Fibrinogen and factor XIII at the intersection of coagulation, fibrinolysis and inflammation

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Summary
Fibrinogen and factor XIII are two essential proteins that are involved directly in fibrin gel formation as the final step of a sequence of reactions triggered by a procoagulant stimulus. Haemostasis is the most obvious function of the resulting fibrin clot. Different variables affect the conversion of fibrinogen to fibrin as well as the mode of fibrin polymerisation and fibrin crosslinking, hereby, critically influencing the architecture of the resulting fibrin network and consequently determining its mechanical strength and resistance against fibrinolysis. Due to fibrinogen’s structure with a multitude of domains and binding motifs the fibrin gel allows for complex interactions with other coagulation factors, with profibrinolytic as well as antifibrinolytic proteins, with complement factors and with various cellular receptors. These interactions enable the fibrin network to control its own further state (i.e. expansion or degradation), to influence innate immunity, and to function as a scaffold for cell migration processes. During the whole process of fibrin gel formation biologically active peptides and protein fragments are released that additionally influence cellular processes via chemotaxis or by modulating cell-cell interactions. Thus, it is not surprising that fibrinogen and factor XIII in addition to their haemostatic function influence innate immunity as well as cell-mediated reactions like wound healing, response to tissue injury or inflammatory processes. The present review summarises current knowledge of fibrinogen’s and factor XIII’s function in coagulation and fibrinolysis giving special emphasis on their relation to inflammation control.

Keywords
Fibrinogen, factor XIII, coagulation, fibrinolysis, inflammation

Introduction
Fibrinogen is a 340 kDa glycoprotein with different binding sites, which either are exposed in the native protein or become accessible or released after specific structural changes. By using these binding sites fibrinogen and its derivatives are able to interact with multiple different plasma proteins and cellular receptors, and these interactions are essential for fibrinogen’s functions and they influence processes like fibrin gel formation or fibrinolysis as well as different cell-mediated functions including inflammation (1). Factor XIII contributes to fibrin clot stability and fibrin gel architecture by crosslinking fibrin monomers to other fibrin units in polymerising fibrin or to other proteins like α2-antiplasmin (α2AP) or fibronectin. There are now clear data underscoring that factor XIII helps to control inflammatory processes, as well (2). In the general perception the fibrin-stabilising function seemingly is factor XIII’s main function. However, evidence accumulates that beside these haemostasis-related functions factor XIII regulates and mediates different cellular functions, as well. These functions of cellular factor XIII, which are out of the scope of this review, are extensively described elsewhere (3, 4). The present review summarises current knowledge on fibrinogen’s and factor XIII’s influence on inflammatory processes and how fibrin polymerisation, factor XIII mediated crosslinking and fibrinolysis are involved in this relation.

Fibrinogen’s structure: Conditions for multifunctionality
Fibrinogen is a multidomained molecule consisting of two sets of αA-, Bβ- and γ-chains with multiple inter- and intra-chain disulfide bridges. A central E domain, which harbours two N-terminal fibrinopeptide A (FPA) and two N-terminal fibrinopeptide B (FPB) sequences, is connected with two outer D domains with the protruding C-termini of the α- (αC domain) and the γ-chains (▶ Figure 1) (5). Due to alternative splicing about 15% of the fibrinogen molecules circulate as heterodimers that additionally influence cellular processes directly in fibrin gel formation as the final step of a sequence of reactions, like wound healing, response to tissue injury or inflammatory processes. The present review summarises current knowledge of fibrinogen’s and factor XIII’s function in coagulation and fibrinolysis giving special emphasis on their relation to inflammation control.

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Infections and the role of plasma proteins and platelets
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Fibrinogen and factor XIII – coagulation and inflammation

Figure 1: Integrin binding motifs on fibrinogen. Different integrin binding motifs and other functionally relevant sites are given. FPA, fibrinopeptide A, FPB, fibrinopeptide B.

Fibrinogen synthesis and gene regulation

In humans the Aα-, Bβ- and γ-fibrinogen chains are encoded by gene loci FGA, FGB and FGG, respectively, clustered on chromosome 4. Minor isoforms of the Aα- (AαE) and γ-chains (γ′) result from alternative splicing (18).

Fibrinogen is synthesised in a well-controlled way to allow for abundant basal fibrinogen levels sufficient for adequate haemostasis as well as for increased fibrinogen levels in response to different stimuli. Fibrinogen expression primarily is regulated at the transcriptional level. For both, basal and acute-phase-reaction (APR) related transcription control distinct proximal promoter regions on all three fibrinogen gene loci have been characterised. Steady-state fibrinogen expression primarily is controlled by consensus binding sites on FGA and FGB, to which transcription factors like Hepatocyte Nuclear Factor (HNF)-1 (positions upstream of the transcriptional start sites (TSS): FGA: –59 to –47; FGB: –91 to –79) or CCAAT/Enhancer-Binding-Proteins (C/EBP) (FGA: –142 to –134; FGB: –132 to –124) bind as well as an upstream stimulatory factor at nucleotides –77 to –66 of FGG. Increased expression during APR is induced by glucocorticoids and interleukin 6 (IL6). Corresponding glucocorticoid responsive enhancer elements (GRE) and IL6 responsive elements (IL6RE) can be found on the promoters of all three fibrinogen gene loci (e.g. GRE and IL6RE of FGB at –2,900 to –1,500 and –143 to –137, respectively) (18). In addition, several data indicate that fibrinogen synthesis is regulated on post-transcriptional level by microRNAs (18).

Basal levels of fibrinogen as well as the amplitude of fibrinogen level variation during APR exhibit an inter-individual variability, and it is assumed that up to 50% of this variation is determined by genetic factors (19). Single nucleotide polymorphisms (SNPs) located in the fibrinogen gene cluster itself, in loci related to chronic inflammatory diseases (e.g. SLC22A5, SLC22A4, IRF1, CD300LF, SLC9A3R1, NAT9) or in the IL6 receptor gene have been described to contribute to this genetic background (20). However, up to now only less than 2% of the inter-individual fibrinogen level variation can be attributed to SNPs characterised in this context (21).
In respect to monocyte-derived cells cFXIII is assumed to exert regulatory functions on different processes like locomotion, phagocytosis or gene expression (4). The expression of cFXIII varies between different monocyte differentiation stages. Additionally, along distinct monocyte activation pathways cFXIII expression is altered differentially. Thus, in monocytes cFXIII expression is downregulated by interferon γ via the so-called classical activation pathway. On the other hand, interleukin 4 is involved in differentiation of monocytes into antigen-presenting dendritic cells and this stimulation via the so-called alternative pathway highly increases cFXIII expression (3, 4).

Interactions between fibrinogen and factor XIII with the complement system

Coagulation and complement systems are assumed to be descendants of a common ancestral pathway and an intensive molecular intercommunication between both systems has been described (34). When focusing on fibrinogen and factor XIII data are accumulating that indicate an intense bidirectional interaction with the complement system. In the early 1990th, factor XIII was reported to be responsible for the generation of complement C5a during plasma clotting (35). While complement C5a could not be detected during coagulation of factor XIII deficient blood samples, C5 generation could be restored by substitution of purified factor XIII. For fibrinogen and to a larger extent for fibrin interactions with mannose-binding lectin (MBL) and ficolins A have been described (36). These interactions are assumed to enhance the activity of the so-called lecithin complement pathway.

Beside these reports on fibrinogen/factor XIII induced complement activation there are other data indicating a sequestration of complement components by these coagulation factors. It is hypothesised that this sequestration could be of importance for processes like wound healing by supporting inflammatory and immune response as well as lysis and phagocytosis of pathogens and damaged cells (37). Thus, complement C3 is a substrate for factor XIIIa’s γ-transglutaminase activity and it becomes incorporated into blood clots by factor XIII mediated crosslinking to the fibrin network (38, 39). For complement C1q a high-affinity interaction with fibrinogen and fibrin has been described, which could help to sequester C1q-complexes in foci with fibrin network formation (40).

Finally, different groups have characterised the influence of the complement system on fibrinogen and factor XIII. The binding of MBL and ficolins to foreign structures results in an activation of mannose-binding lectin-associated serine proteases (MASP) (41). Of these, MASP-2 is known to activate complement C4 and C2, hereby generating the lectin/classical pathway C3 convertase C4b2b. Furthermore MASP-2 activates prothrombin. MASP-1 has been reported to activate factor XIII and to cleave fibrinogen to release FPB (42, 43). A more detailed analysis of the effects of MASP-1 on different coagulation factors confirmed the activation of factor XIII and the release of FPB and it identified the activation of prothrombin and of Thrombin Activatable Fibrinolysis In-
hibitor (TAFI) (44). Interestingly, when comparing the kinetics of factor XIII activation induced by thrombin and MASP-1, the FXIII-A Val34Leu genotype seems to exert inverse effects. In the case of MASP-1, FXIII-A 34Val is activated faster than FXIII-A 34Leu (44).

**Fibrin gel formation and variables affecting fibrin network architecture**

Fibrin polymerisation is initiated by the thrombin-mediated cleavage of FPA and the exposure of the residues Aa17–20 (Gly-Pro-Arg-Val), the so-called α-chain knob on Eα, that binds to a complementary binding pocket (“hole”) on the D domain (Da) formed by the γ-chain. Due to these interactions a staggered overlapping end-to-middle domain arrangement forms double stranded fibrin fibrils (1). FPB is cleaved with a short delay and in analogy to the process described above after the exposure of Bβ15–18 (Gly-His-Arg-Pro) on Eα an interaction with the binding pocket on the D domain (Db), which is build up by the β-chain, takes place. FPB removal and Eα, Db interaction induce different conformational changes that promote lateral fibrin fibril associations resulting in a more extensive network assembly (1).

The architecture of the fibrin network influences its physical strength and fibrinolysis resistance, at least in part due to a higher clot mass and a more intensive integration of antifibrinolytic proteins like α2AP in dense clot structures (26). It is critically influenced by the fibrinogen concentration as well as the kinetics of factor XIII mediated fibrin crosslinking. This phenomenon has been conclusively characterised by Lim and co-workers that described an inverse relation between fibrinogen concentration and permeability of the resulting fibrin gel, i.e. at high fibrinogen concentrations a tight fibrin network with low permeability is formed and at low fibrinogen concentrations a highly permeable loose fibrin clot structure results (45). Interestingly, this relation is especially pronounced in individuals with FXIII-A 34Val/Val genotype (exhibiting slow thrombin induced factor XIII activation) and it is nearly missing in case of FXIII-A 34Leu/Leu genotype (45).

**Fibrinolysis: Interactions between circulating, stationary and cellular factors**

The physiological course following a prothrombotic trigger eventually terminates in the regulated removal of the fibrin network by fibrinolysis. The key enzyme in this context is plasmin, which is generated from plasminogen by tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA). Both pathways are highly regulated and exhibit different feedback loops. On fibrinogen different cryptic low affinity tPA and plasminogen binding sites have been identified that are located on the γ-chain (γ312–324) and the α-chain (Aα148–160) as well as an unexposed region on the globular aC domain (Aα392–610) that binds both tPA and plasminogen with high affinity (46). After conversion of fibrinogen to fibrin and during fibrin polymerisation these binding sites become exposed and able to interact with tPA and plasminogen resulting in generation of enzymatically active plasmin, which degrades the fibrin network. During this degradation a plenitude of fibrin fragments is released, which modify fibrin polymerisation, fibrinolysis as well as different other processes (5, 47). The complexity of fibrinolysis becomes enhanced further by restriction on a pericellular context (48), by different inhibitory pathways (e.g. TAFI, α2AP) (1) as well as by the dependence of fibrinolysis sensitivity on the fibrin gel architecture (49).

**Fibrin(ogen) derivatives and the fibrin gel matrix as inflammation mediators**

In an early work, Lanir et al. described that macrophage migration in a fibrin gel matrix is influenced by different variables that modify its structure as well as its adhesive properties (50). While macrophages are unable to penetrate filters of comparable pore size, they migrate through fibrin networks by using specific contact sites on fibrin and co-crosslinked proteins for coordinated deformation and locomotion. In this migration model, fibrinogen concentration was inversely related to macrophage migration in crosslinked as well as in non-crosslinked fibrin gels. Presence of factor XIII or fibronectin in the matrix resulted in a significant reduction of macrophage migration as measured by migration velocity or by the number of migrating cells. Integration of some types of glycosaminoglycans like hyaluronic acid (HA) or heparin modified migration characteristics in a more complex way. Thus, this effect was dependent on the presence of fibronectin in the fibrin network. Moreover, the effect of HA and heparin was significantly dose-dependent.

The reduction of macrophage migration with increasing fibrinogen concentrations as well as the inhibitory effect of fibrin crosslinking fits in a model where high fibrin gel density and a higher number of fibrin crosslinks reduce the potential of the fibrin gel matrix to support migration. Different domains of fibrin and other characteristics of the fibrin network have been identified to specifically interact with cellular structures, hereby supporting or modulating migratory processes (51–53). Of special importance in respect on cell-cell interactions is the fragment harbouring the six N-termini of fibrinogen’s Aα-, Bβ- and γ-chains called N-terminal disulphide knot (NDSK). This bundle of sequences carrying different binding motifs is especially suited to function as a multivalent and differential binding partner and it has been characterised to be critical for the interaction of leukocyte integrins with endothelial VE-cadherins in the process of transendothelial migration of leukocytes (54).

There are many other in vitro data describing an involvement of fibrinogen/derivatives in inflammation (7). Thus, the N-terminal Bβ-chain sequence forming FPB has been characterised as a very potent chemotactic agent for neutrophils and monocytes (55, 56). The fragments Bβ1–42 as well as Bβ15–42 exert chemoattractant forces solely on neutrophils (11). During bacterial infections a coagulation activation with consecutive generation of these and other chemotactic fibrinogen derivatives occurs, which prompt
leukocyte to infiltrate the affected site (57). Finally, there is evidence that fibrin(ogen) is directly involved in cellular activation processes. Thus, native fibrinogen as well as fibrin(ogen) derivatives have been described to stimulate different types of leukocytes at least in part through toll-like receptor 4 and to induce secretion of different cytokines in in vitro and in vivo studies (58–63). Furthermore, exposure of endothelial cells to fibrin induces the expression of interleukin 8 (64).

**Fibrinogen, factor XIII and fibrinolysis:**

**Involvement in inflammation control and innate immunity – evidence from animal models**

In addition to the data described above, evidence deriving from animal models as well as from epidemiological approaches demonstrates an involvement of fibrinogen/factor XIII in inflammatory processes going clearly beyond haemostasis.

**Evidence from fibrinogen-transgene mice models**

As in vitro studies underscored the potential importance of fibrinogen and factor XIII for inflammatory processes, this relation has been corroborated in different animal models in respect of its biological significance. In this context, one of the first topics addressed in an animal model was the support of inflammatory processes due to the integrin α₅β₂-fibrinogen interaction. As characterised earlier, this interaction depends on conformational changes induced during conversion of fibrinogen to fibrin and during fibrin polymerisation, i.e. while circulating, no high affinity binding between native fibrinogen and integrin α₅β₂ could be demonstrated (65, 66). To study the role of this interaction pathway, Flick et al. generated transgene mice, carrying altered C-termini at fibrinogen’s γ-chain, in which the α₅β₂-binding motif (γ390–396, NRKLIGE) was converted to a series of alanine residues (Fibγ390–396A) (67). These transgene mice do not exhibit any haemostatic disorder; however, the interaction between fibrin gel and integrin α₅β₂ carrying neutrophils or monocytes is missing. When studying the innate immune response in a peritonitis model, after intraperitoneal injection of *Staphylococcus aureus*, transgene Fibγ390–396A mice are unable to control this bacterial challenge. Interestingly, the numbers of resident and inflammation-induced accumulated leukocytes did not differ between wild-type and transgene Fibγ390–396A mice. Thus, diminished bacterial elimination is due to the inability of Fibγ390–396A mice to implement full antimicrobial function rather than to disturbed leukocyte trafficking.

Fibrinogen might be important in autoimmune processes like rheumatoid arthritis, as well (2, 68). This relation was studied in a murine collagen-induced arthritis model, which is assumed to mimic different steps of rheumatoid arthritis pathogenesis. Again, interaction between fibrinogen and leukocyte integrin α₅β₂ was found to be of crucial importance for arthritis development (69). After collagen immunisation wild-type mice develop a sterile arthritis. The arthritic process is significantly ameliorated in fibrinogen knockout mice as well as in transgene Fibγ390–396A mice.

**Evidence from factor XIII-transgene mice models**

Fibrin crosslinking by factor XIII is of importance not only for assuring clot stability and haemostasis but also for inflammation control (70). This function of factor XIII was studied in mice artificially infected by *Streptococcus pyogenes*. After inoculation, factor XIII is activated on the bacterial surface and bacteria become entrapped in the generating fibrin network and immobilised by co-crosslinking to the fibrin fibrils. Consequently, bacteria are killed by antimicrobial substances released in thrombin-activated plasma. In F13A knockout mice the application of *Streptococcus pyogenes* induces loose fibrin networks that miss covalent crosslinks. Hereby, bacterial entrapment and immobilisation is impaired significantly, which results in reduced localisation of the bacterial foci and a more severe clinical course. Based on phylogenetic considerations, the authors assume coagulation and factor XIII to be parts of the early innate immune defense.

**Evidence from fibrinolysis-altered models**

Inflammation control not only depends on clot formation and stabilisation but also from regulated fibrinolytic fibrin network degradation. Bacteria have evolved a broad repertoire of haemostasis-modulating factors. Giving an example, *Staphylococcus aureus* has evolved staphylocoagulase (71), clumping factor A (72) or staphylokinase (73), which enable the pathogen to induce the generation of a fibrin network, to allow adhering to it and to promote its degradation. Different studies underscore the importance of fibrinolysis regulation during inflammation. Thus, streptokinase, which is generated by group A streptococci and which is a specific activator of human plasminogen but not from other mammalian species has emerged as a key pathogenicity factor, when studying its effect in mice transgenes carrying human plasminogen (74). Wild-type mice are largely insensitive to group A Streptococci. The artificial expression of human plasminogen results in a strong increase of mortality in mice infected with group A Streptococci, and this effect was dependent on the expression of streptokinase. A comparable dependence of infections outcome on fibrinolysis could be demonstrated in *Yersinia pestis* infected mice (75). In mice this pathogen induces widespread foci with high numbers of free bacteria and only a small amount of inflammatory cells. When knocking out the bacterial plasminogen activator (PA), mice infected with this transgene pathogen exhibit a significantly improved survival and a strongly enhanced inflammatory response. The same holds true, when infecting plasminogen knockout mice with wild-type *Yersinia pestis*. In both artificial constellations the improvement of infection control is clearly dependent on the presence of fibrinogen, as the beneficial effect of PA knockout or plasminogen removal is missing in fibrinogen knockout mice. These data predominantly have been interpreted in a way that adequate fibrin network generation and persistence is necessary to physically entrap bacteria and to support adhesion and invasion of in-
flammmatory cells to the affected foci. The premature degradation of the fibrin network is assumed to allow for bacterial evasion and dissemination (75). However, this interpretation seems to be only one side of the coin. When considering the effects of fibrinogen derivatives released during fibrin gel degradation on chemotaxis and cell-cell interactions an additional explanation for the pathogenicity of fibrinolysis in this context could be the modulation of the innate immune response by fibrin(ogen) derivatives. This hypothesis is supported by data from studies on the effect of fibrinogen derivatives on the reperfusion injury after myocardial ischaemia (10, 12) and on the course of bacterial peritonitis (12). In these studies, the application of monomeric β15–42 and to a stronger extent of dimeric β15–44 or β15–66 peptides reduces the inflammatory infiltration following artificially induced myocardial ischaemia or intraperitoneal bacterial inoculation. These effects most likely are explained by inhibition of transendothelial migration via modulation of VE-cadherin interactions.

### Fibrin network generation and inflammation control: Evidence from epidemiological approaches

The translation of *in vitro* and animal data into a human context is burdened with much imponderability. Thus, this review includes a description of epidemiological data that clearly support a concept of fibrinogen and factor XIII to be part of the human system of inflammation control.

As mentioned above, variants located in the fibrinogen gene loci, e.g. FGB -455G>A (rs1800790) or FGA T312A (rs6050), are known to contribute to different amplitudes of fibrinogen level changes during acute-phase-reactions or under proinflammatory stresses with FGB -455G>A favouring high and FGA T312A favouring low amplitudes (19, 22–24). An early study on a relation between fibrinogen genotype and inflammatory processes was published in 2007 and described the association of genetic fibrinogen variants with outcome of patients with sepsis (76). Patients carrying a FGB haplotype with the minor allele of FGB -455G>A exhibited a significantly lower 28 day-mortality in multivariate analysis as well as decreased organ dysfunction (76). In a small study, Kovar et al. characterised the effect of FGB -148C>T on cytokine levels in healthy volunteers under proinflammatory stimulus (77). FGB -148C>T and FGB -455G>A are in strong linkage disequilibrium. After lipopolysaccharide infusion they found a reduced response of inflammatory markers (IL6 and tumour necrosis factor α) in carriers of the variant genotype FGB -148T. The epidemiological data given above would fit in a hypothetical model, in which the extent of fibrinogen level increase during an inflammatory challenge would influence the individuals ability for inflammation control via individual characteristics of fibrin gel architecture and released fibrin(ogen) derivative profiles (Figure 2A). These characteristics of the conversion of fibrinogen to fibrin and of fibrin network formation exhibit a considerable genetic background (45) and are known to influence adhesive and migratory processes (50–53). As FXIII-A Val34Leu genotype plays an essential role for the described fibrinogen genotype-phenotype relation (45), we tested this model in two study populations under different proinflammatory conditions (78). One cohort consisted of patients with rheumatoid arthritis, the other comprised patients suffering from inflammatory processes of non-autoimmune origin. FGB -455G>A and FGA T312A genotypes were associated with reduced and increased inflammatory responses, respectively, with comparable results in both cohorts. The presence of FXIII-A 34Val/Val genotype, which is permissive for the relation between fibrinogen level and fibrin clot density (45), also, was a necessary condition for this association between fibrinogen genotypes and inflammatory intensity (78). Another epidemiological study focussing on cardiovascular disease in RA described the FXIII-A 34Leu allele to be significantly more frequent in RA patients with a history of deep-vein thrombosis and/or pulmonary embolism (79). However, in this study an analysis on the relation of this genotype to inflammatory activity in RA has not been performed.

The AIRGENE Study Group reported an association of rs1800790 (FGB -455G>A) with IL6 levels (80). In an apparent conflict with the model mentioned above, describing FGB -455A limiting inflammatory response, in this study an increased early IL6 response on exposure to air pollution in FGB -455A carriers was described, which peaked 6–11 hours (h) after exposure and declined rapidly thereafter (80). However, as fibrinogen expression responds with a latency of some days (25), in this study focussing on the 24 h–interval following the stimulus the effect of fibrin crosslinking on inflammation control most likely will escape the observation.

### Inflammation and coagulation: A bidirectional relation

As described in the previous sections, coagulation in general and fibrinogen and factor XIII in special influence inflammatory processes in many ways. However, this relation clearly is bidirectional, i.e. inflammation influences coagulation and fibrinolysis, as well (81, 82). Today, coagulation and fibrinolysis are assumed to take place primarily on cell surfaces (48, 83). When describing the mechanisms, by which inflammation influences coagulation, the expression of tissue factor (TF) gives an important example (83). TF is an integral membrane protein and the primary physiologic initiator of coagulation via binding and activation of factor VII. Under normal conditions TF presentation is restricted on extravascular cells but proinflammatory stimuli are able to induce its expression on monocytes and endothelial cells (84, 85). Hereby, a strong procoagulant effect is triggered. Furthermore, inflammation affects the expression of thrombomodulin (TM), which is a crucial activator of anticoagulant and antifibrinolytic pathways (86). TM is a membrane protein located on endothelial cells. After binding to TM thrombin looses its procoagulant activity and becomes an activator of the protein C system, i.e. thrombin’s properties are switched from pro- to anticoagulant (86). Different inflam-
Inflammatory cytokines as well as vascular injury have been described to reduce TM expression on endothelial cells, which increases the procoagulant net effect (83). In addition to its effect on the coagulation inhibiting protein C system, the complex of thrombin and TM results in an accelerated activation of TAFI (87). TAFI is a carboxypeptidase potently inhibiting fibrinolysis if its local concentration exceeds a certain threshold (88). Interestingly, TAFI is also known to be a regulator of vascular inflammation (89). Thus, complement C3a and C5a as well as bradykinin are substrates of TAFI’s carboxypeptidase activity, and there is evidence that TAFI ameliorates diseases like acute lung injury (90) or immune complex-mediated glomerulonephritis (91) by inhibiting involved proinflammatory complement components.

The influence of inflammation on fibrinolysis as well as coagulation can also be described on the example of elastase. During blood coagulation polymorphonuclear leukocytes (PMN) become stimulated to release different proteases (92). One of these proteases is PMN-elastase (48). PMN-elastase cleaves multiple coagulation factors (e.g. factors V, VII, VIII, IX, XII), hereby, reducing thrombin formation (93). Additionally, PMN-elastase has the capacity to degrade fibrin networks, even though its catalytic efficiency is significantly lower when compared to plasmin (94). However, PMN-elastase digests plasminogen and during this process miniplasminogen is generated, which is converted to miniplasmin by plasminogen activators (95). As miniplasmin efficiently degrades fibrin networks (94), the net effect of the release of elastase after PMN activation is anticoagulant and profibrinolytic. It is worth noting, that PMN-elastase can exert these functions only under the precondition that it escapes the inactivation by α1-protease inhibitor (α1PI) by compartmentalisation and/or the α1PI-inhibiting effect of myeloperoxidase (96).

The proteases released by PMN in fibrin clots additionally are involved in suppression as well as activation of factor XIII activity. PMN-elastase has been characterised as a key enzyme degrading both factor XIII subunits, hereby down-regulating factor XIII’s crosslinking activity (97). Later on, the same group described PMN-elastase to generate an enzymatically active truncated factor XIII A subunit (98). Interestingly, the kinetics of this factor XIII activation process are independent of the FXIII-A Val34Leu genotype, which is known to influence the kinetics of thrombin-mediated factor XIII activation.

Figure 2: Hypothetical model for the relation between fibrin gel formation and inflammation control. A) Fibrinogen genotypes modulate the amplitude of fibrinogen level variation under proinflammatory stress. The individual characteristics of fibrin clot structure and fibrin(ogen) cleavage products affect control of inflammatory processes. B) Fibrinogen genotypes are associated with the extent of inflammation. Carriership of the FXIII subunit A (FXIII-A) 34VV genotype (wild-type) is conditional for this relation. FXIII-A 34L: Carriership of at least one FXIII-A 34L copy.
Fibrinogen, factor XIII and inflammation: Potential clinical implications

When considering the relation of coagulation and inflammation it is attempting to speculate on the potential usefulness of coagulation-modulating drugs in inflammatory diseases. Two decades ago, Seitz et al. hypothesised that substitution of factor XIII might be beneficial in patients with ulcerative colitis and Crohn’s disease. This hypothesis was based on the finding that patients suffering from these diseases exhibit lower factor XIII levels and that factor XIII levels tend to be inversely related to disease activity (99). As early case reports indicated a clinical improvement of patients suffering from chronic inflammatory bowel diseases after substitution of factor XIII, this therapeutic option has been investigated in a prospective pilot study, in which treatment with factor XIII resulted in reduced inflammatory activity (100, 101). However, these findings could not be confirmed in a prospective, double blind, placebo-controlled study published some years later (102).

Different other studies indicate that factor XIII treatment could have some beneficial effects in other inflammatory or inflammation-related diseases. Thus, in an experimental sepsis model, administration of factor XIII significantly protected intestinal mucosal capillary perfusion against endotoxin-induced impairment (103). Furthermore, there is evidence that factor XIII diminishes organ dysfunction induced by gut-ischaemia/reperfusion injury or haemorrhagic shock (104, 105). In both cases, an improvement or preservation of endothelial barrier function due to factor XIII is assumed to explain factor XIII’s beneficial effect. Studies on the relevance of extravascular coagulation, fibrin deposition and factor XIII activity in inflammatory pulmonary diseases additionally suggest that a modulation of these terminal steps of coagulation might be a tool to influence inflammatory activity in these diseases (106, 107).

While information on potential inflammation-modulatory effects of fibrinogen is sparse, there are some studies on the effect of antifibrinolytics or other coagulation-modulating drugs on inflammatory processes. Some of these studies are focussing on rheumatoid arthritis (RA) as coagulation and particularly fibrin are assumed to be parts of pathogenetic pathways leading to this chronic inflammatory disease (68). The inhibition of fibrinolysis by tranexamic acid did not exhibit any effect on RA activity in two studies (108, 109). When studying the effect of anticoagulation by hirudin in animal models of RA an amelioration of inflammatory activity could be demonstrated (110, 111). Whether this effect is related to inhibition of coagulation, i.e. reduced or altered fibrin gel formation, or directly to inhibition of thrombin, has to be elucidated yet.

The impact of antifibrinolytics on inflammation has been studied in a surgical context, as well. When considering the course after cardiac surgery, inhibition of fibrinolysis has been described to reduce the inflammatory response (112, 113). Interestingly, depending on the antifibrinolytic drug used, different inflammatory pathways seem to be modulated on a genomic expression level. Thus, in patients treated with aprotinin the expression of 11 genes is altered postoperatively when compared to placebo, whereas in the group treated with tranexamic acid only three genes are affected (113). In this study in general a reduced up-regulation of proinflammatory and an increased up-regulation of anti-inflammatory genes was described in patients treated with antifibrinolytic drugs.

Conclusion

Fibrinogen, factor XIII and fibrinolysis are essential parts of the haemostatic system. Moreover, a multitude of data supports the assumption that they play significant roles in innate immunity and inflammation control. These roles in part might be the result of a merely mechanical barrier function of crosslinked fibrin networks. However, fibrinogen and its derivatives specifically address different interactions with molecular and cellular counterparts that mediate functions in inflammation control in a much more subtle way. The further elucidation of the molecular basis of the interactions between coagulation, fibrinolysis and inflammation will not only improve our knowledge of disease mechanisms, but could also permit the development of innovative therapeutic interventions.

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Conflicts of interest

None declared.

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