**In vivo activation and functions of the protease factor XII**

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**Summary**

Combinations of proinflammatory and procoagulant reactions are the unifying principle for a variety of disorders affecting the cardiovascular system. Factor XII (FXII, Hageman factor) is a plasma protease that initiates the contact system. The biochemistry of the contact system in vivo is well understood; however, its in vivo functions are just beginning to emerge. The current review concentrates on activators and functions of the FXII-driven contact system in vivo. Elucidating its physiologic activities offers the exciting opportunity to develop strategies for the safe interference with both thrombotic and inflammatory diseases.

**Keywords**

Coagulation factors, contact phase, proteases

**Biochemistry of factor XII**

The contact system is a plasma-borne protease cascade that exerts procoagulant and proinflammatory activities. The system comprises the serine proteases factor XII (FXII), plasma prekallikrein (PPK), and factor XI (FXI), the non-enzymatic cofactor high-molecular-weight kinogen (HK) and C1 esterase inhibitor (C1INH). C1INH is the major inhibitor of activated FXII (FXIIa) in plasma kallikrein (PK), respectively (1–3). FXII is the principal initiator of the contact system reaction cascades (Figure 1).

Binding to negatively charged surfaces induces a conformational change in zymogen FXII, leading to the generation of small amounts of FXIIa. FXIIa cleaves PPK to generate active PK, which in turn reciprocally activates FXII. This amplification loop generates sufficient PK activity to liberate BK from HK by limited proteolysis (kallikrein-kinin system) (4). FXIIa also initiates other cascades such as the intrinsic pathway of coagulation via its substrate FXI. Furthermore, FXIIa has the capacity to drive the classic complement system pathway via activation of C1r or to a lesser degree the C1s subunit of C1, and the fibrinolytic system by PK-mediated urokinase or plasminogen activation or indirectly via BK-triggered tissue plasminogen activator (tPA) release (4, 5).

FXII is primarily produced in the liver although some expression has been observed in other cells including endometrial stromal cells or leukocytes (6). FXII has an apparent molecular weight of 80 kDa and circulates in plasma as a single chain zymogen with a concentration of 30–35 µg/ml (0.37 µM) with a half-life of 50 to 70 hours (7). The FXII gene is composed of 13 introns and 14 exons (8) that codes for a zymogen consisting of 596 amino acids. FXII is composed of a N-terminal fibronectin domain type II (Fib II, encoded by exon 3 and 4), an epidermal-growth-factor-like domain (EGF I, exon 5), a fibronectin domain type I (Fib I, exon 6), a second epidermal-growth-factor-like domain (EGF II, exon 7), a kringle domain (exon 8 and 9), a proline-rich region (a 55 amino acid long region, exon 9) and the catalytic domain (exon 10–14, Figure 2). The FXIIa form consists of a disulfide-linked heavy chain (Mw of 52 kDa) and a light chain (Mw of 28 kDa).

The latter one mediates the enzymatic activity, whereas FXII binds to negatively charged surfaces via its heavy chain. The FXII surface-binding site is not precisely known and several regions appear to contribute including the distal N-terminal end (residues 1–28), the Fib II, the Fib I, the EGF II, the kringle domain and possibly the proline-rich region (7).

FXII zymogen is activated by limited proteolysis involving cleavage of the peptide bond Arg³⁵³-Val³⁵⁴ resulting in a two-chain molecule, FXIIa (a-FXIIa). Two principal modes of FXII activation exist. The zymogen is activated through binding to negatively charged surfaces that induces a conformational change (auto-activation) (9, 10). Zinc ions (Zn²⁺) bind to FXIIa intermediate states and increase susceptibility for auto-activation by stabilising conformations in the
Factor XII activation reaction. Cleavage of FXII is also mediated by other proteases such as PK (hetero-activation). FXIIa consists of a heavy chain and a light chain, connected by a single disulfide-bond between two Cysteine residues (Cys340-Cys367). Further cleavage of α-FXIIa at positions 334 and 343 results in β-FXIIa (Hageman factor fragment, HFF). Although retaining its proteolytic activity towards PPK, β-FXIIa is unable to bind to negatively charged surfaces and therefore has no effect on FXI activation and thrombosis. C1INH is the principle endogenous inhibitor of FXIIa and PK with >90% of FXIIa and >50% of PK, respectively, inhibited in plasma of healthy individuals (11). Other inhibitors of the contact system proteases include α1-antitrypsin, α2-antiplasmin, α2-macroglobulin and antithrombin (6, 12–14).

**FXII in coagulation**

Congenital deficiency in FXII (Hageman trait) is an autosomal recessive trait, initially described in 1955 in the index patient Mr. John Hageman (15). Similarly to other contact system proteins (PPK and HK), deficiency in FXII severely prolongs the activated partial thromboplastin time (aPTT), a diagnostic coagulation assay that relies on contact system activation. However, in sharp contrast to deficiency in tissue factor, factors VII, VIII (Haemophilia A) or IX (Haemophilia B), individuals with severe deficiencies in the contact FXII, PPK or HK do not suffer from spontaneous or injury-related excessive bleeding (1). PPK-, HK-, and FXII-deficient patients safely undergo surgical procedures without blood product support and have a completely normal haemostatic capa-

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**Figure 1:** FXII-driven signalling cascades. FXII directly activates the intrinsic pathway of coagulation, the complement system and kallikrein-kinin system; FXII indirectly activates fibrinolysis via PK and BK. C1INH is the major inhibitor of FXIIa and PK.

**Figure 2:** Domain structure of FXII forms. The heavy chain, which harbours the putative surface-binding region of FXII, consists of the five domains Fib II, EGF I, Fib I, EGF II, kringle domain and the proline-rich region. The light chain bears the enzymatic site of the serine protease. The two chains are connected by a single disulfide-bond (Cys340 and Cys367). Cleavage of the peptide bond Arg353-Val354 (arrow 1) results in two-chain activated FXII (α-FXIIa). The catalytic triad of FXIIa consists of His393, Asp442 and Ser544. Further proteolysis of the peptide bonds Arg334-Leu344 and Arg334-Asn335 (arrows 2 and 3) by PK, results in activated FXII-fragment (β-FXIIa).
ity. FXI deficiency predisposes individuals to stress-related bleeding such as that seen with trauma or surgical procedures that involve tissues with high fibrinolytic activity (oropharyngeal, genitourinary). However, independent laboratories have shown that the antigen level of plasma FXI does not correlate with increased bleeding risk suggesting a more complex role of FXI in regulating haemostasis (7). The intact haemostasis in contact system-deficient individuals led to the premise that this pathway is dispensable during bleeding and that fibrin formation at sites of injury is exclusively dependent on the extrinsic pathway. However, previous data have challenged this concept. We generated the first FXII-deficient mice (16) and reported that they are protected from thrombosis both in venous and arterial beds in various experimental models (17). Subsequent studies have shown that FXII-deficient mice are also protected from cerebral ischaemia in an experimental stroke model of transient (18) but not permanent (19) occlusion of the middle cerebral artery (MCAO model). Defects in the FXII-driven intrinsic coagulation pathway also provide thromboprotection in rabbits and baboon models (20). Despite evidence that FXII deficient/inhibited animals are largely protected from vessel occlusive thrombosis, the contribution of FXII in human thrombotic disease remains to be analysed. There are anecdotal reports suggesting that FXII deficiency may actually predispose to thrombosis, dating back to the death of the index FXII deficient patient who succumbed to an episode of post-operative pulmonary embolism. However, larger studies have convincingly shown that thrombosis in FXII-deficient patients is related to other risk factors, independent of the noted FXII deficiency (21, 22). FXII is highly preserved among mice and humans and the FXII homologs share 71 % identity on the protein level. There is experimental evidence that FXIIa triggers similar pathways among the species. Infusion of human FXII into FXII deficiency mice restores their prolonged aPTT (17) and homologous human proteins restore defective thrombus formation in FXII deficient and PK deficient mice (17, 23, 24), further corroborating the close similarity of the contact system among species.

Furthermore, deficiency in the major substrate of activated FXII, FXI, largely reduces the risk of ischaemic stroke (25) and venous thrombosis (26) in human subjects. Vice versa elevated FXI levels are associated with increased risk of myocardial infarction in men (27). Basal BK levels are depressed in FXII-deficient mice and deficiency in the contact system proteins might be beneficial in human inflammatory disease states (28).

Multiple mutations are known to cause loss of FXII activity and deficiency in the clotting factor. Some mutations either reduce FXII plasma levels by interference with synthesis or secretion. Other mutations interfere with the enzymatic activity of FXIIa. These latter mutations are either located in the serine protease catalytic triad His539-Asp442-Ser544 or in close proximity to these residues (29). FXII (Washington DC) has a Cys571-to-Ser571 substitution that leads to complete loss of procoagulant activity in vitro (30). Another example is FXII Locarno, which is a secreted but dysfunctional protein due to an Arg531 substitution. The mutation alters the FXIIa/PK recognition site in FXII and abolished zymogen activation by limited proteolysis (31).

**FXII in hereditary angioedema**

Hereditary angioedema [HAE (MIM #106100)] is a rare life-threatening inherited oedema disorder that is characterised by recurrent episodes of acute swelling, involving the skin, oropharyngeal, laryngeal, or gastrointestinal mucosa (32). The mechanisms of increased vascular permeability in HAE and excessive formation of the proinflammatory peptide hormone BK is a consistent finding in acute episodes in HAE patients (33). HAE develops in individuals who are quantitatively or qualitatively deficient in C1INH (HAE type I and II, respectively) (32). Ablation of Serpin1 gene expression (that codes for C1INH) results in excessive BK production and increased vascular permeability in mice (34) and humans (35). In addition to these two classical HAE types, a third variant exists that mostly affects women, HAE type III (HAEIII). HAEIII patients have normal levels of fully functional C1INH but suffer from angioedema nonetheless (36). Using genome-wide linkage analyses, HAEIII was shown to be associated with a single missense mutation (c.1032CrA) in the F12 gene (37). Independent studies involving other families found HAEIII to be associated with a different mutation affecting the same nucleotide in F12, c.1032CrG (38). Both point mutations translate into amino acid exchanges Thr309Lys and Thr309Arg (identical to position Thr328 if numbering includes the signal peptide), respectively. F12-linked HAEIII is of autosomal dominant inheritance and a mixture of wild-type and Thr309-mutated FXII circulates in plasma of HAEIII patients (37). The position Thr309 is located in the C-terminal proline-rich portion of the FXII heavy chain that mediates FXII surface-induced activation (39) and is associated with increased FXIIa activity in HAEIII patient plasma samples (37). Recently, a F12 gene deletion of 72 base pairs (coding amino acids 305–321) was identified in two unrelated HAEIII families (40). Additionally, in a 37-year-old woman and her daughter with recurrent C1INH-independent angioedema a duplication of 18 base pairs in the F12 gene was found (41). The duplication codes for six additional amino acids in FXII (positions 298–303). The molecular mechanism of oedema formation in patients carrying HAEIII-associated FXII mutations is unknown and may involve altered FXII activation or processing, reduced binding of C1INH (42), modulation of zymogen cleavage by FXIIa/PK, or other mechanisms.

**Activation of FXII in angioedema**

Formation of the vasoactive and proinflammatory peptide hormone BK can in vitro be initiated by a variety of polyanionic surfaces such as kaolin, glass, ellagic acid, certain polymers including nucleotides (DNA and RNA), sulfatides, polyphosphates (polyP), misfolded proteins and some types of collagen or glycosaminoglycans (43). BK binding to its cognate B2 receptor (B2R) activates various intracellular signalling pathways that dilate vessels, induce haemotaxis of neutrophils and increase vascular permeability and fluid efflux (44). HAE patients experience recurrent attacks of swelling, but the stimuli that trigger these periodic episodes of ex-
cessive vascular leakage are poorly defined (32, 45). In allergic disease, BK is generated and contributes to increased vascular permeability (46). In vitro, heparin liberates BK by triggering contact system activation (33). Using oedema models in genetically modified mice we have shown that heparin activates BK formation in vivo (47). IgE/antigen-activated mast cell-released heparin readily initiates FXII activation. Interference with this pathway either by blocking FXII or B2R largely blunts aberrant mast cell-mediated oedema in mice. Clinical data support a role of heparin-triggered BK formation in patients (48). Elevated plasma concentrations of BK directly trigger coughing, a classic side effect of angiotensin converting enzyme (ACE) inhibitors. ACE inhibitors block the major BK degrading enzyme and increase BK plasma concentrations (44). Vice versa, the risk and severity of mast cell-triggered oedema is increased in patients with low ACE activity (49).

Heparin appears to have a dual role in FXII activity. It provides the negatively charged surface upon which FXII binds and becomes activated. However, heparin also interacts with antithrombin III (ATIII) (50), through a unique 3-O-sulfated glucosamine unit within the heparin backbone (51). Experimental data show that ATIII-heparin complexes inhibit FXIIa with similar activity as free ATIII (52). Indeed, theoretical models predict a threshold of complete FXII activation or inactivation that is determined by the kinetic balance between the catalytic rate of auto-activation and the rate of FXIIa inhibition (53) that warrant further investigation.

During anaphylactic shock the aPTT is markedly prolonged in patient plasma (54, 55). Consistently, plasma of IgE/antigen-challenged mice is unclottable due to a systemic heparin concentration of >4 µg/ml, that is sufficient to initiate BK formation (47). Initially, small amounts of locally secreted heparin may generate BK activity on the mast cell surface. Mast cells express B2R (56) and BK stimulation induces mast cell degranulation (57). Due to this amplification loop an initial BK activity might be multiplied by liberated mast cell-heparin that triggers the contact system. Heparin specifically triggers FXII-mediated BK formation. Under these conditions no proteolytic-activation of FXII is detectable. Similarly, both the non-natural polysaccharide dextran sulphate and the monoclonal anti-FXII zymogen antibody 15H8 reduced fibrin formation and platelet accumulation in a collagen-coated vascular graft in baboons (79) consistent with earlier data of FXII deficiency without an increase in therapy-associated bleeding (18). Pretreatment with PCK markedly reduced cerebral infarction in the transient MCAO model. Furthermore, PCK protected mice from platelet polyinduced oedema formation (69). The recombinant FXIIa inhibitor rHA-infestin-4 that also inhibits plasmin and modestly factor Xa (70) is based on the fourth domain of the nonclassic Kazal-type serine protease inhibitor from the midgut of the insect *Tritiaoma infestans* fused to human albumin (71). Intravenous infusion of the inhibitor prior to the challenge protects mice from FeCl₃-induced arterial thrombus formation, ischaemic stroke (transient MCAO model) (71), silent brain ischaemia (72) and from lethal pulmonary embolism (69) and salvages rabbits and rats from arterial thrombosis (70, 71). Similarly, the recombinant inhibitor Ir-CPI, a Kunitz-type protein from the salivary gland of *Ixodes ricinus* inhibits FXIIa, PK, and FXIa and provides protection from venous and arterial thrombus formation in mice (73). The specific FXIIa inhibitor Corn trypsin inhibitor (CTI) attenuated the prothrombotic properties of catheters in rabbits (74). Other protein inhibitors, such as cabbageseeds protease inhibitor (75), pumpkin seed inhibitor CMTI-V (76) and Ecotin (77) block FXIIa in plasma, but also inhibit other coagulation proteases including thrombin, FXa, FXIa, PK and plasmin.

The monoclonal anti-FXI antibody 14E11 interferes with FXI activation by FXIIa and provides protection against acute ischaemic stroke (78), arterial occlusion induced by FeCl₃ in mice, and reduced platelet-rich thrombus growth in baboons (24). Similarly, the monoclonal anti-FXII zymogen antibody 15H8 reduced fibrin formation and platelet accumulation in a collagen-coated vascular graft in baboons (79) consistent with earlier data of FXII null mice in collagen/epinephrine-triggered pulmonary embolism models (17). The antibody 15H8 directed to zymogen FXII interferes with platelet accumulation in a collagen-coated arterio-venous shunt in baboons. The antibody binding characteristics, its epitope and mechanisms of inhibition are not currently known and interference with the zymogen form bears the risk of an antigen sink. In contrast, recombinant fully human antibody 3F7 binds with high affinity (Kᵣ=6.2 ± 0.2 nM and 4.0 ± 0.1 nM for human and rabbit FXIIa, respectively) into the enzymatic pocket of FXIIa and specifically inhibits FXIIa activity and FXIIa-driven coagulation in human, mouse and rabbit plasma (80). Recently, the clinical applicability of FXIIa inhibition was established in a clinical

**Targeting FXII**

Currently available anticoagulants used for the acute treatment and prevention of thrombotic diseases target enzymes of the coagulation cascade that are critical for fibrin generation. As a result, bleeding is the primary complication of anticoagulation therapy (68). In contrast, the selective importance of FXII in thrombus formation while being dispensable for haemostasis, suggests that inhibition of this plasma protease is a safe thromboprotective strategy. In murine models pharmacologic targeting of FXII with H-D-Pro-Phe-Arg-chloromethylketone (PCK) that irreversibly inhibits the amidolytic activity of FXIIa and PK-mediated activation of FXII, provided similar protection from ischaemic stroke as congenital FXII deficiency without an increase in therapy-associated bleeding (18). Pretreatment with PCK markedly reduced cerebral infarction in the transient MCAO model. Furthermore, PCK protected mice from platelet polyinduced oedema formation (69). The recombinant FXIIa inhibitor rHA-infestin-4 that also inhibits plasmin and modestly factor Xa (70) is based on the fourth domain of the nonclassic Kazal-type serine protease inhibitor from the midgut of the insect *Tritiaoma infestans* fused to human albumin (71). Intravenous infusion of the inhibitor prior to the challenge protects mice from FeCl₃-induced arterial thrombus formation, ischaemic stroke (transient MCAO model) (71), silent brain ischaemia (72) and from lethal pulmonary embolism (69) and salvages rabbits and rats from arterial thrombosis (70, 71). Similarly, the recombinant inhibitor Ir-CPI, a Kunitz-type protein from the salivary gland of *Ixodes ricinus* inhibits FXIIa, PK, and FXIa and provides protection from venous and arterial thrombus formation in mice (73). The specific FXIIa inhibitor Corn trypsin inhibitor (CTI) attenuated the prothrombotic properties of catheters in rabbits (74). Other protein inhibitors, such as cabbageseed protease inhibitor (75), pumpkin seed inhibitor CMTI-V (76) and Ecotin (77) block FXIIa in plasma, but also inhibit other coagulation proteases including thrombin, FXa, FXIa, PK and plasmin.

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setting, when rabbits were adapted to a cardiopulmonary bypass system (ECMO system) used for infant therapy. 3F7 provided thromboprotection as efficient as heparin, however, in contrast to heparin, 3F7 treatment did not impair the haemostatic capacity of treated animals (80).

An alternative method to interfere with FXII action is the use of antisense oligonucleotides (ASOs) (81). Repetitive subcutaneous ASO injection for several weeks depressed expression of FXII in mice and rabbits. Consistent to the gene-ablated mouse data, depletion of FXII by ASO reduced arterial and venous thrombosis in mice (81). ASO attenuates catheter-induced thrombosis in rabbits (82), confirming 3F7-mediated inhibition of occlusive clot formation in polymer-tubing shunts (80). Furthermore, inhibition of FXII by ASO reversed C1INH deficiency-induced increased vascular permeability in mice (83). The major drawback of ASO is the slow onset of action that may hamper its use as an anticoagulant in invasive procedures or any other medical setting that requires acute intervention. Taken together, targeting FXII using different technologies shows safe thromboprotection in mice, rabbits and baboons and interferes with oedema formation in mice.

The FXII activator polyphosphate

Although FXII is activated in vitro by a variety of non-physiologic polyanions, the in vivo activator of FXII remained an enigma for decades. FXII activation by contact to the inorganic polyanionic mineral kaolin (a silicate), is commonly used to trigger aPTT, however an inorganic silicate does not exist under physiologic conditions in humans. FXII activation has been linked to procoagulant platelets in plasma and multiple studies have shown that activated platelets promote coagulation in a FXII-dependent manner (58, 84–87). Consistently, platelet-derived microparticles induce thrombin generation independently of tissue factor via activation of FXII (88). Taken together the ex vivo data show that procoagulant platelets initiate FXII-mediated fibrin formation. The critical role of FXII in thrombus formation has led to the search for naturally occurring platelet-derived FXII activators. Initially, extracellular RNA was identified as a FXII activator and targeting the phosphodiester bonds in the polymer backbone with RNAse provided thromboprotection in mouse models (89). Polyphosphates (polyP) comprise an inorganic polymer that shares a similar polyanion structure as RNA. Synthetic polyP of 70 phosphate units initiate coagulation in a FXII-dependent manner in plasma (90). Soluble platelet polyP are composed of 60–100 linear linked phosphate subunits and are released from platelet dense granules upon PAR-receptor stimulation (91). Using experiments in plasma, thrombosis and oedema models in genetically altered mice, along with a human disease model, we have identified platelet polyP as an activator of FXII and have shown that polyP-driven FXII activation has critical functions in platelet-driven thrombosis and inflammation in vivo (69). Independent laboratories have confirmed that platelet polyP initiate coagulation in a FXII-dependent manner in vitro (90, 92–95) and thrombus formation in vivo (96). Platelet polyP are unstable and the polyP/FXII pathway operates independently of tissue factor-driven coagulation (97). Ex vivo, the ability of polyP to activate FXII is dependent on the chain length (95). Polymers of <45 residues do not sustain FXII activation (69) and FXII-activating capacity increases with the polyP chain length. However, the FXII activating property of polyP may not be solely dependent on chain length in vivo. Long chain polyP are insoluble (98) and do not naturally occur in humans under physiologic conditions in circulation or the extracellular compartment. In contrast, platelet-derived polyP are soluble, present in plasma and can reach high local local concentrations in an entrapped environment which activate FXII in the context of a platelet rich thrombus. Indeed, inherited deficiency in platelet polyP results in defective thrombus formation in mice (96) and prolonged clotting in platelet rich plasma that is restored to normal levels by addition of platelet size synthetic polyP (69). In addition to activation of coagulation via FXII, polyP accelerates generation of factor V activation. PolyP also accelerate FXI acti-

Figure 3: Platelet polyphosphate activities. Activated platelets release polyP from their dense granules. The polymer activates FXII and induces clot formation via the intrinsic pathway of coagulation and oedema formation via the kallikrein-kinin system. Furthermore, polyP accelerate factor V (FV) activation (FVa), factor XI (FXI) activation by thrombin and enhance fibrin clot structure. PolyP bind to histone H4 (H4) that in turn activates platelets.
viation by thrombin, and enhance the stability of the fibrin clot (90, 92–95). Targeting polyP activity provides protection from thrombosis (69, 99) and vascular leakage (100) in animal models (Fig 3).

Extracellular histone H4 contributes to organ failure and sepsis-associated death (101). Histones activate platelets, interact with platelet-secreted polyP thus, amplifying thrombus formation (93). The binding of platelet-size polyP to the inflammatory mediators histone H4 and high mobility group box 1 (HMGB1) potentiates proinflammatory activities in vitro and in vivo (102).

Conclusions

FXII influences thrombosis risk without altering haemostasis. It also plays a role in inflammation, sepsis and HAEC. Recently identified in vivo activators of FXII include mast cell-derived heparin, misfolded protein aggregates, nucleotides and platelet polyP. While heparin and misfolded protein aggregates selectively activate the kallikrein-kinin system and increase vascular leakage, platelet-derived polyP has a precise role in coagulation amplification and oedema formation. Anti-FXIIA antibodies have a long half-life in the circulation and have been shown to provide safe anticoagulation in a clinically relevant extracorporeal circulation bypass model. These properties have renewed interest in FXII as a therapeutic strategy to treat aberrant vascular leakage and thrombosis disorders.

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Conflicts of interest

None declared.

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