmol/L). Plasmin generation was monitored by measurement of A405 at 2-minute intervals.

**Factor XIIIa-catalyzed cross-linking of fibrin.** The normal and Marburg fibrinogen (0.5 mg/mL) were clotted at 25°C with α-thrombin (2.5 NIH U/mL) and factor XIII (1.25 U/mL), prepared from pooled plasma essentially described elsewhere, and the activity of factor XIIIa was expressed as amine-incorporating units as described by Lorand et al. In the presence or absence of α2-plasmin inhibitor (α2-PI, 10 µg/mL; Calbiochem-Novabiochem, La Jolla, CA) in 32 µL of TBS containing 5 mmol/L CaCl2. At timed intervals, the reaction was stopped by addition of ethylenediaminetetraacetae-Na2 (EDTA, 2 mmol/L), and the clots were dissolved in the reducing SDS-PAGE solution. For this experiment, α2-PI was labeled with 125I by the Iodobeads method using Na125I essentially according to the manufacturer’s instruction (Pierce, Rockford, IL). After extensive washing with Tris-HCl, pH 7.4 containing 0.5 mol/L NaCl and 0.1 % Tween 20, the radiolabeled clots were subjected to SDS-PAGE followed by autoradiography.

**Plasmin degradation of factor XIIIa–cross-linked fibrin.** Normal and Marburg fibrinogen (0.5 mg/mL) were clotted with 5 NIH U/mL α-thrombin in the presence of 2 U/mL factor XIII, 4 U/mL t-PA, 10 mmol/L plasminogen, and 2 mmol/L CaCl2 at 37°C. At timed intervals, the fibrin clots were dissolved in the reducing SDS-PAGE solution, and 2 µg of proteins per lane was subjected to SDS-PAGE.

**Characterization of factor XIIIa–cross-linked fibrin formed in the presence of α2-PI.** To characterize the Marburg fibrin in relation to clinical thromboembolic diseases, we attempted to analyze the subunit compositions of cross-linked Marburg fibrin formed in the presence of α2-PI. In this experiment, 3 µg of α2-PI was added to 90 µg of fibrinogen, 0.75 NIH U of α-thrombin, and 0.1 U of factor XIII in 300 µL of TBS containing 5 mmol/L CaCl2, and the mixture was allowed to clot for 30 minutes at 37°C. After treatment with 2 mmol/L EDTA, the clots were precipitated by centrifugation for 30 minutes at 12,000 rpm and solubilized with 150 µL of the reducing SDS-PAGE solution. To get precise band separation in SDS-PAGE gels and efficient recovery of the resolved peptides therefrom, as much as 90 µg of proteins was divided in two parts and loaded separately onto 7.5% to 12.5% polyacrylamide gradient gels (2-mm thick and 15-cm long separation gels). The resolved polypeptides were blotted onto Problot membrane (PE; Applied Biosystems) according to the manufacturer’s instructions. After protein staining with Coomassie Brilliant Blue (CBB), amino acid sequence analysis of polypeptide bands was conducted with a protein sequencer, model 476 A (PE; Applied Biosystems). The recovery of individual polypeptides was estimated from the recovery of phenylthiohydantoin (PTH) amino acids in the first five cycles.

**RESULTS**

**Amount of albumin disulfide linked to the Marburg fibrinogen.** Based on the recoveries of the first six amino acid residues assigned to the subunit polypeptides of fibrinogen and albumin, we estimated the amount of albumin linked to fibrinogen in duplicate runs (Table 1). At each cycle, recoveries of only representative amino acid residues for individual polypeptides were used for estimation as indicated by bold letters. The amount of albumin per mole of fibrinogen was calculated to be 0.34 mol for the first run and 0.32 mol for the second run from the ratio of albumin versus 2γ-chains (2γ) representing a dimeric molecule of fibrinogen. Thus, approximately 0.33 mol of albumin was found to be linked to the Marburg fibrinogen by a disulfide bond. Because no free sulphydryl (SH) groups in the Marburg fibrinogen were present, the remainder of unpaired Aax Cys442 was expected to be linked with other substances such as a Cys molecule as reported for fibrinogen Osaka II.

**Polypeptide recovery was calculated from the PTH-amino acid as indicated by bold letters.** Albumin content was estimated from the polypeptide recovery ratio of albumin/2γ.

**Aggregation of acid-solubilized fibrin monomer and facilitation by the polymerizing fibrin monomer of t-PA–catalyzed plasminogen activation.** Although the turbidity of the acid solubilized fibrin monomer failed to increase when monitored by A350 (Fig 1), t-PA–catalyzed plasminogen activation was considerably enhanced in the presence of the polymerizing Marburg fibrin monomer at pH 7.4, though not as avidly as in the control (Fig 2). The result indicated that the Marburg fibrin

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**Table 1. Albumin Content Calculated on the Basis of Amino Acid Sequence Analysis Data**

<table>
<thead>
<tr>
<th>Sequence Identified</th>
<th>Polypeptide</th>
<th>Polypeptide Recovered (pmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assigned</td>
<td>1st Run</td>
</tr>
<tr>
<td>YVATRD</td>
<td>γ</td>
<td>88</td>
</tr>
<tr>
<td>ADSGEG</td>
<td>Aα</td>
<td>65</td>
</tr>
<tr>
<td>DSAGED</td>
<td>Aα</td>
<td>10</td>
</tr>
<tr>
<td>DAHKEV</td>
<td>Albumin</td>
<td>30</td>
</tr>
</tbody>
</table>

Polypeptide recovery was calculated from the PTH-amino acid as indicated by bold letters. Albumin content was estimated from the polypeptide recovery ratio of albumin/2γ.

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**Fig 1.** Polymerization of acid-solubilized fibrin monomer was measured by monitoring A350 nm. The normal and Marburg acid-solubilized des-AB fibrin monomers were prepared as described in Materials and Methods. The reaction was started by dilution of 18.4 µL of fibrin monomer (20 µg) with 500 µL of 25 mmol/L imidazole-buffered saline, pH 7.4, and aggregation was monitored by A350.
monomer molecules were able to form double-stranded prototribrils to a certain extent and that failure to form fibrin gels could largely be attributed to impairment of lateral association of the double-stranded prototribrils, normally mediated by unethered carboxy-terminal regions of the α-chains (αC domains).14

**Factor XIIIa–catalyzed cross-linking of the fibrin γ- and α-chains.** Despite severely altered fibrin monomer aggregation, factor XIIIa–catalyzed cross-linking of the Marburg fibrin γ-chains took place in a normal fashion (Fig 3). The result indicated that the initial double-stranded oligomers had been constructed by the A polymerization site in the E domain and its complementary a site in the D domain.15-17 Besides bands for the γ-dimer, at least two higher-molecular-weight bands containing the γ-chain were present as indicated by numbers 1 and 2 in the patient’s sample. There were also bands denoted by N1 and N2 in the normal sample, apparently corresponding to the two bands for the Marburg fibrin, suggesting that they are heteromultimers composed of the α- and γ-chains. Indeed, this was confirmed by immunoblotting with an antibody recognizing the fibrin α-chain (148-160) segment. Furthermore, formation of high-molecular-weight α-polymers was almost missing in the patient’s cross-linked fibrin, indicating that intramolecular α-chain cross-linking was severely disturbed by the lack of putative amine donor lysine residues at positions 508 and 556 or 562.18

**Plasmic degradation of factor XIIIa–cross-linked fibrin.** The Marburg fibrinogen was hardly clotted by an ordinary amount of thrombin used for the clotting assay, but addition of large amounts of thrombin together with factor XIII and CaCl₂ resulted in formation of solid but fragile gels. Although the fibrin gels thus formed appeared to be fragile and translucent, they were found to be highly resistant against plasmin. In the degradation experiments of t-PA and plasminogen-enriched cross-linked fibrin, the Marburg fibrin clots remained as solid gels for more that 72 hours at 37°C. In fact, their subunit polypeptides were found to be largely preserved even at 48 hours as compared with those of normal control, which had been digested into much smaller segments at 36 hours of incubation as observed by SDS-PAGE (Fig 4).

**Factor XIIIa–catalyzed cross-linking of α₂-PI to the Marburg fibrin.** α₂-PI is known to be cross-linked by factor XIIIa to the fibrin α-chain,19 where Gln2 of α₂-PI serves as amine acceptor and Aε Lys303 of fibrin as amine donor.20 When the cross-linking profile of α₂-PI to the Marburg fibrin was studied by autoradiography, the radiolabel was distributed to a 115-kD band corresponding to a complex of the Marburg α-chain and α₂-PI (band 2) and to higher-molecular-weight proteins (band 4, Mr ≫ 205 × 10³) representing the polymerized Marburg α-chains (Fig 5). The extremely high-molecular-weight protein complex containing α₂-PI in the normal sample (band 5) was, however, missing in the patient’s sample. These results were in agreement with the observation as reported by Sobel et al21 on an in vitro plasma clotting system using the patient’s plasma.

**Behavior of the α-chain–linked albumin on factor XIIIa cross-linking of the Marburg fibrin.** When the Marburg fibrinogen was clotted with thrombin, factor XIIIa, and CaCl₂ and analyzed by immunoblotting using an antialbumin antibody, albumin was found to be distributed to a 115-kD protein complex (Fig 6, band 2 in lane A) as well as a 66-kD protein (Fig 6, band 1 in lane A), suggesting that some of the α-chain–linked albumin molecules had been cross-linked to an about 48-kD polypeptide subunit, ie, either the γ-chain or the truncated α-chain, by serving as substrate for factor XIIIa. The

![Absorbance at 405 nm](image)

**Fig 2.** Facilitation of t-PA–catalyzed activation of plasminogen by polymerizing fibrin monomer. Enhancement of t-PA–catalyzed plasminogen activation by fibrin monomer was measured in 180 µL of the reaction mixture composed of acid-solubilized fibrin monomer (0.2 mmol/L), plasminogen (1.0 µmol/L), t-PA (4 U/mL), and S-2251 (0.3 µmol/L) as described in Materials and Methods. Plasmin generation was measured by monitoring A405 nm at 2-minute intervals.

![Factor XIIIa-catalyzed cross-linking of the fibrin γ- and α-chains](image)

**Fig 3.** Factor XIIIa-catalyzed cross-linking of the fibrin γ-chain analyzed by immunoblotting. Fibrinogen was clotted with thrombin and factor XIII in the presence of CaCl₂. At timed intervals, the clots were subjected to SDS-PAGE followed by immunoblotting using an anti-γ-chain antibody. Besides the γ-dimer, high-molecular-weight polypeptides 1 and 2 were formed in the Marburg fibrin, and their corresponding peptides, N1 and N2, were formed in the normal fibrin. The molecular mass and the positions of the marker proteins are indicated in the left margin.
factor XIIIa–catalyzed cross-linking was also observed regardless of the presence or absence of $\alpha_2$-PI (band 2 in lane B), indicating that the fibrinogen-linked albumin did not share the cross-linking site of $\alpha\alpha_{\text{Lys303}}$ with $\alpha_2$-PI and that the albumin was most likely cross-linked to the $\gamma$-chain but not to the $\alpha$-chain.

To further characterize the factor XIIIa–catalyzed cross-linking of the fibrinogen-linked albumin in the presence of $\alpha_2$-PI, we conducted amino acid analysis of the cross-linked polypeptide complexes resolved by SDS-PAGE under reducing conditions. To obtain enough amounts of polypeptides for sequence analysis of the 115-kD band, an unusually large amount, as much as 90 µg, of the Marburg fibrinogen was used for this study (for details, see Materials and Methods). In SDS-PAGE gels, at least 10 major polypeptide bands were noted (Fig 7, bands 1 to 10 in lane P). In a 115-kD polypeptide band (band 7), we were able to assign albumin and $\alpha_2$-PI in addition to the $\alpha\alpha$- and $\gamma$-chains of fibrin at an approximate molar ratio of 5:3:1:1, based on PTH–amino acids recovered in the first five cycles (Table 2). In other polypeptide bands we could assign the monomeric fibrin subunits, $\alpha_2$-PI and albumin (bands 1 to 4), the $\gamma$-dimer (band 6), or heteromultimers consisting of the $\alpha$- and $\gamma$-chains (bands 8 to 10). Together with approximate molecular sizes of these polypeptide bands, we assigned most probable heteromultimers for the polypeptide complexes (Table 3).

**DISCUSSION**

Fibrinogen Marburg is a unique dysfibrinogen, in that (1) the carboxy-terminal 150 residues are missing due to premature appearance of a stop codon TAA for AAA coding for $\alpha\alpha_{\text{Lys461}}$; (2) because of truncation of the $\alpha\alpha$-chain, $\alpha\alpha\text{Cys442}$ loses its disulfide bond partner $\alpha\alpha\text{Cys472}$, and as a conse-

sequence some $\alpha\alpha\text{Cys442}$ residues are linked with albumin by a disulfide bond. Indeed, the amount of disulfide-linked albumin to the Marburg fibrinogen was calculated to be 0.33 mol per mol of fibrinogen. In other words, one in every three Marburg fibrinogen molecules, or one in every six Marburg $\alpha\alpha$-chains is linked with albumin near its carboxyl-terminus; and (3) the abnormality is associated with concomitant severe bleeding and thromboembolic diseases.8,9

In normal fibrinogen, the two carboxy-terminal $\alpha\alpha$-chain segments ($\alpha\alpha$C domains) interact with each other and associate with the central E domain. On thrombin-cleavage of fibrinopeptides A and B, the $\alpha\alpha$C domains are loosened from the E domain and then untethered, thereby becoming available for association with other $\alpha\alpha$C domains in promoting lateral association of fibrin protofibrils.12 In the Marburg fibrinogen, cleavage of fibrinopeptides A and B proceeded in a normal fashion (profiles not shown), and subsequent fibrin monomer assembly to form...
double-stranded protofibrils may also have progressed nearly normally, as evidenced by normal factor XIIIa–catalyzed cross-linking of the fibrin \( \gamma \)-chain and substantially enhanced t-PA–catalyzed plasminogen activation in the presence of polymerizing Marburg fibrin monomer (Fig 2). The failure for the Marburg fibrin monomer to increase the turbidity as monitored by A350 (Fig 1) could be accounted for by impaired lateral association of fibrin protofibrils. Based on our observation, we presume that the Marburg fibrin monomer molecules are able to bind with one another via the set of A-a polymerization sites and to form double-stranded fibrin protofibrils. These protofibrils are, however, unable to associate laterally in a normal fashion because of the truncated \( \alpha \)-chain lacking the interaction sites assigned to the \( \alpha \)C domain and the presence of the albumin molecule between the strands. In addition, factor XIIa–catalyzed intermolecular ligation of the \( \alpha \)-C domains may not occur because the putative amine donor Lys residues at positions 508 and 556 or 562 are all missing in the Marburg \( \alpha \)-chain. This interpretation may well agree with the delayed \( \alpha \)-polymer formation and lack of the extremely high-molecular-weight \( \alpha \)-polymer complex in the patient’s fibrin in SDS-PAGE gels (data not shown). When the Marburg fibrinogen was clotted with thrombin in the presence of factor XIII, a2-PI, and Ca\(^{2+}\), a variety of heteromultimers composed of \( \alpha \)- and \( \gamma \)-chains, such as \( \alpha \gamma \), \( \alpha \gamma \gamma \), \( \alpha \gamma \gamma \gamma \), and \( \alpha \gamma \gamma \gamma \) (m = 4) were identified (Fig 7 and Table 3). Moreover, some of the \( \alpha \)-chain–linked albumin molecules were found to be cross-linked to an about 48-kD polypeptide, most probably \( \gamma \)-chain, forming a 115-kD polypeptide complex (Fig 6), which was noticeable only when factor XIII was present in the reaction mixture. This complex was not present in the normal sample either. Interestingly, formation of the 115-kD complex was not inhibited by a2-PI (Fig 6A), indicating that the albumin did not share the amine donor A Lys303 with Gln2 of a2-PI. If the albumin is ligated to the \( \alpha \)-chain at another sites, a potential (a2-Plα) trimer can be

| Fig 6. Behavior of fibrinogen-associated albumin in the cross-linked Marburg fibrin as analyzed by immunoblotting. Fibrinogen Marburg was clotted with thrombin and factor XIII in the presence (A) or absence (B) of a2-PI and then subjected to immunoblotting using an anti-human albumin antibody. Band 1 represents noncross-linked albumin, and band 2 represents the cross-linked albumin with a fibrin-derived subunit. |
| Fig 7. Polypeptide compositions of proteins derived from a2-PI–incorporated cross-linked fibrin. Fibrinogen (90 \( \mu \)g) was clotted with thrombin and factor XIII for 30 minutes in the presence of CaCl\(_2\) and a2-PI. The clots were solubilized and subjected to PAGE in two lanes under reducing conditions followed by blotting onto PVDF-membranes as described in Materials and Methods. The protein bands were stained with CBB. Major bands 1-9 in the patient’s sample were separately subjected to amino-terminal sequence analysis. |

| Table 2. Amino Acid Sequence Analysis of the 115-kD Band |

<table>
<thead>
<tr>
<th>Protein Assigned</th>
<th>Amino Acid Recovered at Each Cycle (pmoles of PTH-Amino Acid)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \gamma )-chain</td>
<td>Y V A T R (3.5) (3.8) (4.2) t* (3.9)</td>
</tr>
<tr>
<td>( \alpha )-chain</td>
<td>G P R V (6.4) (6.1) (3.8) (4.2) V</td>
</tr>
<tr>
<td>Albumin</td>
<td>D A H K S (0.9) (1.2) (0.9) (1.2)</td>
</tr>
<tr>
<td>a2-Pl</td>
<td>N Q E Q V (1.2) (1.5) (1.2) (7.4)</td>
</tr>
</tbody>
</table>

*Trace amounts were detected. Abbreviation: nd, not detected.
CROSS-LINKING OF ALBUMIN-BOUND MARBURG FIBRIN

albumin and either Gln398 (or 399) or Lys406 of the α factor XIIIa–mediated cross-link is introduced between the adjacent fibrin molecule in another strand of the protofibril, and closely to the carboxy-terminal segment of the α protofibrils, the albumin-linked total albumin molecules. The transfer efficiency was around 30%, the amount of albumin even after electroblotting. Furthermore, the recovery of amino acids formed in this experiment.

On formation of factor XIIIa–cross-linked double-stranded proteofibrils, the albumin-linked αC domain may be aligned closely to the carboxy-terminal segment of the γ-chain of an adjacent fibrin molecule in another strand of the proteofibril, and a factor XIIIa–mediated cross-link is introduced between the albumin and either Gln398 (or 399) or Lys406 of the γ-chain. Consequently, extraordinary α-chain–albumin–γ-chain bridges are formed in the Marburg fibrin. At this stage of the investigation, we have no evidence for the amine donor-acceptor relationship in this cross-linking. In addition to cross-linking of the albumin to the γ-chain, the α-chain–linked albumin not involved in the cross-linking with the γ-chain must have been integrated into the cross-linked Marburg fibrin clots an affected their tertiary structure. Taking this sort of disoriented cross-linking into consideration, the Marburg cross-linked fibrin must have a distorted tertiary structure, manifesting unusual properties and behaviors. In fact, the cross-linked Marburg fibrin clots appeared to be fragile and less turbid, but they were extremely resistant against plasmin, remaining as solid gels for more than 72 hours and considerably retaining the subunit polypeptides even at 48 hours of incubation at 37°C (Fig 4). In view of the fact that fibrin clots containing thin fibers are digested more slowly by plasmin than intact normal fibrin clots, the Marburg fibrin may also be composed of thin fibers.

Recently, cross-linked and noncross-linked fibrin gels, derived from the two types of congenitally abnormal fibrinogens, were characterized by electron microscopic analyses. The Caracas II fibrin, which has a mutation of Aα Ser434 to Asn linked with an extra oligosaccharide, was shown to have thinner fibers in diameter and large pore or open areas bounded by local fiber networks. The presence of such irregular large pores allows fluids to get through the fibrin gels without any disturbance as evidenced by high permeation rates. This finding seems to account for the absence of thrombosis in the Marburg fibrin.

At this stage, our study is still incomplete, but pieces of information provided in this study may partly account for the unique Marburg fibrin clot structure and behaviors relevant to concomitant bleeding and thromboembolic diseases observed in this patient.

ACKNOWLEDGMENT

We thank Michiko Takano for her expert secretarial assistance.

REFERENCES


Table 3. Polypeptide Complexes in the Reduced Factor XIIIa-cross-linked Fibrin

<table>
<thead>
<tr>
<th>Band No.</th>
<th>Mr (×10^3)</th>
<th>Ratio of Polypeptides</th>
<th>Assigned Polypeptide Complex</th>
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<tbody>
<tr>
<td>1</td>
<td>49.5</td>
<td>α</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>52</td>
<td>β</td>
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<td>3</td>
<td>66</td>
<td>γ</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>68</td>
<td>αζ-PI</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>84</td>
<td>αζ-γ</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>95</td>
<td>γζ</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>115</td>
<td>αζ-αζ-PI, γζ; Albζγ</td>
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</tr>
<tr>
<td>8</td>
<td>235</td>
<td>αγζ</td>
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</tr>
<tr>
<td>9</td>
<td>258</td>
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</tr>
<tr>
<td>10</td>
<td>&gt;440</td>
<td>mζ; mζγ</td>
<td></td>
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</tbody>
</table>

Abbreviation: Mr, relative molecular mass.
†Ratio of polypeptide complexes; αζ-αζ-PI, γζ, Albζγ; 1:1:2.
§m, positive integral number, m = 4.

Formed, but this sort of trimolecular complex was not identified in this experiment.
17. Laudano AP, Doolittle RF: Studies on synthetic peptides that bind to fibrinogen and prevent fibrin polymerization. Structural requirements, number of binding sites, and species differences. Biochemistry 19:1013, 1980
Factor XIIIa Cross-Linking of the Marburg Fibrin: Formation of $\alpha_m$-$\gamma_n$ -Heteromultimers and the $\alpha$-Chain–Linked Albumin-$\gamma$ Complex, and Disturbed Protofibril Assembly Resulting in Acquisition of Plasmin Resistance Relevant to Thrombophilia

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