Examining Thrombin Hydrolysis of the Factor XIII Activation Peptide Segment Leads to a Proposal for Explaining the Cardioprotective Effects Observed with the Factor XIII V34L Mutation*

Toni A. Trumbo and Muriel C. Maurer†

From the Department of Chemistry, University of Louisville, Louisville, Kentucky 40292

In the blood coagulation cascade, thrombin cleaves fibrinopeptides A and B from fibrinogen revealing sites for fibrin polymerization that lead to insoluble clot formation. Factor XIII stabilizes this clot by catalyzing the formation of intermolecular cross-links in the fibrin network. Thrombin activates the Factor XIII a2 dimer by cleaving the Factor XIII activation peptide segment at the Arg57-Gly58 peptide bond. Using a high performance liquid chromatography assay, the kinetic constants $K_m$, $k_{cat}$, and $k_{cat}/K_m$ were determined for thrombin hydrolysis of fibrinogen Aα-(7–20), Factor XIII activation peptide-(28–41), and Factor XIII activation peptide-(28–41) with a Val44 to Leu substitution. This Val to Leu mutation has been correlated with protection from myocardial infarction. In the absence of fibrin, the Factor XIII activation peptide-(28–41) exhibits a 10-fold lower $k_{cat}/K_m$ value than fibrinogen Aα-(7–20). With the Factor XIII V34L mutation, decreases in $k_{cat}$ and increases in $k_{cat}/K_m$ produce a 6-fold increase in $k_{cat}/K_m$, relative to the wild-type Factor XIII sequence. A review of the x-ray crystal structures of known substrates and inhibitors of thrombin leads to a hypothesis that the new Leu generates a peptide with more extensive interactions with the surface of thrombin. As a result, the Factor XIII V34L is proposed to be susceptible to wasteful conversion ofzymogen to activated enzyme. Premature depletion may provide cardioprotective effects.

Fibrinogen is composed of three chains Aα, Bβ, and γ arranged into the dimer (AαBβγ)$_2$. In blood coagulation, the serine protease thrombin cleaves the N-terminal portions of the Aα and Bβ chains. For the Aα chain, cleavage occurs at the Arg16-Gly17 peptide bond and fibrinopeptide A (FpA) is released; whereas, for the Bβ chain, cleavage occurs at the Arg14-Gly15 peptide bond and fibrinopeptide B (FpB) is released. Removal of the fibrinopeptides leads to exposure of fibrin polymerization sites that react to form an insoluble blood clot (reviewed in Ref. 1).

Activated Factor XIII helps stabilize this clot structure by catalyzing the formation of intermolecular $\gamma$-glutamyl-ε-lysine cross-links in the fibrin network and in fibrin-enzyme complexes. Factor XIII is a member of a family of enzymes known as transglutaminases that have a catalytic triad, similar to cysteine proteases, composed of amino acids Cys$^{214}$, His$^{273}$, and Asp$^{306}$. In plasma, Factor XIII is expressed as a zymogen of the form a2b2. In the presence of thrombin and calcium, the a2 unit is released and activated. By contrast, platelet Factor XIII is expressed as the zymogen a2 unit (reviewed in Ref. 2).

The Factor XIII a2 dimer contains in the N-terminal portion of each monomer a sequence known as the activation peptide (3, 4). Each activation peptide segment crosses the dimer interface and extends over the catalytic site of the opposing Factor XIII a subunit. Cleavage of the activation peptide segments by thrombin at the Arg37-Gly58 peptide bond aids in exposure of the Factor XIII active site residues. X-ray crystallography on thrombin-cleaved Factor XIII indicates that the activation peptides do not immediately dissociate following cleavage (4). The activation of plasma Factor XIII a2b2 by thrombin is accelerated in the presence of fibrin-I (5–7) resulting in an 80-fold increase in the $k_{cat}/K_m$ value for this reaction. A segment of fibrin-I is known to bind at thrombin anion-exosite I, whereas other separate segments of fibrin-I are hypothesized to bind to Factor XIII.

Within the Factor XIII activation peptide segment, there is a stretch of amino acids that contains features reminiscent of several diverse agents that interact with thrombin. Table I shows sequences for Fibrinogen Aα (amino acids 7–20) (Fbg Aα-(7–20)), Factor XIII activation peptide (aa 28–41) (FXIII AP-(28–41)), n-Phe-Pro-Arg-chloromethylketone (PPACK), and thrombin receptor (aa 32–45) (PAR1-(32–45)). In each peptide, there is an Arg residue at the P1 position$^5$ that binds within the catalytic cleft of thrombin forming a salt bridge with thrombin amino acid$^3$ Asp$^{189}$ FXIII AP-(28–41), PAR1-(32–45), and PPACK each contain a proline at the P2 position. X-ray

---

* This work was supported by a research grant from the University of Louisville Research Initiation Grant program. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

† To whom correspondence should be addressed. Tel.: 502-825-7008; Fax: 502-852-8149; E-mail: muriel.maurer@louisville.edu.

‡ The abbreviations used are: FpA, fibrinopeptide A; FpB, fibrinopeptide B; Fbg Aα-(7–20), fibrinogen Aα amino acids 7–20; FXIII AP-(28–41), Factor XIII activation peptide amino acids 28–41; FXIII AP-(28–41) V34L, Factor XIII activation peptide mutant Val44 to Leu amino acids 28–41; Fbg Aα-(7–16), fibrinogen Aα amino acids 7–16; FXIII AP-(28–37), Factor XIII activation peptide amino acids 28–37; FXIII AP-(28–37) V34L, Factor XIII activation peptide mutant V34L amino acids 28–33; PPACK, n-Phe-Pro-Arg-chloromethylketone; PAR1, protease-activated receptor 1, a thrombin receptor; PAR1-(32–45), thrombin receptor amino acids 32–45; HPLC, high performance liquid chromatography.

Gly$^{15}$ peptide bond and fibrinopeptide B (FpB) is released.

---

The P nomenclature system (..., P$_n$, P$_{n-1}$, P$_{n-2}$, P$_{n-3}$,...) is used to assign the individual amino acid positions on the substrate peptides (8). The P$_1$P$_2$P$_3$P$_4$... peptide bond becomes hydrolyzed by the enzyme. The peptide amino acids to the left of the cleavage site are labeled P$_2$, P$_3$, P$_4$, etc. whereas those to the right of the cleavage site are labeled P$_2$, P$_3$, P$_4$, etc. The amino acids of thrombin are numbered relative to their topological similarities with chymotrypsinogen (9). Insertion residues are defined using an alphabetical nomenclature (for example, Trp$^{102}$ corresponds to the fourth residue inserted at position 60).
crystal studies of PAR1-(32–45) and PPPACK reveal that thrombin contains a hydrophobic surface that can accommodate this proline (9, 10). Fbg Aα(7–20), by contrast, contains a Val at the P2 position instead of the Pro. The Phe at the P3 position, however, is proposed to compensate for the absence of the Pro. This Phe has been shown by x-ray crystallography (11) and NMR (12–14) studies to participate in a multiple turn conformation that brings this aromatic residue in close proximity to the thrombin cleavage site Fbg Aα Arg-Gly. The FXIII AP-(28–41) segment contains a Val at the P3 position instead of the Phe seen with Fbg Aα(7–20). The role that Val plays in anchoring the activation segment on to the surface of thrombin is not known.

A mutation within the Factor XIII AP segment, Val34 to a Leu (V34L), has been correlated with protection against myocardial infarction (15–18). This protection may be mediated through the formation of weaker fibrin structures. In contrast, a tendency to form rigid fibrin networks has been reported in men who have experienced an episode of myocardial infarction at an early age (19). In addition to its possible role in minimizing myocardial infarction, the Factor XIII V34L mutation has also been correlated with protection against venous thromboembolism (20, 21) and increased susceptibility to cerebrovascular disease (22).

Factor XIII V34L is a common polymorphism estimated to occur in 20–25% of the Caucasian population (23–25). The characteristics and prevalence of Factor XIII V34L have been examined in different ethnic groups including Finnish, Russian, German, Japanese, and Native American Pima (23–25). A G to T point mutation in codon 34, exon 2 of the Factor XIII a subunit gene, is responsible for the Val (GTG) to Leu (TTG) change. The beneficial effects of the V34L mutation are negated by the presence of additional hemostatic risk factors such as increased plasminogen activator inhibitor-1, decreased plasmin, and increased tissue plasminogen activator (17). These agents compete for ability to maintain or lyse the fibrin clots. Possible explanations for how V34L protects against myocardial infarction include the following: 1) the mutation hinders activation of Factor XIII a2, thus slowing down initiation of fibrin cross-linking, or 2) the mutation accelerates activation of the Factor XIII a2 before sufficient fibrin is produced and as a result leads to early depletion of usable levels of Factor XIII.

To aid in elucidating the source of the cardioprotective effects of Factor XIII V34L, a kinetic study was initiated. An HPLC result leads to early depletion of usable levels of Factor XIII. A mutation within the Factor XIII Activation Peptide (FXIII AP-(28–41)) and the native Factor XIII Activation Peptide V34L to be 1470.8, 1521.88, and 1535.95, respectively. The final thrombin-containing mixture was desalted on Amersham Pharmacia Biotech PD-10 columns and then purified on a Amersham Pharmacia Biotech Mono S cation exchange column (HR 5/5) using a Waters HPLC system (model 600 controller and pump system, Rhoodyne manual injector, and a 2447 dual λ absorbance detector). The pooled thrombin solution was subjected to ultrafiltration. The final concentration of protein was determined by using an extinction coefficient, ε19.5 = 19.5 at 280 nm (27).

For this project, bovine thrombin was used as the enzyme and the synthetic substrate peptides were based on human sequences. These complexes were prepared so that a direct comparison could be made with previously published HPLC kinetic results (28–30) and NMR/x-ray studies (11–14) on thrombin-ligand complexes. Thrombin exhibits a high conservation of sequence between human and bovine forms (31). There are no differences in the residues involving the active site, the thrombin β-insertion loop (also the Tprloop), or the allosteric Na+–binding site. The minor differences that do exist between species are not anticipated to interfere with interactions of the substrate peptides at the thrombin active site surface (32).

**Materials—**Bovine plasma barium citrate eluate, bovine Fibrinogen, and Echis carinatus snake venom were purchased from Sigma. HPLC grade acetonitrile, trifluoroacetic acid, Trizma (Tris base), NaCl, PEG 8000, and phosphoric acid were purchased from Fisher and Sigma.

**Experimental Procedures—**Bovine plasma barium citrate eluate containing prothrombin was activated with E. carinatus snake venom. The resultant thrombin-containing mixture was desalted on Amersham Pharmacia Biotech Mono S cation exchange column (HR 5/5) using a Waters HPLC system (model 600 controller and pump system, Rhoodyne manual injector, and a 2447 dual λ absorbance detector). The pooled thrombin solution was subjected to ultrafiltration. The final concentration of protein was determined by using an extinction coefficient, ε19.5 = 19.5 at 280 nm (27).

**Kinetic—**Experimental kinetic methods similar to those of Maurer et al. (26) were employed. Unique features of the experimental design are summarized. A solution of peptide and assay buffer (50 mM H3PO4, 100 mM NaCl, 0.1% PEG, pH 7.4) was warmed to 25 °C in a heat block. Hydrolysis of the individual peptides was then initiated by addition of thrombin into a total assay volume of 250 μl. The final thrombin concentrations were 34, 2.2, and 2.2 nM for hydrolysis of FXIII AP-(28–41), FXIII AP-(28–41) V34L, and Fbg Aα(7–20), respectively. At designated time intervals, 38 μl of reaction mixture were removed and quenched with 7 μl of 12.5% H3PO4. Time points were chosen such that <15% of the total peptide concentration was hydrolyzed. The reaction products were analyzed by reversed-phase HPLC, using a Brownlee Aquapore Oxyt RP-300 C8 cartridge column on a Waters HPLC system containing an autosampler (model 600 controller and pump system, 717plus autosampler, and 2487 dual λ absorbance detector). Absorbance was measured at 205 nm. A linear gradient of 15% CH3CN, 0.09% trifluoroacetic acid in water to 50% CH3CN, 0.09% trifluoroacetic acid in water in 20 min at a flow rate of 1 ml/min was employed for FXIII AP-(28–41) and Fbg Aα(7–20). A linear gradient of 15% CH3CN, 0.09% trifluoroacetic acid in water to 50% CH3CN, 0.09% trifluoroacetic acid in water in 45 min at a flow rate of 1 ml/min was employed for FXIII AP-(28–41), FXIII AP-(28–41) V34L, and Fbg Aα(7–20).
Factor XIII Activation Peptide V34L

**Kinetic constants for the hydrolysis of Arg-Gly bonds by thrombin**

Kinetic constants for thrombin-catalyzed hydrolysis of peptides based on the fibrinogen Aα chain and the Factor XIII activation peptide segment were determined from an HPLC assay as described under "Experimental Procedures." The results shown here represent averages for at least three independent experiments. Kinetic values reported were calculated using nonlinear regression analysis methods.

<table>
<thead>
<tr>
<th>Substrate peptide</th>
<th>$K_m$ ($\mu M$)</th>
<th>$k_{cat}$ ($s^{-1}$)</th>
<th>$k_{cat}/K_m$ ($s^{-1} \mu M^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fbg Aα-(7–20)</td>
<td>312 ± 42</td>
<td>39.3 ± 2.6</td>
<td>0.126 ± 0.019</td>
</tr>
<tr>
<td>FXIII AP-(28–41)</td>
<td>508 ± 44</td>
<td>6.4 ± 0.03</td>
<td>0.013 ± 0.001</td>
</tr>
<tr>
<td>FXIII AP-(28–41) V34L</td>
<td>272 ± 57</td>
<td>18.5 ± 1.6</td>
<td>0.068 ± 0.015</td>
</tr>
<tr>
<td>PAR1-(29–45)</td>
<td>900</td>
<td>35</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* Kinetic values for thrombin-catalyzed hydrolysis of a segment of the thrombin receptor PAR1 were reported by Vu et al. (40).

For thrombin hydrolysis of the mutant segment FXIII AP-(28–41) and FXIII AP-(28–41) V34L (Table II), the $K_m$ value increased 1.6-fold to 508 ± 44 $\mu M$ relative to that of the Fbg Aα-(7–20) and the $k_{cat}/K_m$ value decreased 6-fold to 6.4 ± 0.03 $s^{-1}$. The resultant $k_{cat}/K_m$ value decreased 10-fold from that of Fbg Aα-(7–20) to give a value of 0.013 ± 0.001. It should be noted that to maintain the same extent of hydrolysis within a given time point range more thrombin was needed to carry out the measurements for the Factor XIII activation peptide segment than for the Fibrinogen Aα-like segment. The experimentally determined kinetic parameters indicate there is a substantial difference in the specificity of thrombin for Fbg Aα-(7–20) versus FXIII AP-(28–41).

For thrombin hydrolysis of the mutant segment FXIII AP-(28–41) V34L, nonlinear regression analysis of the data revealed a $K_m$ of 272 ± 57 $\mu M$, a $k_{cat}$ of 18.5 ± 1.6 $s^{-1}$, and a $k_{cat}/K_m$ of 0.068 ± 0.015 $s^{-1} \mu M^{-1}$ (Table II). The substitution of leucine for valine at position 34 has led to the creation of a substrate with improved kinetic properties over those of the wild-type FXIII AP segment. The properties begin to approach those of Fbg Aα-(7–20). Taking the error limits into account, the $K_m$ values for FXIII AP-(28–41) V34L versus Fbg Aα-(7–20) are quite similar (272 ± 57 versus 312 ± 42 $\mu M$). In the presence of the V34L mutation, the $k_{cat}$ value increased for Factor XIII activation peptide cleavage from 6.4 ± 0.03 to 18.5 ± 1.6 $s^{-1}$ and is now approximately half that of Fbg Aα-(7–20).
(39.3 ± 2.6 s⁻¹). Furthermore, the amount of thrombin used to generate the kinetic results for the V34L work was the same as those used for Fbg Acα-(7–20). A review of the \( k_{\text{cat}}/K_m \) values suggests that thrombin exhibits a greater specificity for the V34L mutant sequence than the wild-type sequence. The results reported here, for bovine thrombin in the presence of human Factor XIII AP segments, are consistent with the findings of Kohler et al. (15) on Factor XIII V34L isolated from patients. Preliminary data from their laboratories indicate that lower thrombin levels are required to activate Factor XIII V34L than to activate wild-type Factor XIII.

**DISCUSSION**

The kinetics associated with thrombin hydrolysis of a Fibrinogen Aα-like peptide and two Factor XIII activation peptide segments have been examined. A Val to Leu substitution at position 34 of the Factor XIII activation peptide segment generates a substrate with improved kinetic properties relative to that of the wild-type sequence. A review of the sequence, kinetic, and structural properties of thrombin substrates/inhibitors leads to a proposal for how Factor XIII V34L might promote beneficial cardiovascular effects.

**Analysis of Kinetic Results and Substrate Peptide Amino Acid Sequence**—The peptide substrates analyzed here contain amino acids that only interact with thrombin along a surface surrounding the active site of the enzyme. Work with peptides of this length allows for examination of the influence of individual substrate amino acids on the catalytic properties of thrombin. The human Factor XIII activation peptide segment contains 34VVPR37 at the P4-P1 substrate positions. The strongest benefits for thrombin binding are likely derived from the Pro and Arg residues (33–36). X-ray crystallographic studies (9, 37) on PPACK (\( \beta\)-Phe-Pro-Arg-chloromethylketone) bound to thrombin have shown that the Pro at P2 is positioned to interact with a hydrophobic cage formed by the thrombin side chains of Trp215, Leu298, His297, Tyr60a, and Trp60d. This region is also known as the apolar-binding site.

Thrombin exhibits greater substrate specificity for the Factor XIII activation peptide segment when the 34VVPR37 sequence is converted to 34LVPR37. The presence of the larger hydrocarbon side chain on leucine may promote further interactions with the thrombin surface, allowing for more contact within the apolar-binding site on thrombin. The new leucine may promote the decreases in \( k_m \) relative to the wild-type sequence and, as a result of better interactions with the thrombin surface, the increase in \( k_{\text{cat}} \). Together these changes have allowed the \( k_{\text{cat}}/K_m \) value to increase 6-fold relative to the wild-type sequence.

The Factor XIII V34L mutant sequence 34LVPR37 is similar to the 38LDPR41 of the PAR1 thrombin receptor. However, hydrolysis of a thrombin receptor PAR1 peptide (29PESKAT-NATLDPRSFLK (29)) exhibits a higher \( K_m \) value than both Factor XIII activation peptides (see Table II) (38–40). NMR (41) and x-ray (10) studies suggest the LDPR segment binds along the apolar-binding site but the Asp39 causes electrostatic interference that hinders optimal binding along this thrombin surface (10, 37). The Factor XIII AP segment does not contain an interfering acidic residue, and as a result, FXIII-like peptides targeted to the active site of thrombin serve as better substrates than either PAR1-like peptides.

In contrast to the FXIII- and PAR1-based peptides, the Fbg Acα-(7–20) peptide does not generate beneficial interactions with the surface of thrombin through a proline. In the bound structure, a multiple-turn conformation involving Fbg Ac α Phe8, Leu9, and Val15 provides key sites for interaction with the thrombin apolar-binding site. As a result of this interaction, the non-optimal nature of the Aα chain can be overcome and the sequence can be cleaved effectively. The \( k_{\text{cat}}/K_m \) value for hydrolysis of the Factor XIII AP segment only begins to approach that of Fbg Acα-(7–20) in the presence of the V34L substitution.

The kinetic results obtained with the Factor XIII activation peptides thus provide convincing evidence that a relatively conservative amino acid substitution to the P2 substrate position causes a significant improvement in substrate specificity. An increase in the \( k_{\text{cat}} \) value for hydrolysis of the mutant Factor XIII sequence plays a major role in this change. The different kinetic parameters obtained for hydrolysis of the peptide models therefore help explain the reports that human Factor XIII V34L requires less thrombin for activation than the wild-type Factor XIII (15).

**Proposed Model to Explain the in Vivo Effects of the Factor XIII V34L Mutation**—In nature, the proteins thrombin, fibrin, and plasma Factor XIII function in a triad, with fibrin serving as a cofactor for Factor XIII activation (5, 6). Recent results from Brummel et al. (7) on the extrinsic coagulation pathway of human whole blood suggest that Factor XIII activation and its subsequent cross-linking capabilities occur immediately in response to removal of fibrinopeptide A from fibrinogen. In the presence of the resultant fibrin-I, activation of plasma Factor XIII is accelerated with the \( k_{\text{cat}}/K_m \) for a ternary complex of thrombin, Factor XIII, and fibrin becoming comparable to the \( k_{\text{cat}}/K_m \) for thrombin-fibrinogen interactions. The use of a triad in the enzymatic blood coagulation mechanisms ensures that activated plasma Factor XIII is generated close to its substrates, the linear fibrin monomers, thereby minimizing wasteful generation of the Factor XIII when fibrin levels are low. This sort of strategy allows Factor XIII zymogen levels to remain conserved when substrate is not available (42, 43).

Information from the blood coagulation/anticoagulation cascades may be used to propose why the Factor XIII V34L mutation may exert cardioprotective effects. Individuals bearing this mutation may be capable of producing higher levels of activated plasma Factor XIII than those bearing the wild-type Factor XIII. Furthermore, the Factor XIII V34L may have less of a dependence on fibrin-I to accelerate its activation by thrombin. Thus, the presence of the V34L mutation may lead to wasteful generation of activated Factor XIII. The excess activated Factor XIII a2 subunits may then be susceptible to further proteolysis by thrombin at the secondary Factor XIII cleavage site Lys513-Ser514. Proteolytic enzymes other than thrombin could also be involved in inactivation or degradation processes. As a consequence of the V34L mutation, the ability to promote extensive covalent cross-linking of fibrin and fibrin-enzyme complexes may become diminished prematurely (42–45).

This type of premature depletion of an activated enzyme has also been observed for the conversion of plasminogen to plasmin (46). Plasmin is involved in promoting lysis of the blood clots. If tissue plasminogen activator is employed in the zymogen activation process, a fibrin surface is required, and plasmin is produced in the vicinity of its own substrate (47). By contrast, if streptokinase is employed, the fibrin surface is no longer required (48, 49). Plasmin can be generated at a site distant from fibrin, and the levels of plasmin may become prematurely depleted before this plasmin has an opportunity to reach its target.

In addition to playing a role in Factor XIII activation, the V34L mutation has also been reported to affect the cross-linking activity of this transglutaminase. Work with native and recombinant Factor XIII indicates that the V34L enzyme exhibits a higher specific activity than wild-type enzyme (50, 51). This result suggests that the activation peptide may actually participate in promoting the transglutaminase reaction of Fac-
tor XIII. Somehow this participation is further amplified and/or changed in the presence of the mutant sequence. The activation peptide does not leave immediately following cleavage and is proposed to remain bound until after introduction of Factor XIII substrates (3, 4). In the presence of the V34L mutation, the number and/or type of substrates that can be accommodated by the Factor XIII active site surface and subjected to cross-linking may become altered. Further work on binding of substrates to the intact enzyme is necessary to elucidate the source of the increase in specific activity for the mutant and to correlate this increase with the observed physiological responses. The increase in Factor XIII specific activity may contribute a yet unidentified role in protection against myocardial infarction. Alternatively, the mutation may generate an increased catalytic effect that becomes diminished before its benefits can be realized.

Conclusions—Our kinetic studies reveal that thrombin-catalyzed hydrolysis of a Factor XIII-based activation peptide containing the V34L mutation leads to decreases in $k_{\text{cat}}$ and as a result, increases in $k_{\text{cat}}/K_m$ relative to the wild-type sequence. The Factor XIII sequence V34L is converted to LVPR. The Leu substitution is proposed to make more contacts with the apolar-binding site region on thrombin eventually leading to increases in substrate specificity relative to the wild-type sequence. As a result of these changes, Factor XIII V34L is hypothesized to be susceptible to wasteful conversion of zymogen to activated enzyme. Premature depletion may provide protective effects against cardiovascular disease.

Acknowledgments—We thank T. W. Thannhauser, J.-L. Peng, and R. W. Sherwood of the Cornell Biotechnology Resource Center for synthesis of peptides and quantitative amino acid analysis measurements. We thank A. F. Spatola for generously providing access to his lyophilized peptides and quantitative amino acid analysis measurements. We thank T. W. Thannhauser, J.-L. Peng, and B. Turner for generously providing access to his lyophilized peptides and quantitative amino acid analysis measurements. We thank A. F. Spatola for generously providing access to his lyophilized peptides and quantitative amino acid analysis measurements. We thank T. W. Thannhauser, J.-L. Peng, and B. Turner for generously providing access to his lyophilized peptides and quantitative amino acid analysis measurements. We thank T. W. Thannhauser, J.-L. Peng, and B. Turner for generously providing access to his lyophilized peptides and quantitative amino acid analysis measurements. We thank T. W. Thannhauser, J.-L. Peng, and B. Turner for generously providing access to his lyophilized peptides and quantitative amino acid analysis measurements. We thank T. W. Thannhauser, J.-L. Peng, and B. Turner for generously providing access to his lyophilized peptides and quantitative amino acid analysis measurements. We thank T. W. Thannhauser, J.-L. Peng, and B. Turner for generously providing access to his lyophilized peptides and quantitative amino acid analysis measurements.

REFERENCES

Examining Thrombin Hydrolysis of the Factor XIII Activation Peptide Segment Leads to a Proposal for Explaining the Cardioprotective Effects Observed with the Factor XIII V34L Mutation
Toni A. Trumbo and Muriel C. Maurer

doi: 10.1074/jbc.M000209200 originally published online May 2, 2000

Access the most updated version of this article at doi: 10.1074/jbc.M000209200

Alerts:
- When this article is cited
- When a correction for this article is posted

Click here to choose from all of JBC's e-mail alerts

This article cites 52 references, 11 of which can be accessed free at http://www.jbc.org/content/275/27/20627.full.html#ref-list-1