

Anniversary Issue Contribution

Factor XI in haemostasis and thrombosis: Past, present and future

Uri Seligsohn

The Amalia Biron Research Institute of Thrombosis and Hemostasis, Chaim Sheba Medical Center, Tel-Hashomer and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

The discipline of haemostasis and thrombosis has set an example, perhaps more than other disciplines of Medicine, in discoveries based on observations of the so called “experiments of nature”. During a relatively short time of 13 years (1947 – 1960), most coagulation factors were identified in patients who presented with a bleeding tendency and were worked up by rather simple laboratory assays. This era of discoveries was followed by the characterization of the biochemical reactions involved in blood coagulation, delineation of the sequence of reactions in the coagulation pathways and more recently by unraveling the molecular genetic aspects of the various coagulation components. The objective of this review is to describe some of the major developments in understanding the role of factor (F)XI in haemostasis and thrombosis that have occurred over more than 50 years of research, and to highlight recent evidence which suggests that FXI deficiency can have an antithrombotic effect.

The early years

Soon after the distinction of haemophilia B (FIX deficiency) from haemophilia A (FVIII deficiency), Rosenthal et al. described in 1953 and 1955 a third haemophilia (FXI deficiency) which was associated with a mild to moderate bleeding tendency (1, 2). The presence of the disorder in two sisters and their maternal uncle was regarded as an indication that it is inherited as an autosomal dominant trait (2). However, a seminal study by Rapaport et al. in 1961 clearly established that transmission of the disorder was autosomal recessive and distinguished between subjects with a major deficiency exhibiting FXI levels of less than 20 U/dl from subjects with a minor deficiency (FXI level 30–60 U/dl) (3). This study as well as others indicated that FXI deficiency is particularly prevalent in Jews. This was indeed proven in 1978 by me in two large surveys of Ashkenazi (European) Jews indicating that the estimated frequency (95% confidence interval) of major FXI deficiency was 0.1 – 0.3% and of minor FXI deficiency 5.5 – 11% (4).

In the classical sequence of the coagulation reactions designed in 1964, FXI was assigned with a role in the initial contact activation phase. It was shown that negatively charged surfaces

trigger activation of FXII, later found to occur in the presence of prekallikrein (PK) and high-molecular-weight kininogen (HK). FXIIa then activates FXI, and FXIa activates FIX leading through additional reactions to thrombin generation. However, this sequence of the so-called intrinsic coagulation pathway was difficult to reconcile with the observations that patients affected by severe deficiencies of FXII, PK or HK did not have a bleeding tendency, whereas FXI-deficient patients did present with an injury-related haemostatic defect. This apparent paradox was resolved in 1991 by the demonstration that thrombin is the physiological activator of FXI (5, 6) bypassing the initial contact induced reactions. These seminal studies lead to the design of a revised scheme of the coagulation pathway in which FXII, PK and HK play no role in physiologic haemostasis, while FXI is important for amplifying thrombin generation following its initial formation by the tissue factor (TF)-FVII pathway (5).

Biochemistry of FXI

FXI is a 160 kDa homodimer in which each 80 kDa monomer comprises 607 residues organized in a heavy chain with four tandem repeats of 90 – 91 residues (apple domains), and a light chain harboring a serine protease (7).

Apple 1 domain contains binding sites for HK forming a FXI:HK complex in the circulation and a thrombin binding site, apple 3 domain bears binding sites for FIX and platelet glycoprotein Ib α , and apple 4 harbors the binding site for FXII (8, 9) and contains the interface between the monomers as recently defined in the FXI crystal structure (10). FXI is activated by thrombin that cleaves an Arg369-Ile370 bond yielding a 47 kDa heavy chain bound by a disulfide bond to a 33 kDa light chain. FXIa activates FIX in the presence of calcium ions by sequential cleavages of Arg146 – Ala147 and Arg180 – Val181 bonds yielding activated FIXa β and an activation peptide.

The FXI gene consists of 15 exons and 14 introns (GenBank M 18295) and is located on chromosome 4q34–35 (11, 12). FXI is produced in the liver and circulates in blood at a concentration of 3–7 μ g/ml.

Correspondence to:
Uri Seligsohn, MD
The Amalia Biron Research Institute of Thrombosis and Hemostasis
Chaim Sheba Medical Center, Tel Hashomer 52621, Israel
Tel.: +972 3 530 2104, Fax: +972 3 535 1568
E-mail: Seligson@sheba.health.gov.il

Received April 4, 2007
Accepted May 21, 2007

Prepublished online June 12, 2007
doi:10.1160/TH07-04-0246

Mutations, founder effects and ethnic distribution

In 1989 the first three mutations causing FXI deficiency were identified in six Jewish patients (13). Two of the three mutations, Glu117X (type II) and Phe283Leu (type III) predominate in Jews; they were found to be harbored by 98% of 295 unrelated patients with severe FXI deficiency (14). The third mutation, type I, is located at the last splice site of the FXI gene and has so far been identified in seven unrelated patients (14). Polymerase chain reaction and restriction analysis for detection of the two common mutations in Jews (15) as well as a series of polymorphisms (16) enabled us to obtain the following information: i) Homozygotes for the Glu117X mutation have a mean FXI level of 0.012 U/ml, homozygotes for the Phe283Leu have a mean FXI level of 0.097 U/ml and compound heterozygotes for Glu117X and Phe283Leu have a mean FXI level of 0.033 U/ml; ii) the allele frequency of the Glu117X mutation in Ashkenazi and Iraqi Jews was 0.0217 and 0.0167, respectively (16), while among other Jewish ethnic groups and Palestinian Arabs it was significantly lower, i.e. 0.0026 and 0.0065, respectively (17); iii) the Phe283Leu mutation was only present in Ashkenazi Jews in whom the allele frequency was 0.0254 (16, 17); iv) distinct founder effects for the Glu117X and Phe283Leu mutation were defined by haplotype analysis (17); v) mutation age estimates revealed that the Glu117X mutation occurred approximately 2,500 years ago when all Jews resided in the Middle East before they were exiled by the Romans in 70 A.D., whereas the Phe283Leu occurred more recently (18). These age estimates fit with the current distribution of Glu117X in various Jewish ethnic groups, and with the confinement of Phe283Leu to Ashkenazi Jews who separated from other Jewish ethnic groups approximately 1,900 years ago.

Two additional clusters of FXI-deficient patients were recently ascertained by us. One was identified in French Basques, a Cys38Arg mutation, and the second, a Cys128X mutation, was identified in Britons, with allele frequencies of 0.005 and 0.009, respectively (19, 20). For each mutation, haplotype analysis was consistent with a founder effect, but an age estimate was not possible to perform because of insufficient data.

As of February 2007, 120 mutations causing FXI deficiency have been described in peer-reviewed journals. All are listed in a database of rare clotting factor deficiencies (www.med.unc.edu/isth/welcome). Characterization of these mutations has shed light on understanding the structure-function relationships of FXI and has defined several dysfunctional mutations such as Gly555Glu and Pro520Leu (21, 22). Interestingly, four mutations were shown to exert a dominant negative effect which stems from impaired secretion of heterodimers consisting of a normal and a mutant monomer (23, 24). Such heterozygotes may present with bleeding episodes caused by FXI levels that are considerably lower than observed in usual heterozygotes in whom dimerization of a normal monomer and a mutated monomer does not impair the secretion of FXI dimer from producing cells.

Discovery of a new function of FXI

The procoagulant activity of FXI was further refined in 1995 by an elegant in-vitro study performed by the group of B. Bouma

from the Netherlands (25). At high TF concentrations, the rate of fibrin formation in plasma was independent of FXI, but at decreasing amounts of TF, there was a gradual increase in the contribution of FXI to the rate of fibrin formation. This observation and a more recent study (26) are consistent with a model in which initial clot formation occurs at the site of TF exposure independently of FXI, while at the propagation phase, when the clot increases in size, the process becomes dependent on FXI. Another novel finding was that thrombin-induced activation of FXI leads to inhibition of tissue plasminogen activator (tPA)-induced fibrinolysis of the clot (25). This effect was mediated by FXI-dependent generation of substantial amounts of thrombin after clot formation, which in turn activates the thrombin-activatable fibrinolysis inhibitor (TAFI) that removes carboxy-terminal lysine residues from fibrin, the sites of plasminogen binding to fibrin (27). In the presence of a monoclonal antibody to TAFI, this effect was abolished as in the presence of a monoclonal antibody to FXI implicating TAFI as a mediator of the antifibrinolytic activity of FXI. Further support for the role of FXI in inhibiting fibrinolysis comes from observations in patients with severe FXI deficiency who are particularly prone to bleed following injury at sites where there is augmented local fibrinolysis like the oral cavity, nose, tonsils and urinary tract (15, 28, 29). Furthermore, tooth extractions in such patients can be carried out uneventfully by using tranexamic acid instead of replacement therapy (30).

Clinical features

The common presentation of severe FXI deficiency is injury-related bleeding, e.g. tooth extractions, tonsillectomy, nasal surgery, or prostatectomy. Alternatively, a prolonged activated partial thromboplastin time found in a routine examination leads to the diagnosis. Bleeding occurs less frequently following surgery performed at sites where there is no local fibrinolytic activity, e.g. orthopedic surgery, appendectomy, circumcision or herniorrhaphy (15, 29). In contrast, surgery at sites with local fibrinolysis (vide supra) is associated with excessive bleeding in 49–67% of cases (29). Regarding post-partum haemorrhage, a retrospective analysis of 62 women with severe FXI deficiency revealed that 43 (70%) had 93 uneventful deliveries (85 vaginal and 8 caesarian) without blood component therapy (31). Consequently, an on demand policy of blood component therapy was proposed for such patients.

Whether or not heterozygotes with partial FXI deficiency display a bleeding tendency is controversial. A bleeding risk assessment in a large cohort of patients with FXI deficiency yielded an odds ratio (OR) of 13 (95% CI 3.8–45) in patients with FXI levels less than 0.2 U/ml and an OR of 2.6 (95% CI 0.8–9) in patients with FXI levels of 0.2–0.69 U/ml (32). Hence, major FXI deficiency confers a markedly higher risk of bleeding than minor deficiency. Patients with a minor deficiency who have a bleeding history should be tested for an additional hemostatic disorder. Guidelines for therapy in FXI-deficient patients can be found elsewhere (14, 33).

Development of inhibitors to FXI in patients with severe FXI deficiency has been described. In our recent study of 118 unrelated patients with severe FXI deficiency, seven were found with an inhibitor (34). The seven patients were among 21 patients who

had received replacement therapy and were homozygotes for the Glu117X mutation that is associated with extremely low FXI levels. Since none of the 43 patients with other genotypes associated with higher FXI levels ranging between 0.02–0.15 U/ml developed an inhibitor despite replacement therapy, it was concluded that development of an inhibitor to FXI can be expected in one third of patients with an extremely low FXI level following treatment with blood components. Interestingly, patients with an inhibitor usually do not bleed spontaneously but do present a challenge when surgery is needed. Recombinant FVIIa is helpful under such circumstances.

The prothrombotic effect of elevated levels of FXI

The procoagulant and antifibrinolytic effects of FXI could hypothetically imply that increased FXI levels confer an increased risk of venous and/or arterial thrombosis. Indeed, in the Leiden thrombophilia study of 474 patients with venous thromboembolism and 473 controls, the adjusted OR for patients whose FXI was above the 90th percentile was 2.2 (95% CI 1.5–3.2) compared to patients with FXI levels below 90th percentile (35). In another study, recurrence of venous thrombosis was significantly more frequent in patients in whom both FXI activity and TAFI antigen level were increased (36).

Regarding arterial thrombosis, a recent study of 200 women with acute myocardial infarction before the age of 49 years and 626 controls indicated that elevated FXI levels were not associated with an increased risk (37). Another study of 174 men and 26 women with myocardial infarction at an age range of 32–72 years also did not reveal an increased relative risk for subjects in the upper quartile of FXI levels (adjusted OR 0.8; 95% CI 0.2–2.7) (38). However, another study of 560 men with an acute myocardial infarction before the age of 70 and 646 controls showed that the adjusted OR in those subjects whose FXI level was in the highest quintile was 1.8 (95% CI 1.2–2.7) compared to those with the lowest quintile (39). Interestingly, the highest risk was observed in a subgroup of patients with both high FXI level and low FXII level (adjusted OR 6.4, 95% CI 2.2–18.0). The discrepancy among these studies and the question whether an increased FXI level confers a risk of myocardial infarction in men but not in women will await further studies.

An increased relative risk of ischemic stroke in patients aged less than 55 years was also recently reported to be associated with increased FXI levels (40). FXI above the 95th percentile was observed in 17 (22%) of 78 patients with stroke ($n = 65$) or transient ischemic attack ($n = 13$) versus two of 40 controls (5%), OR 5.3 (95% CI 1.2–24.1).

Is severe FXI deficiency protective against thrombosis?

Severe inherited bleeding disorders have for many years served as paradigms for understating the pathogenesis of thrombosis, and for development of antithrombotic therapy. Reports of thrombosis in patients with severe hemostatic defects have introduced some skepticism about the value of mimicking these experiments of nature. However, because of the limited number of

observations in such patients and because thrombosis is multi-causal, interpretation of these anecdotal cases is difficult. One matter has been clarified; patients with profound defects in haemostasis, e.g. haemophilia A, haemophilia B, severe type 3 von Willebrand disease and Glanzmann thrombasthenia are not protected against atherosclerosis (41–43). Nevertheless, longitudinal studies in the Netherlands showed that haemophilia A and haemophilia B are associated with a decreased incidence of myocardial infarction (44, 45), which suggests that the low coagulability does prevent thrombotic occlusion. Whether or not severe FXI deficiency also provides protection against thrombosis has been recently addressed by observations in animal models and patients.

Animal studies

Several animal models have been employed for addressing the question whether FXI deficiency confers a fibrinolytic and/or an antithrombotic effect. An initial study revealed that a jugular vein thrombus in rabbits treated locally or systemically by a FXI antibody underwent thrombolysis two-fold faster than a control thrombus (46). A similar effect was elicited by an anti-TAFI antibody, suggesting that thrombolysis induced by FXI deficiency was mediated by diminished TAFI activation. In a murine model of FXI deficiency, FeCl₃-induced injury of the carotid artery resulted in significantly better blood flow than observed in wild type mice (47, 48). Full protection was also observed in FIX-deficient mice, but while tail bleeding time was normal in FXI-deficient mice, FIX-deficient mice had a markedly prolonged tail bleeding time (48). This suggests a selective antithrombotic effect imparted by FXI deficiency without a demonstrable anti-haemostatic effect. In another thrombosis model in baboons, the growth of a thrombus initiated by knitted dacron or TF presenting teflon grafts deployed in arteriovenous shunts was markedly reduced by infusion of a goat anti-human FXI antibody (49). This antithrombotic effect was comparable to heparin infusion. Similar protective effects by FXI deficiency were obtained in an iliac artery balloon injury model in rabbits (50), and in FeCl₃-induced thrombosis of the inferior vena cava in mice (51). In another study in mice, the antithrombotic effects of FXI or FXII deficiency was examined by four thrombosis models, i.e. pulmonary embolism induced by infusion of collagen and epinephrine, FeCl₃-induced injury of mesenteric arterioles, mechanical injury of the aorta and carotid artery injury accomplished by ligation with a surgical filament. Striking antithrombotic effects were discerned in FXII-deficient mice that were examined by all four models of thrombosis (52). A recent study by the same investigators demonstrated that both FXII- and FXI-deficient mice were similarly protected from transient middle cerebral artery occlusion (53). Collectively, these data suggest that, at least in animals, FXII and FXI play a role in inducing thrombosis, but are dispensable for haemostasis.

Human studies

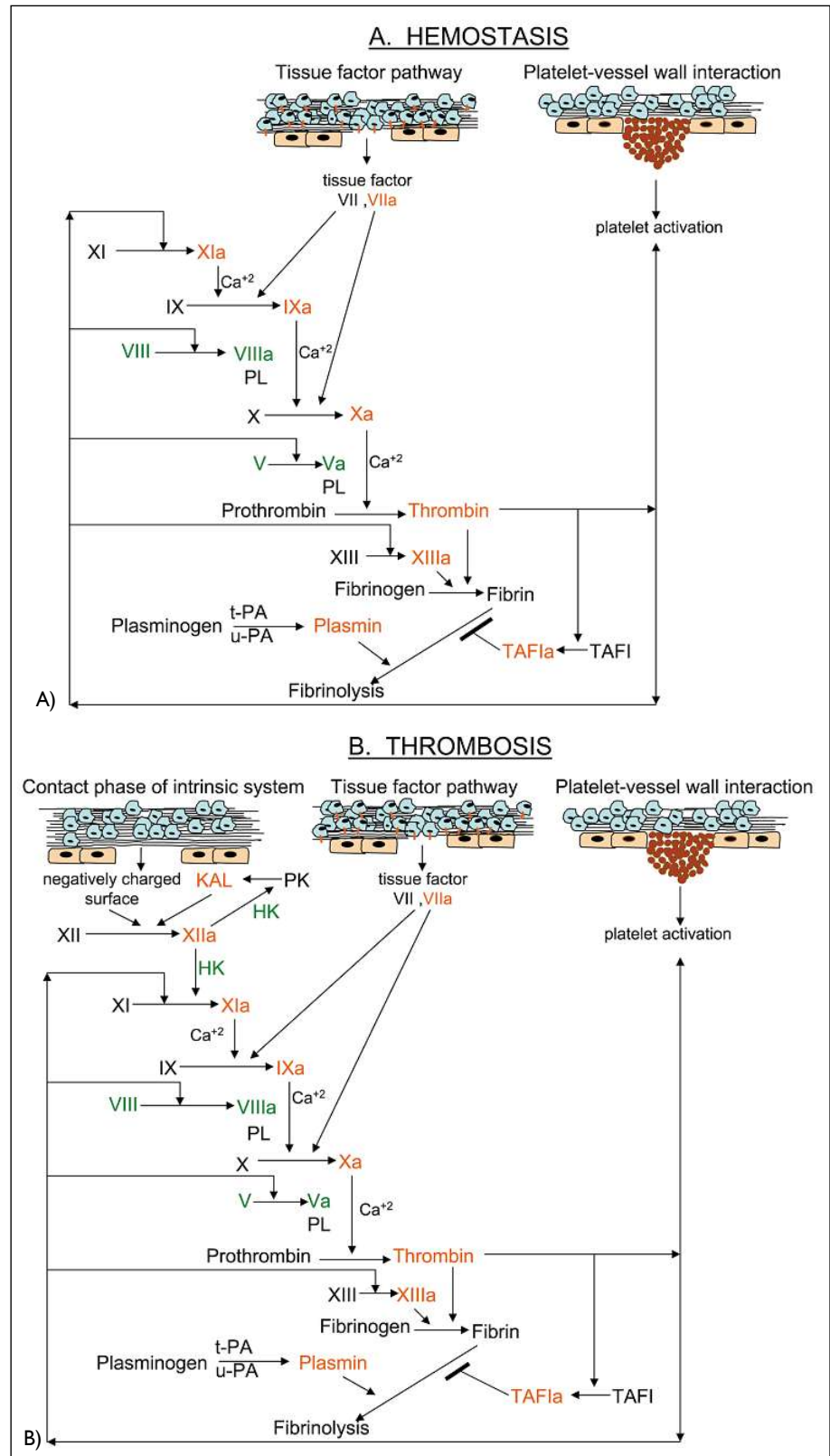
The rather low prevalence of uprovoked venous thromboembolism at different age groups (1:300–1:1,000) makes it hard to assess whether patients with severe FXI deficiency are protected against venous thrombosis. Five anecdotal cases of venous thromboembolism were included in a recent review (54) of whom two occurred following infusion of a FXI concentrate

(known to sometimes induce thrombosis) and one had systemic lupus erythematosus.

The incidence of acute myocardial infarction was recently assessed systematically in Israeli patients with severe FXI defi-

ciency (55). Of 96 unrelated patients (55 women and 41 men) who were more than 35 years old, 16 had a history of acute myocardial infarction, of whom six underwent coronary artery bypass grafting and four had recurrent events. One or more athero-

Figure 1: Revisited schemes of the coagulation cascade highlighting the potential differences between haemostasis and thrombosis. The schemes (A and B) are based on recent experiments in animal models of thrombosis which underscore the importance of the contact phase of coagulation for propagation of thrombi, and on the clinical observations that patients with a severe deficiency of FXII, PK or HK do not have a bleeding tendency which renders the contact phase of coagulation unimportant for haemostasis. Alternative sites for triggering FXII activation are activated platelets and clot surface (see text). Coagulation factors are depicted in Roman numbers, activated factors are shown in red, and cofactors are in green. PL indicates phospholipids mainly provided by activated platelets, HK – high-molecular-weight kininogen, PK – prekallikrein, KAL – kallikrein, TAFI – thrombin activatable serine protease inhibitor, u-PA – urokinase plasminogen activator, t-PA – tissue plasminogen activator.



sclerotic risk factors were observed in 13/16 (81%) of patients who had a myocardial infarction compared to 44/47 (56%) in patients who had no myocardial infarction ($p < 0.001$). The calculated annual rate of acute myocardial infarction in male patients was similar to the expected rate in the general Israeli population, whereas in female patients it was almost two-fold higher but did not reach statistical significance. These data indicate that severe FXI deficiency confers no protection against acute myocardial infarction. Whether or not severe FXI deficiency protects against ischemic stroke is at the time of this writing under investigation.

Quo vadis

More than 50 years of research on FXI and FXI deficiency have witnessed oscillations in understanding the role of FXI in haemostasis and thrombosis. The first conceptual change emanated from the discovery that FXI can be activated by thrombin rather than by FXIIa. This finding and the observations that FXI-deficient patients have a bleeding tendency, while patients deficient in FXII, HK or PK do not, led to a revision of the clotting cascade assigning no role for the initial contact reactions in haemostasis (Fig. 1A), and making them relevant only for in-vitro coagulation until proven otherwise. The second conceptual change was that FXI is not only a procoagulant but also an antifibrinolytic factor. The third conceptual change emanated from the observations in animal models of arterial and venous thrombosis in which both FXII or FXI deficiency exhibited an antithrombotic effect. These findings are consistent with a “thrombosis scheme” of the coagulation pathways (Fig. 1B) that swings back the pendulum to the originally described cascade. Recent evidence indicates that apart from negatively charged surfaces at injury sites of the vessel wall, activated platelets or clot surface can serve as templates for triggering FXII activation and propagation of the growing thrombus (52). Moreover, polyphosphates released from dense granules of activated platelets (56), and RNA re-

leased from damaged cells at injury sites (57) were recently shown to augment contact activation. Whether or not this third conceptual change is relevant for thrombosis in humans remains to be established. Supportive evidence is that elevated FXI levels confer a risk of venous thromboembolism (35), myocardial infarction in men (39) and stroke (40). Evidence which does not support the concept includes: i) Lack of protection conferred by severe FXI deficiency against myocardial infarction (55); ii) Elevated FXI levels in women are not associated with an increased risk of myocardial infarction (37); iii) Decreased rather than increased levels of FXII are associated with a risk of myocardial infarction in men (39). iv) Patients with severe FXII deficiency are not protected against thrombosis (58, 59). Thus, more observations on arterial and venous thrombosis, particularly in patients with severe FXI or FXII deficiency would be helpful before accepting the revised scheme. If indeed FXI deficiency will be found to be protective against one or more types of thrombosis, development of humanized monoclonal antibodies against FXI or other agents that interfere with FXI function could serve as excellent antithrombotic drugs that would have no or minimal haemorrhagic potential.

Also foreseen are improvements in the treatment of patients with severe FXI deficiency who undergo surgery. A more parsimonious use or no use of plasma or FXI concentrate for certain types of surgery and labor will decrease the frequency of transmission of infectious agents and development of a FXI inhibitor. Also, use of tranexamic acid without replacement therapy during surgery at sites with increased fibrinolytic activity seems justified to evaluate given the experience gained with tooth extractions. Finally, development of rFXI is anticipated.

Acknowledgments

I am indebted to Ariella Zivelin, PhD and Ophira Salomon, MD for useful comments and Tami Livnat, PhD for performing the art work (Fig. 1).

References

- Rosenthal RL, Dreskin OH, Rosenthal N. New hemophilia-like disease caused by deficiency of a third plasma thromboplastin factor. *Proc Soc Exp Biol Med* 1953; 82: 171–174.
- Rosenthal RL, Dreskin OH, Rosenthal N. Plasma thromboplastin antecedent (PTA) deficiency; clinical, coagulation, therapeutic and hereditary aspects of a new hemophilia-like disease. *Blood* 1955; 10: 120–131.
- Rapaport SI, Proctor RR, Patch MJ, Yettra M. The mode of inheritance of PTA deficiency: evidence for the existence of major PTA deficiency and minor PTA deficiency. *Blood* 1961; 18: 149–165.
- Seligsohn U. High gene frequency of factor XI (PTA) deficiency in Ashkenazi Jews. *Blood* 1978; 51: 1223–1228.
- Gailani D, Broze GJ, Jr. Factor XI activation in a revised model of blood coagulation. *Science* 1991; 253: 909–912.
- Naito K, Fujikawa K. Activation of human blood coagulation factor XI independent of factor XII. Factor XI is activated by thrombin and factor XIa in the presence of negatively charged surfaces. *J Biol Chem* 1991; 266: 7353–7358.
- Fujikawa K, Chung DW, Hendrickson LE, Davie EW. Amino acid sequence of human factor XI, a blood coagulation factor with four tandem repeats that are highly homologous with plasma prekallikrein. *Biochemistry* 1986; 25: 2417–2424.
- Gailani D, Ho D, Sun MF, et al. Model for a factor IX activation complex on blood platelets: dimeric conformation of factor XIa is essential. *Blood* 2001; 97: 3117–3122.
- Baglia FA, Walsh PN. Prothrombin is a cofactor for the binding of factor XI to the platelet surface and for platelet-mediated factor XI activation by thrombin. *Biochemistry* 1998; 37: 2271–2281.
- Papagrigoriou E, McEwan PA, Walsh PN, et al. Crystal structure of the factor XI zymogen reveals a pathway for transactivation. *Nat Struct Mol Biol* 2006; 13: 557–558.
- Asakai R, Davie EW, Chung DW. Organization of the gene for human factor XI. *Biochemistry* 1987; 26: 7221–7228.
- Kato A, Asakai R, Davie EW, et al. Factor XI gene (F11) is located on the distal end of the long arm of human chromosome 4. *Cytogenet Cell Genet* 1989; 52: 77–78.
- Asakai R, Chung DW, Ratnoff OD, et al. Factor XI (plasma thromboplastin antecedent) deficiency in Ashkenazi Jews is a bleeding disorder that can result from three types of point mutations. *Proc Natl Acad Sci USA* 1989; 86: 7667–7671.
- Seligsohn U. Factor XI deficiency. In: *Textbook of Haemophilia*. Oxford: Blackwell Publishing 2005; pp. 321–327.
- Asakai R, Chung DW, Davie EW, et al. Factor XI deficiency in Ashkenazi Jews in Israel. *N Engl J Med* 1991; 325: 153–158.
- Shpilberg O, Peretz H, Zivelin A, et al. One of the two common mutations causing factor XI deficiency in Ashkenazi Jews (type II) is also prevalent in Iraqi Jews, who represent the ancient gene pool of Jews. *Blood* 1995; 85: 429–432.
- Peretz H, Mulai A, Usher S, et al. The two common mutations causing factor XI deficiency in Jews stem from distinct founders: one of ancient Middle Eastern origin and another of more recent European origin. *Blood* 1997; 90: 2654–2659.
- Goldstein DB, Reich DE, Bradman N, et al. Age estimates of two common mutations causing factor XI deficiency: recent genetic drift is not necessary for

- elevated disease incidence among Ashkenazi Jews. *Am J Hum Genet* 1999; 64: 1071–1075.
19. Zivelin A, Bauduer F, Ducout L, et al. Factor XI deficiency in French Basques is caused predominantly by an ancestral Cys38Arg mutation in the factor XI gene. *Blood* 2002; 99: 2448–2454.
 20. Bolton-Maggs PH, Peretz H, Butler R, et al. A common ancestral mutation (C128X) occurring in 11 non-Jewish families from the UK with factor XI deficiency. *J Thromb Haemost* 2004; 2: 918–924.
 21. Zivelin A, Ogawa T, Bulvik S, et al. Severe factor XI deficiency caused by a Gly555 to Glu mutation (factor XI-Glu555): a cross-reactive material positive variant defective in factor IX activation. *J Thromb Haemost* 2004; 2: 1782–1789.
 22. Gailani D, Schmidt A, Sun MF, et al. A cross-reactive material positive variant of coagulation factor XI (FXI) with a catalytic defect. *J Thromb Haemost* 2007; in press.
 23. Kravtsov DV, Wu W, Meijers JC, et al. Dominant factor XI deficiency caused by mutations in the factor XI catalytic domain. *Blood* 2004; 104: 128–134.
 24. Kravtsov DV, Monahan PE, Gailani D. A classification system for cross-reactive material-negative factor XI deficiency. *Blood* 2005; 105: 4671–4673.
 25. von dem Borne PA, Meijers JC, Bouma BN. Feedback activation of factor XI by thrombin in plasma results in additional formation of thrombin that protects fibrin clots from fibrinolysis. *Blood* 1995; 86: 3035–3042.
 26. von dem Borne PA, Cox LM, Bouma BN. Factor XI enhances fibrin generation and inhibits fibrinolysis in a coagulation model initiated by surface-coated tissue factor. *Blood Coagul Fibrinolysis* 2006; 17: 251–257.
 27. Von dem Borne PA, Bajzar L, Meijers JC, et al. Thrombin-mediated activation of factor XI results in a thrombin-activatable fibrinolysis inhibitor-dependent inhibition of fibrinolysis. *J Clin Invest* 1997; 99: 2323–2327.
 28. Seligsohn U. Factor XI deficiency. *Thromb Haemost* 1993; 70: 68–71.
 29. Salomon O, Steinberg DM, Seligshon U. Variable bleeding manifestations characterize different types of surgery in patients with severe factor XI deficiency enabling parsimonious use of replacement therapy. *Haemophilia* 2006; 12: 490–493.
 30. Berliner S, Horowitz I, Martinowitz U, et al. Dental surgery in patients with severe factor XI deficiency without plasma replacement. *Blood Coagul Fibrinolysis* 1992; 3: 465–468.
 31. Salomon O, Steinberg DM, Tamarin I, et al. Plasma replacement therapy during labor is not mandatory for women with severe factor XI deficiency. *Blood Coagul Fibrinolysis* 2005; 16: 37–41.
 32. Brenner B, Laor A, Lupo H, et al. Bleeding predictors in factor-XI-deficient patients. *Blood Coagul Fibrinolysis* 1997; 8: 511–515.
 33. Bolton-Maggs PH. Factor XI deficiency and its management. *Haemophilia* 2000; 6 (Suppl 1): 100–109.
 34. Salomon O, Zivelin A, Livnat T, et al. Prevalence, causes, and characterization of factor XI inhibitors in patients with inherited factor XI deficiency. *Blood* 2003; 101: 4783–4788.
 35. Meijers JC, Tekelenburg WL, Bouma BN, et al. High levels of coagulation factor XI as a risk factor for venous thrombosis. *N Engl J Med* 2000; 342: 696–701.
 36. Eichinger S, Schonauer V, Weltermann A, et al. Thrombin-activatable fibrinolysis inhibitor and the risk for recurrent venous thromboembolism. *Blood* 2004; 103: 3773–3776.
 37. Tanis B, Algra A, van der Graaf Y, et al. Procoagulant factors and the risk of myocardial infarction in young women. *Eur J Haematol* 2006; 77: 67–73.
 38. Merlo C, Willemin WA, Redondo M, et al. Elevated levels of plasma prekallikrein, high molecular weight kininogen and factor XI in coronary heart disease. *Atherosclerosis* 2002; 161: 261–267.
 39. Doggen CJ, Rosendaal FR, Meijers JC. Levels of intrinsic coagulation factors and the risk of myocardial infarction among men: Opposite and synergistic effects of factors XI and XII. *Blood* 2006; 108: 4045–4051.
 40. Yang DT, Flanders MM, Kim H, et al. Elevated factor XI activity levels are associated with an increased odds ratio for cerebrovascular events. *Am J Clin Pathol* 2006; 126: 411–415.
 41. Sramek A, Reiber JH, Gerrits WB, et al. Decreased coagulability has no clinically relevant effect on atherogenesis: observations in individuals with a hereditary bleeding tendency. *Circulation* 2001; 104: 762–767.
 42. Sramek A, Bucciarelli P, Federici AB, et al. Patients with type 3 severe von Willebrand disease are not protected against atherosclerosis: results from a multicenter study in 47 patients. *Circulation* 2004; 109: 740–744.
 43. Shpilberg O, Rabi I, Schiller K, et al. Patients with Glanzmann thrombasthenia lacking platelet glycoprotein alpha(IIb)beta(3) (GPIIb/IIIa) and alpha(v)beta(3) receptors are not protected from atherosclerosis. *Circulation* 2002; 105: 1044–1048.
 44. Rosendaal FR, Briet E, Stibbe J, et al. Haemophilia protects against ischaemic heart disease: a study of risk factors. *Br J Haematol* 1990; 75: 525–530.
 45. Triemstra M, Rosendaal FR, Smit C, et al. Mortality in patients with hemophilia. Changes in a Dutch population from 1986 to 1992 and 1973 to 1986. *Ann Intern Med* 1995; 123: 823–827.
 46. Minnema MC, Friederich PW, Levi M, et al. Enhancement of rabbit jugular vein thrombolysis by neutralization of factor XI. In vivo evidence for a role of factor XI as an anti-fibrinolytic factor. *J Clin Invest* 1998; 101: 10–14.
 47. Rosen ED. FXI is essential for thrombus formation following FeCl₃-induced injury of the carotid artery in the mouse. *Thromb Haemost* 2002; 87: 774–776.
 48. Wang X, Cheng Q, Xu L, et al. Effects of factor IX or factor XI deficiency on ferric chloride-induced carotid artery occlusion in mice. *J Thromb Haemost* 2005; 3: 695–702.
 49. Gruber A, Hanson SR. Factor XI-dependence of surface- and tissue factor-initiated thrombus propagation in primates. *Blood* 2003; 102: 953–955.
 50. Yamashita A, Nishihira K, Kitazawa T, et al. Factor XI contributes to thrombus propagation on injured neointima of the rabbit iliac artery. *J Thromb Haemost* 2006; 4: 1496–1501.
 51. Wang X, Smith PL, Hsu MY, et al. Effects of factor XI deficiency on ferric chloride-induced vena cava thrombosis in mice. *J Thromb Haemost* 2006; 4: 1982–1988.
 52. Renne T, Pozgajova M, Gruner S, et al. Defective thrombus formation in mice lacking coagulation factor XII. *J Exp Med* 2005; 202: 271–281.
 53. Kleinschnitz C, Stoll G, Bendszus M, et al. Targeting coagulation factor XII provides protection from pathological thrombosis in cerebral ischemia without interfering with hemostasis. *J Exp Med* 2006; 203: 513–518.
 54. Girolami A, Ruzzon E, Tezza F, et al. Arterial and venous thrombosis in rare congenital bleeding disorders: a critical review. *Haemophilia* 2006; 12: 345–351.
 55. Salomon O, Steinberg DM, Dardik R, et al. Inherited factor XI deficiency confers no protection against acute myocardial infarction. *J Thromb Haemost* 2003; 1: 658–661.
 56. Smith SA, Mutch NJ, Baskar D, et al. Polyphosphate modulates blood coagulation and fibrinolysis. *Proc Natl Acad Sci USA* 2006; 103: 903–908.
 57. Kannemeier C, Shibamiya A, Nakazawa F, et al. Extracellular RNA constitutes a natural procoagulant cofactor in blood coagulation. *Proc Natl Acad Sci USA* 2007; 104: 6388–6393.
 58. Goodnough LT, Saito H, Ratnoff OD. Thrombosis or myocardial infarction in congenital clotting factor abnormalities and chronic thrombocytopenias: a report of 21 patients and a review of 50 previously reported cases. *Medicine (Baltimore)* 1983; 62: 248–255.
 59. Zeerleder S, Schloesser M, Redondo M, et al. Reevaluation of the incidence of thromboembolic complications in congenital factor XII deficiency—a study on 73 subjects from 14 Swiss families. *Thromb Haemost* 1999; 82: 1240–1246.