FIBRINOGEN AND MICROVASCULAR PERMEABILITY

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ABSTRACT

Fibrinogen (Fg) is a high molecular weight plasma adhesion glycoprotein. It is a biomarker of inflammation and a high risk factor for cardiovascular disorders. Many inflammatory diseases are accompanied by increased blood content of Fg. Fg is involved in various physiological processes such as blood coagulation, platelet thrombogenesis, erythrocyte aggregation, and cell-cell interactions. High level of Fg in blood exacerbates circulatory complications during inflammatory diseases such as hypertension, diabetes, stroke, traumatic brain injury, and other cardiovascular or cerebrovascular diseases. Enhanced blood content of Fg alters vascular reactivity and compromises endothelial cell layer integrity resulting of leakage of plasma substances from blood stream to interstitium. The purpose of this review is to discuss experimental data that demonstrate effects of Fg causing a vascular protein leakage and to offer possible mechanisms for these effects, which could exacerbate microcirculatory complications during cardiovascular diseases accompanied by increased blood content of Fg.

Key words: fibrinogen, inflammation, permeability, transcellular transport, paracellular transport.

INTRODUCTION

Inflammation is a complex of different biological responses of vascular tissue to harmful stimuli. Acute inflammation is characterized by marked vascular changes such as increased permeability, vasodilation, and worsening in hemorheology, induced by the actions of various inflammatory mediators[25]. Wide variety of human diseases are associated with inflammation that include stroke[38], myocardial infarction[21], hypertension[47,63], diabetes[16,41], atherosclerosis[44], and traumatic brain injury[9]. Inflammation is a key contributor to many vascular diseases and plays a major role in autoimmune diseases[2], allergic reactions[20], and cancer[6].

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Inflammatory processes may induce endothelial dysfunction and vascular remodeling[46,47]. The normal endothelium forms a stable anti-inflammatory interface between circulating blood components and cells within all tissues of the body. The barrier built by endothelium and its associated structures, e.g. glycocalyx and basement membrane are sufficient to maintain the plasma volume and venous return, and prevent tissue edema[12]. However, an alteration of endothelial cell (EC) properties and thus a dysfunction of endothelial lining, which in most of the cases are induced by inflammation, increases permeability of blood vessels resulting in a leakage of blood plasma components out of the blood stream to the interstitium. Accumulation of plasma proteins in interstitium can cause edema. Increase in microvascular permeability leading to edema formation occurs during early stages of acute inflammation[34].

Fibrinogen (Fg), high molecular weight (~ 340 kD) plasma adhesion protein considered a high risk factor for many cardiovascular and cerebrovascular diseases[18]. In addition, higher than normal (2-3 mg/ml) content of Fg in blood is considered as a marker of inflammation[13,45] and it can be a cause of inflammatory responses[27]. In our previous studies, it was shown that high (≈ 4 mg/ml) Fg regulates production of endothelin-1 (ET-1)[48], increases arteriolar constriction[29], enhances EC layer permeability[39], and can itself leak through the EC layer[60]. These findings shed a new light on a role of Fg during inflammation-induced dysfunction of a microvascular bed.

ECs have two main functions. They maintain tissue homeostasis and contribute the functions of the vessel wall through establishing communications between blood and adjacent tissue. The vascular endothelium is a barrier and a permeable filter at the same time[4]. Blood plasma components, such as proteins, may pass through the endothelial barrier via two major transcellular and paracellular transport pathways[11,33,51].

Movement of plasma components via paracellular pathway occurs between ECs and involves alterations in junction proteins (JPs) and their interbinding forces[33]. The transcellular transport of proteins, transcytosis is implemented by their movement across the EC that involves caveolae, fenestrae, and transendothelial channels[51]. The combination and the functional balance of these two, transcellular and paracellular, pathways govern the net transport of blood plasma substances in microcirculation.

Increase in plasma content of Fg increases blood viscosity[28] and therefore increases shear stress[10,14,30]. This activates ECs[14,50] and upregulates expression of various plasma adhesion molecules and integrins[26]. Among them are Fg receptors $\alpha_5\beta_1$ and $\alpha_v\beta_3$ integrins[31,42] and intercellular adhesion molecule-1 (ICAM-1)[42,56]. We have shown that at increased blood level Fg enhances expression and activation of ICAM-1 in mouse cortical vessels[36]. Although expression of ICAM-1 was viscosity and thus shear stress-dependent, its enhanced functionality was Fg-specific[36]. It has been shown that enhanced binding of Fg to ICAM-1[22,29] activates extracellular signal-regulated kinases 1 and 2 (ERK-1/2)[43,48], which increases production of ET-1[48], that in turn is involved in vascular tone modulation[29].

In addition, Fg binding to vascular endothelium activates matrix metalloproteinase-9[36] and alters paracellular and transcellular transport pathways by decreasing an expression of JPs[36,40] and increasing expression of Caveolin-1 (Cav-1) and plasmalemma vesicle associated protein -1 (PV-1)[36]. The latter two point to a possibility that at higher level Fg can be involved in formation of caveolae.

FG AND PARACELLULAR PATHWAY

Endothelial cells are connected to each other by JPs. There are three types of JPs: tight junction proteins (TJs), gap junction proteins (GJs) and adherence junction proteins (AJs)[33]. The allocation of endothelial junctions varies by function of organ-specific requirements[33]. It well accepted that brain microvessels are less permeable to plasma components than microvessels in, for example, skeletal muscle. Endothelial cell layer in brain vessels is a first line of blood brain barrier (BBB). It is considered that endothelial junctions in the brain vessels have tighter arranged JPs[19].

The properties of endothelium vary based of vessel type. Arteries have a well-organized system of TJs, while in venules, junctions are poorly organized. JPs in the endothelium are responsible for vascular homeostasis and permeability that requires precise regulation of opening and closing of cell-cell contacts[15]. JPs also transfer intracellular signals[5]. Only one-fifth of the cell junctions in the endothelium are TJs[1]. They are responsible for maintaining the integrity of the endothelial barrier[61].

Occludin, claudins, and tight junction associated proteins such as zona occludin-1 (ZO-1) and zona occludin-2 (ZO-2) are the main TJPs[33] and are expressed in ECs. Occludin is located at the apical side of a cell[33]. It is bound to the main cytoskeleton protein actin via proteins of the ZO family[33].

It was shown that high content of Fg causes an increase in EC layer permeability through formation of filamentous actin (F-actin)[60]. Formation of F-actin may cause increase in rigidity and retraction of the cells, leading to widening of gaps between the ECs by pulling the edges of the cell toward the cell center[17,27,58]. Increased content of Fg causes downregulation of expression and translocation to cytosol of TJPs, such as occludin, ZO-1, and ZO-2[39].

Vascular endothelial cadherin (VE-cadherin) or endothelial specific adhesion molecule Cadherin-5 is located at the basolateral side of ECs[33,62] ECs. It is present in all types of vessels[5]. It mediates Ca^{2+}-dependent interactions through extracellular domain[3]. Presence of VE-cadherin at cell contacts essentially indicates the extent of permeability of blood vessels[37,62].

We showed that increase in blood content Fg alters EC layer junctional integrity and its attachment to subendothelial matrix, causes downregulation of VE-cadherin and its disordered distribution along the cells' membranes[37]. It also increased EC layer permeability by opening the gaps between the cells[60]. Since the expression of VE-cadherin was just less but it was still present in ECs, it is possible that VE-cadherin was partially translocated to cytosol from the membrane[37].

GJPs are responsible for the cell--to-cell communications. These proteins are presented by connexins (Cx)[5]. Connexins are organized in connexons, which can play role of channels for the intercellular passage for a small molecular weight molecules[5]. There is a lack of information on effect of Fg on GJPs.

FG AND TRANSCELLULAR PATHWAY

Caveolae, fenestrae, transendothelial channels, vesiculo-vacuolar organelles and endothelial pockets are the main components of transcellular transportation[53,55].

Vesiculo-vacuolar organelles are morphologically defined as chains of vesicles connected to each other that form an intricate transendothelial channels penetrating spanning the cytoplasm of the ECs from one side of ECs to the other[55].

Transendothelial channels are ~ 60-70-nm diameter channels that run across the EC[53]. They seem to be formed by the fusion of one caveolae or by chains of two to four caveolae[53,55].

Endothelial pockets are very rare structures that resemble a pocket or a large vacuole that contain fenestrae[55]. Information on endothelial pockets is very scarce. They have been identified in very low number only in fenestrated endothelium[59].

The fenestrae are characteristic structural elements of all fenestrated endothelia. They are round openings or windows cutting through the ECs, have a remarkably constant diameter of ~ 62-68 nm, and occur only in the attenuated parts of the cell[53,55]. They permit water and small molecules across the endothelial barrier[52].

Caveolae are distinct flask-shaped invaginated structures present at the surface of many cell types including ECs (53). It's outer diameter is around 70-nm and at the neck opening is about 20 nm[57]. Therefore, they can take up larger molecular weight proteins such as albumin[33]. Caveolar walls are enriched in cholesterol, glycosphingolipids, and sphingomyelin[7]. One of the main components of caveolae wall is a protein Caveolin-1 (Cav-1)[64].

Cav-1 is a 22-kD integral membrane protein and is expressed in endothelial, epithelial, and other cells. It is the major protein of endothelial caveolae and is necessary for caveolae assembly[64]0. It is considered as the biochemical marker and structural protein of caveolae in most types of cells[7] Movement of Cav-1 and possibly caveolae is governed by activation of Na-K-ATPase[7], Cav-1 regulates the content of cholesterol in caveolae. It binds to cholesterol and is involved in shuttling of cholesterol from the endoplasmic reticulum to the plasma membrane[32].

PV-1 is an integral membrane--associated protein of caveolae. It is found in fenestral and stomatal diaphragms in fenestrated endothelia and transendothelial channels[8,23,24,53,54] and is considered as a functional biomarker for altered vascular permeability following central nervous system trauma[35]. In central nervous system and thus in brain, PV-1 formation is limited[49]. However it is unclear whether it is associated with caveolae or fenestrae, or both.

Recently we showed that at an increased levels of Fg formation of ca-

veolae or fenestrae was evinced by the enhanced expression of PV-1[36,53] and Cav-1 (unpublished data) in mouse brain ECs. These results were accompanied with Fg-induced increase in cerebrovascular permeability[36]. All these indicate a strong involvement of Fg binding to EC in caveolae formation and thus in transcytosis.

CONCLUSION

Thus increased content of Fg causes an increase in blood viscosity and the resultant increase in shear stress, which activates ECs. Activation of ECs results in upregulation of ICAM-1 expression[36]. At higher level, Fg binding to overexpressed ICAM-1 is increased leading to activation of ERK-1/2. ERK-1/2 signaling triggers production of ET-1, formation of F-actin, translocation of JPs, and formation of caveolae. These effects enhance gap opening between the ECs and increase caveolae motility leading to enhanced microvascular permeability. Thus increase in content of Fg enhances microvascular permeability affecting both paracellular and transcellular pathways. However, prevailing role of one or the other transport pathway still has to be defined.

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