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Why Do We Want To Know How Factor XII Levels Are Modulated?

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New interest in factor XII has been found due to the fact that its murine knockout animal is protected from arterial thrombosis in several models (1,2). The mechanism(s) for these observations have not been precisely described. However, several investigators have shown that factor XII converting to factor XIIa presumably by autoactivation on surfaces such as platelet polysomes, expressed RNA, exposed vascular collagen, and/or aggregated protein contributes to developing thrombus (3–6). Since factor XII participates in the size of an induced-clot formation it has a role in thrombosis. This activity describes for the first time an in vivo pathophysiologic event contributed to by factor XII/XIIa.

It is known from the observations of Ratnoff and others that factor XII is essential for surface activated blood coagulation reactions (7). Recognition that factor XII initiates test-tube blood coagulations was the basis for the waterfall hypothesis for the blood coagulation system (8). However, factor XII deficient patients do not have a bleeding defect even though their surface-activated blood coagulation tests are prolonged. Thus, factor XII is not a hemostatic protein. The dichotomy of factor XII being needed for normal blood coagulation tests, but not hemostasis has confused this field for decades. Now that it is generally agreed that tissue factor is the physiologic initiator of blood coagulation leading to hemostasis, the contact activation system needs to be redefined (9,10). Contact activation mechanisms explain how common blood coagulations tests like the activated partial thromboplastin time (APTT) or activated coagulation time (ACT) which are performed on millions of patients annually work. The molecular mechanism for factor XII autoactivation still is not known. Factor XII autoactivation at the molecular level occurs by imposing specific orientation and ordering on the adsorbed protein molecules on sum frequency generation vibrational spectroscopy (11). Alternatively, factor XII in vivo may be activated by contact as described above with various biologic substances in developing thrombus or secondary to formed plasma kallikrein, its only known enzyme activator.

The kinetics of factor XII activation by plasma kallikrein ($K_m=11 \mu\text{M}$) is similar to factor XIIa activation of prekallikrein ($K_m=2.4 \mu\text{M}$). However, the K_m of prekallikrein activation in vivo by its endothelial cell membrane expressed serine protease, prolylcarboxypeptidase, is 9 nM (12). These latter kinetic data suggest that physiologic factor XII activation is secondary to plasma kallikrein formation. However, it has yet to be shown if prolylcarboxypeptidase is important for in vivo prekallikrein activation for factor XII activation. Although C1 inhibitor deficient mice have angioedema, indicating higher constitutive bradykinin formation from

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either unregulated plasma kallikrein or factor XIIa, factor XII deficient mice have lower levels of basal plasma bradykinin, indicating factor XII's importance in the peptide's formation (13,14).

The observation that the presence of factor XII contributes to the size of induced thrombus formation indicates that its inhibition may be a pharmacologic target to decrease the extent of thrombosis. Although factor XII deficiency was initially thought to be a risk factor for venous thrombosis, more recent studies indicate that it is not. However, human in vivo studies on the role of factor XII in arterial thrombosis also are not clear. Kanaji *et al.* reported that a polymorphism 46C to T substitution in the 5'-untranslated region of factor XII gene is associated with low translational efficiency and decreased plasma levels (15). This polymorphism may account for the commonly recognized fact that factor XII levels are lower in Asians when compared to Caucasians. An initial report suggested that the homozygous 46TT allele protects from acute coronary syndrome and that lower XII levels may be associated with lower thrombosis risk (16,17). Two other reports suggested that opposite, i.e., the TT genotype is associated with a higher risk of coronary artery disease (18,19). The degree of lowering of factor XII levels by the TT allele is probably insufficient to significantly reduce the amplifying effect of factor XII's autoactivation on developing clot to really influence thrombosis risk (20).

Not much is known how factor XII levels in plasma are regulated. Estrogen therapy increases plasma factor XII levels which are mainly produced in the liver as zymogens. The factor XII gene contains a sequence resembling the consensus estrogen-responsive element (20). The hepatocyte nuclear factor-4 (HNF-4) transcription factor inhibits estrogen induction of factor XII promoter in fibroblasts but not in HepG2 cells where its binding contributes to estrogen induction of the gene (21). HNF-4 null mice exhibit reduced expression of factor XII (22). In the present report of *Thrombosis Research*, Sabater-Lleal et al. contribute to our understanding on what regulates factor XII plasma levels (23). These authors describe two new mutations, a C/G substitution at position -8 and a C/T substitution at position -13 of the factor XII gene that result in decreased expression levels. These mutations interfere with nuclear proteins interacting with the factor XII promoter. This region is in the putative HNF-4 binding site of the factor XII gene promoter. These polymorphisms summated with the 46C/T polymorphism to lower plasma factor XII levels.

What is the physiologic role of factor XII? The answer to this question also is not completely known but new interpretations are coming to this field. In addition to its possible influence on arterial thrombosis, factor XII also may be a growth factor. In the intravascular compartment, factor XII has a multiprotein receptor that consists of the urokinase plasminogen activator receptor, gC1qR, and cytokeratin 1 (24). Factor XII has been recognized as a growth factor leading to ERK1/2 activation (25). Factor XII's artificial and cell binding site has been localized to its fibronectin type II domain which is adjacent to its epidermal growth factor domain, suggesting its growth promoting activities may be mediated by its cell binding site. Since collagen-activated platelets provide sufficient zinc ion to promote factor XII binding to cells and developing clot and collagen exposure is sufficient for its activation in flowing blood, factor XII in the developing thrombosis may also stimulate repair for this injury (6,24–26). An appreciation for the role of factor XII as a growth factor is emerging. This activity may be important for repair after thrombosis or inflammation. Better understanding of factor XII expression and activities should lead to better characterization of thrombus formation and its repair.

Bibliography

1. Renne T, Pozgajova M, Gruner S, Schuh K, Pauer HU, Burfeind P, Gailani D, Nieswandt B. Defective thrombus formation in mice lacking coagulation factor XII. *J Exp Med* 2005;202:271–281. [PubMed: 16009717]
2. Kleinschnitz C, Stoll G, Bendszus M, Schuh K, Pauer HU, Burfeind P, Renne C, Gailani D, Nieswandt B, Renne T. Targeting coagulation factor XII provides protection from pathological thrombosis in cerebral ischemia without interfering with hemostasis. *J Exp Med* 2006;203:513–518. [PubMed: 16533887]
3. Smith SS, Mutch NJ, Baskar D, Rohloff P, Docampo R, Morrissey JH. Polyphosphate modulates blood coagulation and fibrinolysis. *Proc Natl Acad Sci* 2006;103:903–908. [PubMed: 16410357]
4. Kannemeier C, Shibamiya A, Nakazawa F, Trusheim H, Ruppert C, Markart P, Song Y, Tzima E, Kennerknecht E, Niepmann M, von Bruehl M-L, Sedding D, Massberg S, Gunther A, Engelmann B, Preissner KT. Extracellular RNS constitutes a natural procoagulant cofactor in blood coagulation. *Proc Natl Acad Sci* 2007;104:6388–6393. [PubMed: 17405864]
5. Maas C, Govers-Riemslog JWP, Bouma B, Schiks B, Hazenberg BPC, Lokhorst HM, Hammarstrom P, ten Cate H, de Groot PG, Bouma BN, Gebbink MFBG. Misfolded proteins activate factor XII in humans, leading to kallikrein formation without initiating coagulation. *J Clin Invest* 2008;118:3208–3218. [PubMed: 18725990]
6. van der Meijden PEJ, Munnix ICA, Augfer JM, et al. Dual role of collagen in factor XII-dependent thrombus formation. *Blood* 2009;114:881–890. [PubMed: 19372258]
7. Ratnoff OD, Colopy JE. A familial hemorrhagic trait associated with a deficiency of a clot formation fraction of plasma. *J Clin Invest* 1955;34:602–613. [PubMed: 14367514]
8. Davie EW, Ratnoff OD. Waterfall sequence for intrinsic blood coagulation. *Science* 1964;145:1310–1320. [PubMed: 14173416]
9. Rapaport SI, Rao LV. The tissue factor pathway: how it has become a “prima ballerina”. *Thromb Haemost* 1995;74:7–17. [PubMed: 8578528]
10. Gailani D, Broze GJ. Factor XI activation in a revised model of blood coagulation. *Science* 1991;253:909–912. [PubMed: 1652157]
11. Chen X, Wang J, Paszti Z, Wang F, Schrauben JN, Tarabara VV, Schmaier AH, Chen Z. Ordered adsorption of coagulation factor XII on negatively charged polymer surfaces probed by sum frequency generation vibrational spectroscopy. *Anal Bioanal Chem* 2007;388:65–72. [PubMed: 17205260]
12. Shariat-Madar Z, Mahdi F, Schmaier AH. Recombinant prolylcarboxypeptidase activates plasma prekallikrein. *Blood* 2004;103:4554–4561. [PubMed: 14996700]
13. Han ED, MacFarlane RC, Mulligan AN, Scafidi J, Davis AE III. Increased vascular permeability in C1 inhibitor-deficient mice mediated by the bradykinin type 2 receptor. *J Clin Invest* 2002;109:1007–1009. [PubMed: 11956236]
14. Iwaki T, Castellino FJ. Plasma levels of bradykinin are suppressed in factor XII-deficient mice. *Thromb Haemost* 2006;95:1003–1010. [PubMed: 16732380]
15. Kanaji T, Okamura T, Osaki K, Kuroiwa M, Shimoda K, Hamasaki N, Niho Y. A common genetic polymorphism (46 C to T substitution) in the 5'-untranslated region of the coagulation factor XII gene is associated with low translation efficiency and decrease in plasma factor XII levels. *Blood* 1998;91:2010–2014. [PubMed: 9490684]
16. Endler G, Mannhalter C, Sunder-Plassmann H, LaLouschek W, Kapiotis S, Exner M, Jordanova N, Meier S, Kunze F, Wagner O, Huber K. Homozygosity for the C-T polymorphism at nucleotide 46 in the 5' untranslated region of the factor XII gene protects from the development of acute coronary syndrome. *Br J Haematol* 2001;115:1007–1009. [PubMed: 11843842]
17. Soria JM, Almasy L, Souto JC, Bacq D, Buil A, Faure A, Martinez-Marchan E, Mateo J, Borrell M, Stone W, Lathrop M, Fontcuberta J, Blangero J. A quantitative-trait locus in the human factor XII gene influences both plasma factor XII levels and susceptibility to thrombotic disease. *Am J Hum Genet* 2002;70:567–574. [PubMed: 11805911]

18. Zito F, Gordon DO, Rumsley A, McMahon AD, Humphries SE. Association of the factor XII 46C>T polymorphism with the risk of coronary heart disease (CHD) in the WOSCOPS study. *Atherosclerosis* 2002;165:153–158. [PubMed: 12208481]
19. Colhoun HM, Zito F, Chan NN, Rubens MB, Fuller JH, Humphries SE. Activated factor XII levels and factor XII 46C>T genotype in relation to coronary artery calcification in patients with type 1 diabetes and healthy subjects. *Atherosclerosis* 2002;163:363–369. [PubMed: 12052484]
20. Farsetti A, Misiti S, Citarella F, Felici A, Andreoli M, Fantoni A, Sacchi A, Pontecorvi A. Molecular basis of estrogen regulation of Hageman factor XII gene expression. *Endocrinology* 1995;136:5076–5083. [PubMed: 7588244]
21. Farsetti A, Moretti F, Narducci M, Misiti S, Nanni S, Andreoli M, Sacchi A, Pontecorvi A. Orphan receptor hepatocyte nuclear factor-4 antagonizes estrogen receptor α -mediated induction of human coagulation factor XII gene. *Endocrinology* 1998;139:4581–4589. [PubMed: 9794469]
22. Inoue Y, Peter LL, Yim SH, Inoue J, Gonzalez FJ. Role of hepatocyte nuclear factor 4 alpha in control of blood coagulation factor gene expression. *J Mol Med* 2006;84:334–344. [PubMed: 16389552]
23. Sabater-Lleal M, Chillon M, Mordillo C, Martinez A, Gil E, Mateo J, Blangero J, Almasy L, Fontcuberta J, Soria JM. Combined CIS-regulator elements as important mechanism affecting FXII plasma levels. *Thromb Res*. This issue.
24. Mahdi F, Shariat-Madar Z, Figueroa C, Schmaier AH. Factor XII interacts with the multiprotein assembly of urokinase plasminogen activator receptor, gC1qR and cytokeratin 1 on endothelial cell membranes. *Blood* 2002;99:3585–3596. [PubMed: 11986212]
25. Gordon EM, Venkatesan N, Salazar R, et al. Factor XII-induced mitogenesis is mediated via a distinct signal transduction pathway that activates a mitogen-activated protein kinase. *Proc Natl Acad Sci* 1996;93:2174–2179. [PubMed: 8700904]
26. Schmaier AA, Schmaier AH. Thrombosis in flowing blood. *Blood* 2009;114:754–756. [PubMed: 19628716]