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# Role of Fibrinogen in Vascular Cognitive Impairment in Traumatic Brain Injury

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## Abstract

Fibrinogen (Fg) is one of the biomarkers of inflammation and a high risk factor for many cardiovascular and cerebrovascular diseases. Elevated levels of Fg (hyperfibrinogenemia, HFg) are also associated with traumatic brain injury (TBI). HFg in blood alters vascular reactivity and compromises integrity of endothelial cell layer that ultimately can result in extravasation of Fg and other plasma proteins. Proteins deposited in extravascular space may form plaques which can lead to neurodegeneration. Among these plasma proteins are amyloid beta ( $A\beta$ ) and/or cellular prion protein (PrP<sup>C</sup>) that can form degradation resistant complexes with Fg and are known to be involved in memory impairment. The purpose of this chapter is to propose and discuss some possible mechanisms involved in HFg-mediated cerebrovascular dysfunction leading to neuronal degeneration during TBI.

**Keywords:** astrocytes, fibrinogen deposition, neuroinflammation, neurodegeneration, neurovascular unit

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## 1. Introduction

Traumatic brain injury (TBI) is the devastating cause of death and disability worldwide, for which no effective treatment exists other than supportive care [1]. It is a heterogeneous disease that is classically classified as mild, moderate, and severe TBI according to clinical severity using the Glasgow coma scale (GCS) for evaluation [2]. According to epidemiological data falls are the leading cause of TBI, followed by vehicle accidents and physical assaults including sports-related head traumas along with blast injuries that mainly occur in war zones. Pathoanatomic classification of TBI includes penetrating (open) or closed (blunt) head injuries, hemorrhages (epidural, subdural, subarachnoid, intraparenchymal, intraventricular) as well as focal and diffuse patterns of lesions. Classification of TBI by outcome includes categories such

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as death, vegetative state, disability (severe or moderate) and good recovery. Etiologically TBI is subdivided into “primary” and “secondary” injury based on their triggering mechanisms. Thus, while “primary” injury occurs immediately after a direct physical impact of damaging force, the “secondary” injury is a result of adverse effects of responses in the parenchymal tissue developing due to the “primary” injury. Defining TBI classification is very important for further diagnostic, treatment, clinical management, and prevention and prediction of outcome in patients with TBI [3].

TBI is associated with systemic inflammation [4, 5] that includes elevation of plasma content of fibrinogen (Fg, called hyperfibrinogenemia, HFg). According to clinical data blood level of Fg is elevated after mild-to-moderate TBI (when vascular ruptures are minimal or non-existent) [6]. It is known that formation of Fg-containing protein complexes is associated with memory reduction emphasizing role of this inflammatory protein. Therefore, in this chapter we propose and discuss possible mechanisms involved in alterations of neuronal function associated with systemic inflammation particularly with HFg during TBI. Since at elevated levels Fg affects vasculature and only then it is involved in vasculo-astrocyte uncoupling [7], the main emphases are given to neuronal degeneration or dysfunction that occurs due to changes in cerebrovascular properties.

## 2. Traumatic brain injury and blood-brain barrier

The harmful effects of TBI occur during primary injury and secondary complications. Primary damage is induced by a mechanical force that causes compression and physical damage of brain parenchyma that leads to changes in neurovascular unit (NVU) [8, 9]. The secondary complications can occur days or months or years after the initial insult due to further development of chronic inflammation, vascular impairment, chronic ischemia or progressive neurodegeneration [9, 10]. They may involve blood-brain barrier (BBB) impairment, cognitive decline, and memory deficiency [11]. Disruption of BBB has often been documented in patients with TBI [12], but the role of vascular pathology and its consequences in neurological dysfunction has only recently become a sphere of high interest.

BBB is the regulated interface between the peripheral circulation and the central nervous system (CNS). BBB is constituted by the cerebrovascular endothelial cells (ECs) and vascular smooth muscle cells, and together with astrocytes, pericytes, neurons, and associated extracellular matrix proteins represents a NVU [13]. Majority of CNS diseases are associated with mechanical and functional disruption in NVU. The changes and regulation of ion balance and homeostasis, oxygen and nutrition supply, transport of hormones and neurotransmitters depend on normal function of cerebral vessels and blood flow properties. Therefore, because of events initiated in the vasculature as a result of vascular dysfunction, alterations in blood flow and/or changes in blood component properties, which prompt or exacerbate neuronal dysfunction/degeneration, the term “vasculo-neuronal” dysfunction seems more appropriate to emphasize the source of destructive effect in CNS [10].

Studies have shown that increased BBB permeability is involved in initiation of pathological changes in the neuro-vascular network leading to neuronal dysfunction and degeneration.

BBB breakdown in patients with TBI usually confirmed with brain imaging results, and it is suggested to use it as a biomarker in the clinical studies and in drug trials.

The disruption of integrity of vascular walls caused by injury allows proteins such as thrombin, albumin, and/or Fg to enter CNS parenchyma. These proteins have the ability to activate astrocytes and microglia, which are the integral components of the NVU. These effects can be the cause of an increase in synthesis of pro-inflammatory cytokines, including tumor necrosis factor (TNF- $\alpha$ ), interleukin-1 (IL-1), interleukin-6 (IL-6), and others [14].

### 3. Inflammatory markers during TBI

The inflammatory markers can be defined as pro- and anti-inflammatory. The most commonly observed pro-inflammatory cytokines such as TNF- $\alpha$ , IL-1, IL-6 are elevated during TBI [14]. Interestingly, levels of an anti-inflammatory interleukin-10 (IL-10) are also elevated during TBI [15].

TBI-induced inflammation activates acute-phase responses. One of the most known acute-phase proteins is C reactive protein (CRP), which perceptibly increases during inflammation and rapidly decreases after inflammation subsides [16]. On the other hand, blood level of another acute-phase protein—Fg increases slowly and returns to its normal level about 21 days post-inflammatory stimuli [16]. Since Fg itself results in inflammatory responses [17–26], besides being an inflammatory marker, it is considered as a pro-inflammatory protein.

In brain tissue, TNF- $\alpha$ , a well-known pro-inflammatory cytokine, is produced by microglia, astrocytes, endothelial cells, and neurons. The effects of TNF- $\alpha$  are associated with apoptotic/necrotic cell death induction [27]. TNF- $\alpha$  expression takes place shortly after neuronal injury and it is actively involved in process of neutrophil and monocyte recruitment to the site of the damage. The appearance of TNF- $\alpha$  varies from 1 to 24 h following the trauma (the peak is considered at 4–12 h following initial insult). Some scientists consider TNF- $\alpha$  as a marker of severe TBI [28]. There are data indicating a significant association of TNF- $\alpha$  with cognitive impairment during TBI [29]. However, it is known that in addition to induction of apoptotic/necrotic cell death, TNF- $\alpha$  is also involved in stimulation of cell growth and differentiation. Therefore, the role of TNF- $\alpha$  during TBI may still remain unclear since it has been shown to possess both neurotoxic and neuroprotective effects [27].

The main function of IL-1 is regulation and release of other cytokines. It is expressed in multiple cell types in the brain tissue. Expression of IL-1 is mostly associated with acute TBI [30]. There is a discrepancy in literature regarding the IL-1 detection in serum and cerebrospinal fluid (CSF) during TBI. One of the most reported isoforms of IL-1 family in TBI patients is IL-1 $\beta$ . It is highly involved in release of prostaglandins, apoptosis, leukocyte adhesion to ECs, BBB disruption, and edema formation. The use of IL-1 receptor antagonist, which improves cellular and behavioral outcomes emphasizes the basic pro-inflammatory and neurotoxic effect of IL-1 during TBI [30].

While some consider IL-6 a highly sensitive, but not specific biomarker for neurotrauma [28], others claim that it is not exclusively expressed in response of head trauma and predominantly

indicates state of BBB integrity [31]. IL-6 is expressed by astrocytes, glial cells and neurons. Normally it is not detectable in serum and plasma but under pathological conditions level of IL-6 increases and points to mainly axonal injury [28]. Drastically increased levels of IL-6 are observed in CSF during severe TBI that reaches its maximum levels in about 3 to 6 days after the initial insult. The involvement of IL-6 in cognitive impairment during TBI in mice is shown [32]. However, although IL-6 can be a strong marker of TBI-induced inflammation, use of IL-6 as a possible therapeutic target is limited as it cannot readily cross the vascular wall [30].

Interlukin-8 (IL-8) belongs to chemokines, a special class of small cytokines. It is secreted by endothelial cells, glial cells, neurons, macrophages, lymphocytes and neutrophils [28]. IL-8 induces chemotaxis and neutrophil phagocytosis and causes its attraction to the site of damage and inflammation. Generally the persistence of the activated leukocytes in brain from 1 to 4 weeks after injury is neurotoxic, and exacerbates the ongoing neuronal damage [28]. The level of IL-8 in CSF is greater than in plasma or serum during head injuries.

The most well-known anti-inflammatory cytokine IL-10 serves as an inhibitor of pro-inflammatory mediators and regulates the cytokines. It is suggested that IL-10 reduces the neuro-inflammation during TBI. It increases 24 hours after severe initial insult and coincides with decrease in TNF- $\alpha$  levels. In rat model of TBI, treatment with IL-10 results in reduction of IL-1 $\beta$  and TNF- $\alpha$  levels in brain tissue and improves neurological recovery [28].

Activation of transcription factor, nuclear factor kappa B (NF- $\kappa$ B) that is also considered as an inflammatory marker, has been shown to play a key role in inflammatory response, neuronal survival and signaling [33]. First appearance of NF- $\kappa$ B occurs in axons shortly after trauma (1–2 h), and then in neurons (24 h) and lasts up to 1 week. Later (24 hours after initial insult), activated NF- $\kappa$ B is detected in microglia, macrophages, and astrocytes in cortexes [33]. Activated NF- $\kappa$ B is also detected in ECs, as early as 1 h after initial insult, and persists there for up to 1 year [33]. Hence, it can be suggested that NF- $\kappa$ B activation plays a role in long-term inflammatory processes during TBI.

#### 4. Fibrinogen (Fg)

One of the inflammatory mediators which is released after TBI-induced inflammation is Fg. It is a high molecular weight (~ 340 kD) plasma adhesion glycoprotein, that is primarily synthesized in hepatocytes. Inflammatory cytokines such as IL-1 and IL-6 are involved in Fg synthesis and stimulation of its synthesis, while increased plasma level of albumin suppresses it. Overexpression of these cytokines, that occurs during inflammation leads to HFg [34], which is a biomarker of inflammation and high risk factor for many cerebrovascular disorders [35–38]. Normally Fg concentration in blood is around 2 mg/ml. Higher content of Fg in blood is considered as a state of inflammation [39, 40] and it can be a cause of inflammatory responses [41]. It was shown that at high ( $\geq 4$  mg/ml) levels Fg increases arteriolar constriction [18], regulates production of endothelin-1 (ET-1) [19], enhances vascular layer permeability [21] to proteins, and can itself leak through the EC layer [20]. Since Fg is synthesized in hepatocytes and circulates



in blood, it may appear in extravascular space only after crossing the vascular wall. In brain, it may occur only if BBB is dysfunctional. Gradual deposition of Fg accelerates neurovascular damage and promotes neuroinflammation [42, 43].

Some clinical studies indicate that TBI is accompanied by hypo-fibrinogenemia, abnormally decreased blood level of Fg [44]. During severe brain injury that results in rupture of brain vessels and hemorrhage, blood cells and plasma components, including Fg come out of vessels. Particularly in the first 72 hours, the hemorrhage is an obvious cause of hypo-fibrinogenemia [44, 45]. In addition, activation of fibrinolytic system exacerbates hypo-fibrinogenemia [46]. However, 2 weeks after severe trauma and/or mild-to-moderate brain injury (when vascular ruptures are minimal or nonexistent), blood content of Fg increases [6, 47]. HFg can be noticeable in patients even 12 hours after initial insult [45]. Therefore, Fg crossing of vessel walls and its subsequent deposition in extravascular space, after the initial injury, can be a result of systemic or local inflammation.

## **5. Inflammation / vascular permeability / edema**

Inflammation is a complex of different biological responses of vascular tissue to harmful stimuli. The actions of various inflammatory mediators cause significant vascular changes such as increased permeability (hyper-permeability), vasodilation, and worsening of hemorheology [48]. Majority of vascular diseases that are associated with inflammation include stroke [49], myocardial infarction [50], hypertension [51, 52], diabetes [53, 54], atherosclerosis [55], and TBI [4, 5, 12]. Inflammation is a key contributor to many vascular diseases and plays a major role in autoimmune diseases [56], allergic reactions [57], and cancer [58]. Neuroinflammation is one of the crucial stage of injury after brain trauma [28].

Inflammatory processes may induce endothelial dysfunction and vascular remodeling [51, 59]. The normal endothelium forms a stable anti-inflammatory interface between circulating blood components and cells within tissues. The endothelium builds a barrier, which along with its associated structures such as basement membrane and/or glycocalyx maintain the relatively constant plasma volume and venous return, and prevent tissue edema [60]. Maintaining tissue homeostasis and contributing the functions of the vessel wall by establishing communications between blood and adjacent tissue are the two pivotal functions of vascular endothelium, which functions as a barrier and a permeable filter at the same time [61].

Increase in vascular permeability is one of the indications of inflammation. In result of hyper-permeability, blood plasma substances and proteins move out of the blood stream and deposit in subendothelial matrix (SEM) and interstitium and may cause edema [41, 62]. This phenomena can occur during mainly an early stages of acute inflammation [63].

One of the most dangerous secondary consequences of TBI with significant morbidity and mortality is cerebral edema. It is an abnormal accumulation of fluid within the brain parenchyma and is classified as vasogenic and cytotoxic [31]. Vasogenic edema is defined as fluid originating from blood vessels that accumulates around cells. Cytotoxic edema is defined

as fluid accumulating within cells as a result of injury. The most common cytotoxic edema occurs in cerebral ischemia. Heretofore, the edema specific to TBI has generally been considered to be of vasogenic origin, secondary to traumatic opening of the BBB. However, lately clinical studies showed the significant role of cytotoxic edema [31]. It is possible that both forms of edema can coexist. To define the type of edema (mostly by imaging technique) may be a decisive moment, as effective treatment will clearly depend on the major type of edema contributing to the brain swelling process.

## 6. Transvascular transport pathways

There are two major transport pathways for blood plasma components to pass through the endothelial barrier: transcellular and paracellular [62, 64, 65]. Paracellular pathway takes place when plasma components move between the ECs. It involves alterations in junction proteins and their interbinding forces [62]. It is implied that low molecular weight molecules take this pathway as oppose to transcellular transport of high molecular weight molecules such as proteins, which occurs mainly through the ECs and involves formation of functional caveolae (and/or fenestrae, and/or transendothelial channels [64]) and its motility [66]. Thus, movement of proteins across the vascular wall via transcellular transport pathway can be defined as caveolar transcytosis [67]. At elevated levels Fg can enhance caveolar transcytosis [68, 69]. The net transport of blood plasma substances in microcirculation is governed by the combination and the functional balance of transcellular and paracellular pathways.

Head injury-induced inflammation leads to an increased blood content of Fg [6, 47]. At elevated levels, Fg increases vascular permeability to other proteins and itself crosses the vascular wall [20, 47]. During majority of cardiovascular and cerebrovascular inflammatory diseases, increased levels and/or activity of the plasminogen system have not been observed. For example, activity of tissue plasminogen activator (tPA) is diminished in brains of patients with Alzheimer's disease (AD), mouse models of the disease [68], and during various inflammatory traumas [46]. Thus, an increased leakage of Fg, in the context of decreased or unaltered activity of the plasminogen system, leads to an enhanced deposition of Fg in extravascular space in pathologies such as TBI and AD. There, immobilized Fg can form different protein complexes [47, 70]. Furthermore, immobilized Fg is converted to fibrin by thrombin. Since protein fibrinolytic system can no longer counterbalance excess formation of fibrin, enhanced deposition of fibrin exacerbates neurovascular damage and neuroinflammation [42, 71].

## 7. Fg-containing complexes

After extravasation Fg deposits into parenchyma and makes complexes with other proteins. The most known is Fg amyloid beta ( $A\beta$ ) protein complex, called amyloid plaque [72], which is a hallmark of AD and it is associated with loss of memory [73]. The defects in  $A\beta$  and its precursor protein (APP) are considered a cause of AD and dementia. The neurotoxic  $A\beta$  peptide

(oligomers of A $\beta$ ) is derived from the APP and it is considered as a major constituent of the plaques. After deposition in SEM, Fg becomes readily available for binding to A $\beta$  oligomers and even APP. The appearance of Fg-A $\beta$  and/or Fg-APP complexes can be a result of vascular hyper-permeability leading to transcytosis of Fg to SEM [74]. It has been shown that binding of A $\beta$  to Fg leads to its oligomerization [70], and Fg-A $\beta$  complex is highly resistant to degradation [75]. Similarly, there is a strong evidence that Fg, which is found immobilized in extra-vascular space, besides being associated with A $\beta$ , can also be associated with other proteins, such as collagen and cellular prion protein (PrP<sup>C</sup>). Alteration of collagen content in SEM is one of the indications of vascular remodeling. Increased collagen level in cerebral microvessels during AD has been shown [76]. It was shown that collagen can serve as a substrate for Fg-A $\beta$  complex deposition in SEM [74]. The present results indicate an increased formation of collagen along with increased expression of A $\beta$  and enhanced deposition of Fg and A $\beta$ . Data suggest that during inflammation, increased cerebrovascular permeability leads to an enhanced deposition of Fg on SEM collagen through formation of Fg-A $\beta$ -collagen complex, which was found to be correlated with reduction of short-term memory [74].

Some studies indicate that A $\beta$  has a limited effect on memory and point to a greater role of PrP<sup>C</sup> [77, 78]. It was found that Fg interacts with non-digested scrapie prion protein [79]. Results of our studies also point to the role of PrP<sup>C</sup> in memory impairment during HFg [80] and TBI [47]. Therefore, formation of Fg-A $\beta$  and/or Fg-PrP<sup>C</sup> complexes may indicate a mechanism for memory reduction seen in diseases such as TBI, associated with inflammatory cerebrovascular impairment. As a result, these findings highlight a new role of Fg during inflammation-induced impairment of vascular wall properties and thus, vasculo-neuronal unit dysfunction.

## 8. Oxidative damage and neurodegeneration

TBI-induced inflammation and increased cerebrovascular permeability lead to translocation of Fg from vessels to the extravascular space, and its deposition most likely in the vasculo-astrocyte endfeet interface, which may cause astrocyte activation and vascular and astrocyte physical and functional uncoupling [7]. This may result in neuronal degeneration and possible decline in short-term memory [7]. Possible mechanism for this vasculo-neuronal dysfunction can be an activation of astrocytes leading to tyrosine kinase receptor B (TrkB)-mediated enhanced production of reactive oxygen species (ROS) and nitric oxide (NO), which result in neuronal degeneration [81].

Oxidative damage and free radical formation remains one of the important contributors to the pathophysiology of TBI. Generation of ROS causes damage of neuronal membranes, which results in subsequent disruption in ion balance and homeostasis, mitochondrial function failure, and microvascular damage [82]. ROS such as hydrogen peroxide, hydroxyl radical, superoxide anion, peroxy radical (hydroperoxyl), singlet oxygen, and NO are the highly reactive molecules produced during monocyte migration. They contribute to BBB impairment and inflammation in brain after trauma [83]. The cascade of ROS production begins immediately within the first hours after initial insult and lasts for several days [82]. The amplification



of neurodegeneration can be caused by neuronal NO production. This process is highly dependent on TrkB receptor regulation on astrocytes. It was shown that depletion of TrkB protected experimental animals from neurodegeneration [81]. Fg prompts rapid microglial responses toward the cerebrovascular system and axonal damage during neuroinflammation [84]. Extravasation of Fg and deposited fibrin correlate with axonal damage and cause ROS formation in microglia [84]. In vitro, it was shown that astrocytes remove Fg coating from the growth surface that results in their activation and disappearance [85]. Reduction in astrocyte population may be due to their death. Fibrin activates astrocytes by transforming the growth factor beta receptor pathway and promotes astrocyte scar formation after vascular rupture during severe TBI [71]. These findings suggest that there is a strong interactive association between Fg/fibrin and astrocytes [7, 71].

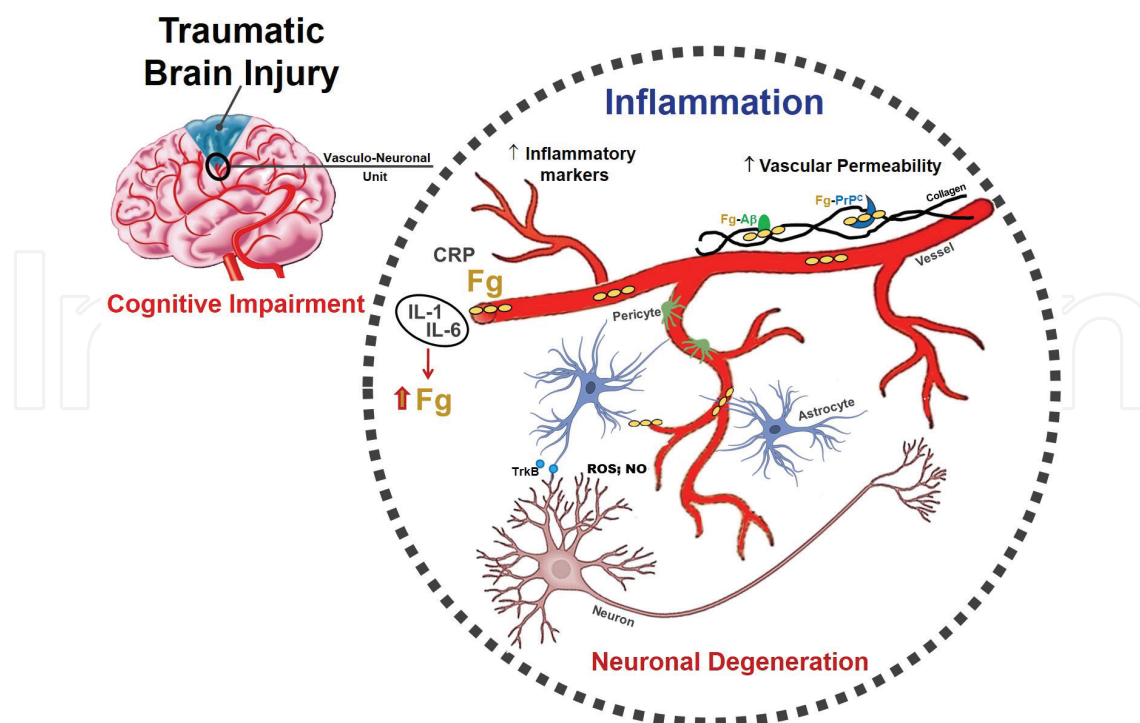
## 9. Role of Fg in loss of memory during TBI

Cognitive impairment and particularly memory deficiency is a result of neurodegeneration and is one of the devastating problems of people with neurotrauma [86]. The role and contribution of Fg in development of AD is known [70, 72, 75]. Strong association of Fg-A $\beta$  complex formation is linked to severity of AD [70, 72, 75]. Thus, deposition of Fg in extravascular space and formation of Fg-A $\beta$  complexes can be a major indicator for memory reduction during TBI. Similarly, possible formation of Fg-PrP<sup>C</sup> complexes may result in memory impairment.

The Prion diseases, one of the forms of encephalopathies, are the group of progressive neurodegenerative conditions with memory impairment. The role of PrP<sup>C</sup> in cognitive dysfunction has been shown [77, 78]. Increased formation of Fg-PrP<sup>C</sup> complex in mice during TBI was accompanied by reduction in short-term memory [47]. Combined, these results indicate that PrP<sup>C</sup> alone as well as its possible association with Fg can have a role in memory reduction during inflammatory cerebrovascular diseases.

## 10. Conclusion

Thus, TBI-induced inflammation besides directly affecting neurons, leads to vasculo-neuronal dysfunction resulting in Fg deposition in extravascular space and formation of Fg-containing protein complexes between the vessels and astrocyte endfeet. Enhanced cerebrovascular permeability can be a first and the most important step in the process leading to alterations in cognitive function. Thus, at elevated levels, Fg can play a significant role in vascular cognitive impairment and dementia (VCID) (**Figure 1**). There is a great attention to the problems related to VCID in the past few years. Presented review indicates that Fg has a significant role in vascular permeability, neuroinflammation and cognitive impairment. Therefore, as a possible diagnostic or outcome predicting approach, it seems important to carefully monitor plasma levels of Fg during TBI. Simultaneously targeting multiple mechanistic components of an altered vasculo-neuronal interaction after head injury, such as blood level of Fg and PrP<sup>C</sup> may be an effective therapeutic approach to ameliorate TBI-induced neurovascular inflammation.



**Figure 1.** Possible mechanism of traumatic brain injury (TBI)-induced cognitive impairment. TBI causes inflammation leading to an increase in inflammatory markers including C reactive protein (CRP), interleukins 1 and 6 (IL-1 and IL-6, respectively) and fibrinogen (Fg). The latter exacerbates TBI-induced cerebrovascular permeability resulting in enhanced deposition of Fg in vasculo-astrocyte endfeet interface, and formation of Fg-containing complexes with proteins A $\beta$  and PrP<sup>C</sup>, which are known to be involved in cognitive decline. In addition, activation of astrocytes causing upregulation of tyrosine kinase receptor B (TrkB) results in formation of reactive oxygen species leading to neurodegeneration.

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