Fibrinogen, Fibrinogen Chains, Its Derivatives, and Fibrinogen-Like Proteins

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Contributor: Nurul H. Sulimai, Jason Brown, David Lominadze

Fibrinogen (Fg), its derivatives and Fg-like other proteins play a considerable role in many diseases. For example, increased levels of Fg have been found in many inflammatory diseases, such as Alzheimer's disease, multiple sclerosis, traumatic brain injury, rheumatoid arthritis, systemic lupus erythematosus, and cancer. Associations of Fg, Fg chains, its derivatives and Fg-like proteins with various diseases have been established and their specific effects and the mechanisms of actions gradually become more evident.

Keywords: fibrin ; fibrinogen synthesis ; fibrinogen effects ; neuroinflammation ; neurodegeneration

1. Introduction

Fibrinogen (Fg) plays an integral role in blood clotting, and it is a vital protein for survival [1]. However, when its normal content in blood changes, it may lead to various pathological alterations. Inflammation causes an increase in the blood content of Fg and other acute-phase reactant plasma proteins [2][3]. A high concentration of Fg in the blood, called hyperfibrinogenemia (HFg), has been found in many inflammation-associated diseases such as cancer [4][5], rheumatoid arthritis [6], systemic lupus erythematosus [7], Alzheimer's disease (AD) [8], traumatic brain injury (TBI) [9][10][11], and vascular diseases [12][13] including heart disease [12][14], stroke [15], hypertension [16][17][18], and diabetes [12][19]. There are also disorders associated with alterations of Fg's function that could be inherited or acquired and can be manifested as altered hemorrhagic and thrombotic susceptibilities. Two examples are afibrinogenemia, a very rare condition characterized by the absence of circulating Fg, and hypofibrinogenemia, which is characterized by a reduced level of circulating Fg. Acquired Fg disorders could be caused by a liver disease that affects the synthesis of normal level of functioning Fg or by a consumptive coagulopathy condition such as disseminated intravascular coagulation [20].

2. Biosynthesis of Fg, Fibrinogen-like 1 (FGL1), and Fibrinogen-like 2 (FGL2) Proteins

Fg is primarily synthesized in liver hepatic parenchymal cells [21]. Fg consists of three pairs of polypeptide chains, Aα, Bβ and γ, joined by disulfide bonds to form a symmetric dimeric structure [21][22][23]. The assembly of the final form of Fg takes place intracellularly in the endoplasmic reticulum (ER) and requires well-coordinated steps that happen rapidly, within less than five minutes [21]. The intracellular oligomers of Fg chains are the α chain (FGA), β chain (FGB), and γ chain (FGG) with the apparent molecular masses of 66,000, 52,000 and 46,500 Da, respectively [22]. The mechanism of Fg assembly has been well studied and it has been widely accepted that it involves several coordinated steps [22], which include translation of each of the chains, their translocation into the lumen of the ER, and interactions of these chains with nascent proteins that assist in the assembly and folding processes [21]. Briefly, first, the single chains of Fg interact with each other to form Aα-γ and Bβ-γ complexes [21]. Then, the two-chain complexes acquire another chain to form three-chain half-molecules $(Aα, Bβ, γ)_1$. Finally, two half-molecules are joined at their N-termini to form a six-chain dimeric hexamer $(Aα, Bβ, γ)_2$ [21]. When fully assembled, Fg is secreted into the circulation at the normal concentration ranging from 2 to 3 g/L of plasma. Chaperone proteins play an important role that assist in protein folding, chain assembly, disulfide bond formation, and ER quality control mechanism to ensure that only correctly assembled and folded proteins exit the ER [21][24]. Early on, nascent Fg chains were found being associated with a resident ER chaperone, BiP (GRP78) [25]. The role of chaperone proteins in Fg assembly has been clarified further by Tamura et al., proposing a slightly different Fg assembly process in a two-step manner [24]. The first step is the integration of the β chain into the pre-formed αγ complex to form the trimer. The second is the integration of the two trimers to assemble the hexamer [24]. The proposed two-step assembly process involved participation of ER chaperone proteins Calnexin (CNX), an ER-resident type I membrane protein, and its soluble homologue, calreticulin (CRT) [24]. CNX and CRT are lectin-type chaperones that assist immature protein folding by recruiting endoplasmic reticulum protein 57 (ERp57). It was proposed that CNX temporarily

holds the preexisting Fg αγ complex through monoglucosylated N-linked glycans until the newly synthesized Fg β chain is integrated into the αγ complex to form a Fg trimer [24]. Then, this trimer is handed off to ERp57 from CNX. Next, the protein disulfide isomerase ERp57 facilitates the integration of the two trimers into the hexamer by catalyzing the disulfide bonds formation of glycoproteins [26]. Subsequently, the properly assembled Fg hexamer is moved forward to the secretory pathway [24].

Not all the Fg chains that are synthesized are used in assembly of a fully functional Fg protein. Studies that were carried out to test Fg biosynthesis in human hepatocellular carcinoma (HepG2) cells in vitro showed that under normal conditions, when Fg is expressed at basal levels, there is a surplus of Aα and γ chains that form a steady state pool presented as Aα-γ and free γ chains [21]. It has been shown that human cultured astrocytes and neurons constitutively express all three Fg chains [27]. The surplus Fg chains that are not secreted are eventually degraded by proteolytic lysosomes and proteasomes [21][28]. In addition, it has been shown that there is a quality control mechanism in Fg secretion, that is tightly regulated, allowing retention of certain chains or unfinished complexes and prevent them from being secreted [29]. Thus, only the fully assembled Fg is secreted into the blood circulation [21]. Besides being primarily synthesized in hepatocytes, Fg synthesis has been reported in fibroblast-like cell lines derived from monkey kidney (COS cells) [25], baby hamster kidney fibroblast cells [30], lung epithelial cells [31], and human breast cancer epithelial cells [32].

FGL1, or hepassocin, is a liver-specific 68 kDa molecular weight protein secreted primarily by hepatocytes [33]. It contains a Fg domain at its C-terminal (similar to those in FGB and FGG), which makes it highly homologous to Fg. However, what makes it different from Fg is that it is missing three functional domains: the platelet binding site, the cross-linking region, and the thrombin sensitive site [34]. This makes it irrelevant to coagulation-related functions.

FGL2, also known as fibroleukin, is identified as two distinct isoforms, membrane associated FGL2 (mFGL2) and soluble FGL2 (sFGL2) [35]. mFGL2 is a 70 kDa transmembrane protein expressed in ECs, epithelial cells, dendritic cells, and macrophages [35]. mFGL2 functions as a prothrombinase and is capable of initiating coagulation in tissue by serine protease activity, which can cleave prothrombin into thrombin through a noncanonical pathway [34][35]. sFGL2, which is a 50 kDa protein, is highly expressed by regulatory T cells [34]. It can be secreted into the vasculature and has been found to suppress T cell activation [35]. FGL2 is constitutively expressed in cells of the heart, lung, small bowel, spleen, ovary, uterus, liver, and kidney [36].

3. Disorders Associated with Plasma Levels of Fg

Plasma Fg levels are regulated by complex interactions between environmental and genetic factors [37][38]. Based on twin studies it is estimated that only 30–50% of the plasma Fg level is genetically determined [37][38]. Data acquired from a long-term, ongoing cardiovascular cohort, the Framingham Heart Study that began in 1948 (now with its 3rd generation of participants), revealed that Fg is a moderately heritable blood protein that is influenced by gene, environment, and disease status [39]. These rare congenital Fg disorders can be subclassified in type I and type II disorders. Type I disorders (afibrinogenemia and hypofibrinogenemia) reflect level of Fg in blood (amount of Fg < 1.8 g/L), whereas type II (dysfibrinogenemia and hypodysfibrinogenemia) affect primarily the quality of Fg in the circulation [40][41]. According to the European Network of Rare Bleeding Disorders (EN-RBD) along with the International Society of Thrombosis and Hemostasis, Fg deficiency may be classified into mild hypofibrinogenemia (lower limit of normal level—1.0 g/L), moderate hypofibrinogenemia (0.9–0.5 g/L), severe hypofibrinogenemia (0.5–0.1 g/L), and afibrinogenemia (<0.1 g/L) [42][43].

Several inherited and acquired Fg disorders have been described that affect the quantity (afibrinogenemia and hypofibrinogenemia) or the quality/property (dysfibrinogenemia) of circulating Fg that cause abnormalities in the function of the Fg molecule in some cases resulting in noticeable pathologies such as bleeding or slower clotting time [44].

The low Fg level is reflected by abnormal clotting times with a tendency to bleeding, which is further exaggerated more in patients with afibrinogenemia than with hypofibrinogenemia [44]. On the other hand, dysfibrinogenemia that is associated with disorder in Fg structure, which can be congenital or acquired in origin may or may not result in abnormal function [45].

During severe trauma, massive bleeding that is associated with a resultant decreased blood level of Fg is quite common. In addition, there are other factors that affect Fg metabolism and reduce its availability in patients with severe trauma. Hypothermia reduces Fg synthesis, acidaemia following hypoperfusion increases the breakdown of Fg, and diluting blood by intravenous infusion of crystalloid fluid or synthetic colloid has been shown to reduce the content of Fg and Fg-fibrin conversion [46].

There is also a genetic disorder that is associated with HFg, a condition comprised of polymorphisms where the β fibrinogen promoter -455A allele has been shown to be associated with a higher (2.8–3.7 g/L) plasma level of Fg and an

increased risk of atherothrombotic disease [38].

Age is one of the factors that could affect the concentration of Fg in blood. Level of Fg tends to increase with age, and it is known that average plasma concentrations of Fg are higher in females (3.5 g/L) compared to that in males (3.3 g/L) [47] [48]. Although it is statistically significant, the clinical significance of this difference is debatable. Interestingly, smokers show higher average plasma concentrations than non-smokers [47] and exposure to traffic pollutants is also associated with higher Fg concentrations [39]. This might be due to particles deposited in the lungs inducing alveolar inflammation. Various factors such as age, obesity, physical activity, and a disease status have been reported to elevate Fg concentration [47]. The influence of diet on the Fg level in plasma is only modest, with patients with high lipid levels having high levels of Fg, however consumption of fish oil and moderate consumption of alcohol are associated with lower Fg level [37].

It has been well documented that Fg levels are positively correlated with metabolic syndrome [47]. Metabolic syndrome is characterized by the presence of abdominal obesity, atherogenic dyslipidemia, raised blood pressure, presence of insulin resistance, and prothrombic and inflammatory states that predispose to cardiovascular diseases [49]. Since these risk factors are also common for patients that suffer from chronic obstructive pulmonary disease (COPD), it is not surprising that blood level of Fg is found to be positively correlated with the development and severity of COPD, COPD-related hospitalization, and increased risk of the resultant death [50].

Although it is known that the singular chains of Fg do not circulate in blood [21], FGA precursor protein has been found in cerebrospinal fluid (CSF) collected from human patients [51]. The FGA precursor was found at a higher level in patients with Alzheimer's Disease (AD) compared to that in patients diagnosed with mild cognitive impairment and age-matched normal controls [51]. The level of FGA precursor was positively correlated with the severity of cognitive impairment with its highest concentration seen in the group of patients demonstrating severe impairment of memory and cognition [51]. Although it is proposed as a good source of the biomarker (FGA) for the severity of cognitive impairment in AD patients, the procedure to collect CSF samples is too invasive and painful to make it practical. Fg, in an amount ranging from 0.002 to 0.008 g/L was detected in the CSF of patients with brain disorders including bacterial or viral meningitis, Guillain-Barré, and major depressive disorder has been documented [52]. How Fg and the FGA precursor enter the CSF remains unclear.

Thrombosis can be defined as an increased hemostatic response that results in the formation of an occlusive blood clot and the obstruction of blood flow in vasculature. Whereas inflammation is characterized by the complex protective immune response to harmful stimuli [53]. Cancer is an inflammatory disease where, in most cases, plasma Fg is increased, and the patients have a higher risk of developing thrombosis. In general, this occurs due to increased blood viscosity, the resultant activation of endothelial cells, and platelet thrombogenic properties. The functional interdependence of thrombosis and inflammation are well-recognized [53].

Activation of the extrinsic coagulation system and the fibrinolytic cascade may be related with growth, invasion, and metastasis of tumor cells [54]. It is indisputable that there is crosstalk between coagulation and inflammation, both being affected by Fg. An inflammatory response shifts the hemostatic system toward a prothrombotic state while coagulation, in parallel, affects inflammation [55]. During coagulation, cleavage of Fg by thrombin results in release of fibrinopeptide A and fibrinopeptide B (FpB) and triggers fibrin polymerization [55]. FpB has been shown to be a potent chemotactic agent for polymorphonuclear neutrophils and fibroblast [56]. Other Fg/fibrin degradation products such as the Fg fragment D, D-dimer generated by plasmin digestion of fibrin that is commonly used as a biomarker for fibrinolysis and disseminated intravascular coagulation, fibrin fragment E, and Bβ15-42, a fragment of the *N*-terminal β chain have also been shown playing a role in the inflammatory reaction [55].

Like Fg, FGL1 was found to be increased in an experimental model of acute inflammation [33][34] indicating its role in an acute phase reaction. FGL2 also has potential to be used as a biomarker for certain condition since circulating sFGL2 was found to be correlated with viral loading and disease severity in patients with human hepatitis B virus or hepatitis C virus (HCV) infections [57]. Plasma level of FGL2 was shown to be positively correlated with chronic HCV infection titers and the degree of inflammation in the liver [57]. Among the HCV patients, higher FGL2 level is associated with the severity of fibrosis.

In the tumor microenvironment, Fg regulates the expression of genes involved in cell cycle regulation and metabolism, promotes tumor growth, and limits tumor cell senescence [58]. During inflammation, the blood level of Fg increases and remains elevated for more than 21 days [2]. In cases of severe TBI, Fg concentration initially dropped due to trauma-induced loss of blood, but its concentration increased above 4 g/L two days after injury, peaked to the level of 5.8 ± 0.35 g/L on day 6, and remain elevated for 2 weeks [10]. It is known that, after head injury, there is an acute BBB disruption not

only in severe but also in some of the mild and moderate TBI [9]. It has been shown that in some of the moderate or severe cases of TBI, the BBB disruption persist long after the impact at the site of contusion [9]. It have shown that at high levels Fg altered cultured EC layer integrity through downregulation of vascular endothelial cadherin and matrix metalloproteinase-9 activation [59] along with alteration in the expression of actin-associated endothelial tight junction proteins [60]. An interaction of Fg with endothelial ICAM-1 and α5β1 integrin caused a dose-dependent increase in EC layer permeability to albumin and to the Fg itself [61]. This Fg-induced increased endothelial permeability occurred in conjunction with enhanced formation of F-actin and the formation of gaps in the EC monolayer [61]. However, during neuroinflammation, such as TBI, HFg enhanced formation of functional caveolae in the mouse brain ECs [62] resulting in increased cerebrovascular permeability mainly through caveolar protein transcytosis [63][64]. The increased cerebrovascular permeability associated with HFg that occurred during TBI [11] and with HFg in general [65] can be one of the strongest mechanisms for deposition of Fg in the brain parenchyma in response to inflammation. Fg deposits were found in postmortem brain samples from humans diagnosed with TBI [9][66]. Fg deposition in the brain perivascular space was more diffused in instances of acute TBI [66], but it was less diffused in samples with long term survival, chronic TBI [9][66]. Similar to findings in human TBI cases [9][10], it was found that mild-to-moderate TBI in mice was accompanied with HFg [11]. Due to increased cerebrovascular permeability Fg was translocated to the extravascular space of the brain [11] where it was deposited in the vasculo-astrocyte endfeet interface [67]. The extravasated Fg formed complexes with proteins such as amyloid beta [65] in addition to astrocytic and neuronal (ICAM-1) and cellular prion protein (PrP^C) [11][68][69]. Formation of these protein complexes were associated with a reduction in short-term memory [11][65] indicating a possible cause and effect relationship between the HFg and cognitive impairment during neuroinflammatory diseases [65][70].

HFg is not only a biomarker of inflammation [3], but it has been shown to be a cause of inflammatory responses [11][13][59][60][61]. It was shown that Fg dose-dependently activates astrocytes [71] and induces upregulation of ICAM-1, TrkB, cytokines such as C-X-C motif chemokine 10, IL-6, and C-C motif chemokine 2 (CCL2) [72][71]. In neurons, HFg induced upregulation of IL-6, and increased generation of reactive oxygen species, mitochondrial superoxide and nitrite [68].

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disorder characterized by lymphocytic infiltration, demyelinating white matter lesions with perivascular inflammation, and axonal damage concentrated in the CNS [73]. HFg is considered a risk factor for patients with MS with plasma levels of Fg exceeding 4.17 g/L and MRI scans demonstrating active lesions [74]. Moreover, it is stipulated that Fg is not only a biomarker for MS, but it is also involved in the development of the disease. The pro-inflammatory role of Fg in the pathology of MS has been shown in the experimental animal model of autoimmune encephalomyelitis [75]. A Fg injection into the cortex of $Cx3cr1^{GFP/+}$ reporter mice for resident monocytes, induced rapid and sustained microglial responses in vivo, was associated with axonal damage and release of reactive oxygen species in microglia [75].

Fibrinogen Hindering Autoimmune Cell Reaction

Fg conversion to fibrin is a part of normal hemostasis necessary for wound healing. In fact, Fg-fibrin grafts have been used as dressing to promote hemostasis and slow wound healing during diabetes [76]. Fibrin mesh that forms over the skin wound has been shown to form a barrier and effectively defend against microbial invasion [77]. Interestingly, it has been reported that the exposure of Fg to disulfide-reducing agents results in the formation of insoluble aggregates, which if adhered to tumor cells act as a barrier to tumor recognition by the innate immune system [78]. Similar aggregates could be formed by involvement of free iron [79]. In the absence of specific chaperons, the exposed hydrophobic epitopes of Fg form scrambled linkages forming fibrin-like fibrils (parafibrin). Parafibrin has a total resistance to proteolytic degradation. As a result, once attached to the surfaces of cells, parafibrin induces a permanent state of inflammation resulting in the release of cytokines and proteases from macrophages impairing their functions [80][81]. Destructive effects of parafibrin have been shown in pathogenesis of AD [80]. It has also been shown that fibrin can form a physical barrier that protects the cancer cells from the action of natural killer (NK) cytotoxicity [82]. Only a limited quantity of NK cells adhered to the tumor cells, suggesting that Fg/fibrin blocked the formation of an effector-target conjugate with approximately up to 80% effectiveness [82].

4. Fibrinogen Signaling

It was found that a Fg interaction with PrP^C induced overexpression of tyrosine receptor kinase B (TrkB) and activation of astrocytes [83]. TrkB is a receptor for brain-derived neurotropic factor which is a critical growth factor in neuronal cell growth, differentiation, morphology, and synaptogenesis [84]. This Fg-induced upregulation of TrkB [83] coincided with other data showing that overexpression of TrkB in astrocytes is associated with increased nitric oxide production and nitrotyrosine deposition that ultimately promote neurodegeneration [85]. It also found that Fg induced upregulation of pro-

inflammatory cytokine interleukin 6 not only in astrocytes [72] but also in neurons [68]. Furthermore, Fg induced enhanced generation of reactive oxygen species and nitrite in astrocytes [86] and mitochondrial superoxide in neurons [68]. All these indicated a presence of oxidative damage, which led to apoptosis and increased cell death in astrocytes and neurons [72][68]. These effects, including Fg-induced upregulation of the pro-inflammatory cytokines, oxidative damage, and increased cell death, were ameliorated when the functions of ICAM-1 or PrP^C were blocked with respective function blockers [72][68], thus indicating a specific effect of Fg.

Fg has been shown to induce activation of NF-κB in human pancreatic stellate cells (PSC) via binding to $\alpha_v\beta_3$ and $\alpha_5\beta_1$ located on the cells [87]. Fg induced upregulation of IL-6 in the PSC in 24 h, similar to the study [72][68]. Fg was also found to activate three classes of MAPKs (extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and p38 MAPK, and Akt) in a time-dependent manner, most prominently between 5 to 60 min after incubation with the PSC cells [87]. The Fg-induced upregulation of IL-6 and interleukin-8 was almost completely inhibited when an NF-κB inhibitor was used, but only partially inhibited by inhibitors of ERK and p38 MAPK [87], suggesting that NF-κB may play a greater role in Fg transduction in the PCS. Although it has never been shown before, it is possible that Fg-induced pathology during TBI involves the NF-κB signaling pathway, which is best known for its regulation of inflammation and innate immunity.

The role of Fg in cerebrovascular dysfunction during TBI has been shown [65][70][88][89]. However, the connecting signaling pathway of Fg-induced pathology during TBI was not clear. Identifying the mechanisms and signaling pathways that govern the contribution of Fg to the pathology during TBI may reveal the window of opportunity for therapeutic target(s) and possible interventions. It has been shown that NF-κb was detected in different type of cells in the brain during TBI including ECs, neurons, astrocytes, and microglia [90].

It has been shown that Fg in the extracellular matrix of colorectal tumor cells interacts with integrin receptors that trigger the downstream effector molecule, focal adhesion kinase (FAK), on the cytosolic segment of focal adhesion complexes [58]. FAK is a cytoplasmic tyrosine kinase located in focal adhesion complexes. It regulates integrin-mediated cell spreading, migration, and signaling events [91]. Fg in the tumor microenvironment regulates expression of genes involved in cell cycle regulation and metabolism, promotes tumor growth, and limits tumor cell senescence [58]. Analogous to its role as a major adhesive glycoprotein involved in the final stages of blood clotting, Fg deposition, along with other adhesive glycoprotein, potentially provides a matrix that serves as a scaffold for adherence with other proteins or receptors on cells to mitigate cellular responses.

It has been shown that Fg interacts with several cell types through cell-specific integrins and other receptors [92]. Fg has been shown to interact with the integrin $\alpha_{IIb}\beta_3$ on platelets and mast cells resulting in platelet aggregation, thrombus formation, affecting systemic blood pressure regulation [92]. Fg's interaction with $\alpha_M\beta_2$ on microglia and macrophages causes their activation, infiltration, cytokine release, and phagocytic activity [92]. In general, since Fg is predominantly found in the blood, it naturally interacts first with blood cells and ECs. Only after crossing the EC layer in brain microvessels, it becomes possible for Fg to interact with astrocytes, microglia and then with neurons.

Some effects of fibrinogen/fibrin, fibrinogen chains, and fibrinogen-like proteins 1 and 2 during various diseases are presented in the table below (**Table 1**).

Table 1. Effects of fibrinogen/fibrin, fibrinogen chains, and fibrinogen-like proteins 1 and 2 during various diseases.

Protein/Chain	Disease	Protein Level or Condition	Role in Pathology and/or Outcome	References
Fg	Colon cancer	↑	Biomarker. Low survival.	[4]
Fg	Gastric cancer	↑	Biomarker. ↑ lymph node and liver metastasis, ↓ clinical outcome.	[93]
Fg	Cervical cancer	↑	Biomarker. Low survival.	[94]
Fg	Renal cell carcinoma	↑	Biomarker. Low survival.	[95]

Fg	Hepatocellular carcinoma	↑	Biomarker. Low survival.	[96]
Fg and D-dimer	Breast cancer	↑ , ↑	Biomarker. Accelerated tumor growth and low survival.	[54]
Fg and D-dimer	DIC	↓ , ↑	Biomarker. Low survival.	[97]
Fg	RA	↑	Biomarker. Hypercoagulation and inflammation.	[6]
Fg	SLE	↑	Biomarker. ↑ atherothrombosis.	[7]
Fg	TBI	↑	↑ cerebrovascular permeability.	[11][65]
Fg	TBI	↑	Extravascular deposition of Fg, ↑ neuronal death, ↓ STM.	[67]
Fg	TBI	↑	↑ extravascular formation of Fg/fibrin containing protein complexes.	[9][11][65]
Fg	AD	↑	↑ perivascular formation of Fg/fibrin containing protein complexes	[98]
Fg	AD	↑	↑ risk of AD and dementia	[8][99]
Fg	COPD	↑	Biomarker. ↑ risk of death.	[50]
FGA precursor protein	AD	↑ in CSF	Biomarker. Mild cognitive impairment and dementia.	[51]
FGA precursor protein	Liver cancer	↑ in CSF	Biomarker. ↑ survival rate.	[100]
FGA	Human lung adenocarcinoma	↑	Cell apoptosis inhibits tumor growth and metastasis.	[101]
FGB	Polymorphism of *FGB* promoter	↑	↑ plasma Fg. ↑ risk of atherothrombosis.	[38][102]
FGB	In patients undergoing coronary artery bypass grafting	*FGB*-C148T polymorphism	Results in preoperative HFg and postoperative ↑ CRP, ↑ IL-6.	[103]
FGG	Hereditary hypofibrinogenemia with hepatic storage	Mutation location in exons 8 and 9 of the *FGG* gene	Protein aggregation in the endoplasmic reticulum, liver diseases of variable severity.	[44]

FGL1	Acute inflammation	↑	Acute phase reactant	[33][34]
FGL1	Cancer (in general)	↑	Immunosuppressor through binding to LAG3. Poor prognosis.	[104]
FGL2	HBV orHCV	↑	Correlates with viral loading, degree of liver inflammation and disease severity.	[35][57]
FGL2	HBV orHCV	↑	Immunosuppressive activities	[105]
FGL2	Autoimmune glomerulonephritis	↓	Autoimmune glomerulonephritis with age	[106]
FpB	Inflammation	↑	↑ chemotaxis of PMN and fibroblast.	[56]

Abbreviations

AD	Alzheimer’s disease
CSF	Cerebrospinal fluid
COPD	Chronic Obstructive Pulmonary Disease
CRP	C-reactive protein
DIC	Disseminated intravascular coagulation
FG	Fibrinogen
FGA	Fg alpha chain
FGB	Fg beta chain
FGG	Fg gamma chain
FGL1	Fg-like protein 1
FGL2	Fg-like protein 2
FpB	Fibrinopeptide B
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HFg	Hyperfibrinogenemia

IL-6	Interleukin-6
LAG3	Lymphocyte-activation gene
MS	Multiple sclerosis
PMN	Polymorphonuclear neutrophils
RA	Rheumatoid arthritis
STM	short-term memory
SLE	Systemic lupus erythematosus
TBI	Traumatic brain injury

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