The Structure and Function of the Glycocalyx and Its Connection With Blood-Brain Barrier

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The vascular endothelial glycocalyx is a dense, bush-like structure that is synthesized and secreted by endothelial cells and evenly distributed on the surface of vascular endothelial cells. The blood-brain barrier (BBB) is mainly composed of pericytes, endothelial cells, glycocalyx, basement membranes, and astrocytes. The glycocalyx in the BBB plays an indispensable role in many important physiological functions, including vascular permeability, inflammation, blood coagulation, and the synthesis of nitric oxide. Damage to the fragile glycocalyx can lead to increased permeability of the BBB, tissue edema, glial cell activation, up-regulation of inflammatory chemokines expression, and ultimately brain tissue damage, leading to increased mortality. This article reviews the important role that glycocalyx plays in the physiological function of the BBB. The review may provide some basis for the research direction of neurological diseases and a theoretical basis for the diagnosis and treatment of neurological diseases.

Keywords: glycocalyx, blood-brain barrier, neurovascular unit, neurological function, neurological diseases

INTRODUCTION

The surface of the vascular endothelium is covered with a layer of villiform substance, which is called the glycocalyx. It is synthesized by vascular endothelial cells and extends to vascular lumen and surface. In 1966, Rambourg et al. (1966) used methylamphetamine labeled with Ag to observe a layer of proteoglycan (PG) protein polymers on the surface of endothelial cells of mice for the first time. With the development of modern methods of fixation and rapid-freeze techniques as well as a variety of confocal microscopy, there have been more in-depth studies on the structure and functions of the glycocalyx (Ebong et al., 2011). The glycocalyx on endothelial cells is a kind of PG polymer. It mainly includes PGs and glycosaminoglycan chains (GAGs). The core protein of PG mainly consists of members of syndecan and glypican families. GAGs, including heparan sulfate (HS), chondroitin sulfate (CS), and hyaluronan (HA), are the most abundant components of the glycocalyx (Salmon and Satchell, 2012; Alphonsus and Rodseth, 2014; Mende et al., 2016). Glycocalyx extends from the membrane of endothelial cells to vascular lumen, prevents leukocytes and platelets from contacting with endothelial cells, and plays a key role in maintaining the stability of the internal environment (Salmon and Satchell, 2012; Ushiyama et al., 2016). Research has proved that glycocalyx can maintain the stability of many physiological functions, such as maintaining the
endothelial cells can bind HS, CS, and keratan sulfate. Syndecan is syndecan-2, syndecan-3, and syndecan-4. Among these members of the syndecan and glypican families. These core proteins firmly like structure maintains the dynamic balance under physiological conditions. The main core protein, but covalently binds the cell membrane through the electric charge effect (Van den Berg et al., 2006; Haaren et al., 2003). It was observed that the in rat myocardial capillaries, the glycocalyx is degraded by enzymes, and the subsequent hyperosmolarity leads to myocardial edema (Araibi et al., 2020). Degradation of 42% of the endothelial glycocalyx closely related to the shear force of blood flow (Koo et al., 2013). Members of the glypican family include glypican-1, glypican-2, glypican-3, glypican-4, glypican-5, and glypican-6. Glypican-1 is the only member of the glypican family expressed on endothelial cells. The branch linkage includes HS (Tarbell, 2010).

The side chain of GAGs binds with the main part of core protein or CD44 receptors on the surface of endothelial cells. There are 5 types of GAGs, namely, HS, CS, dermatan sulfate, keratan sulfate, and HA (or hyaluronic acid). HS, CS, and dermatan sulfate with negative charges bind the core protein through covalent binding. HS is the most abundant components of GAG side chains, comprising 50–90% of these chains (Pries et al., 2000). The next most abundant components are CS and dermatan sulfate, whose content is approximately one-quarter of that of HS (Rapraeger et al., 1985). The details of keratan sulfate are currently unknown. In contrast to the four abovementioned GAGs, non-sulfated HA, which has no charge, does not bind the core protein, but covalently binds the cell membrane through CD44 receptors (Nandi et al., 2000). GAG chains with negative charges can bind plasma proteins and positively charged ions through the electric charge effect (Van den Berg et al., 2006; Reitsma et al., 2007).

Similar to PGs, GLYs are skeleton proteins of the glyocalyx that link the glyocalyx and endothelial cells. GLYs are adhesion molecules on the surface of endothelial cells. They mainly consist of members of the selectin family, the integrin family, and the immunoglobulin superfamily. The selectin family members that are expressed on the surface of endothelial cells mainly include E-selectin and P-selectin. They participate in the adhesion of leukocytes and endothelial cells (Sperandio, 2006). The main function of the integrin family on the surface of endothelial cells is mediating the adhesion of endothelial cells and platelets and the linkage of extracellular matrix, such as lantnin, fibronectin, and collagen (Bombeli et al., 1998; Ruegg and Mariotti, 2003). The immunoglobulin superfamily of glyocalyx includes the cytoplasmic domain, transmembrane domain, and intracellular domain. The main molecules include intercellular adhesion molecules 1 and 2 (ICAM-1 and ~2), vascular cell adhesion molecule 1 (VCAM-1), and platelet/endothelial cell adhesion molecule 1 (PECAM-1) (Reitsma et al., 2007). It has been observed under an electron microscope that the thickness of the glyocalyx of the vascular endothelium is 0.1–11 μm (Becker et al., 2010a). A schematic diagram of cerebral vascular endothelial glyocalyx is shown in Figure 1.

The Role of Glyocalyx in Permeability
The endothelial glyocalyx is an important gatekeeper of vascular permeability. Damage to the glyocalyx increases the transport of water, proteins, and other molecules from the plasma to outside of blood vessels (Butler et al., 2020). The endothelial glyocalyx can restrict certain molecules from passing through the endothelial cell membrane, as confirmed by injecting of fluorescently labeled dextran into rat mesenteric arteries (van Haaren et al., 2003). It was observed that the in rat myocardial capillaries, the glyocalyx is degraded by enzymes, and the subsequent hyperosmolarity leads to myocardial edema (Araibi et al., 2020). Degradation of 42% of the endothelial glyocalyx
in the isolated rat abdominal aorta by hyaluronidase (HAase) facilitates water and low-density lipoprotein transport across the vessel wall, suggesting that the endothelial glycocalyx is a transport barrier (Kang et al., 2021). Not only does the molecular sieve effect of the glycocalyx structure determine the permeability of blood vessels, but the negatively charged nature of glycocalyx also makes blood vessels act as a charge barrier. Heparan sulfate and chondroitin sulfate in glycosaminoglycan side chain components are negatively charged, so the glycocalyx facing the plasma is also negatively charged. Studies have found that neutralizing the negative charge of the glycocalyx by myeloperoxidase can induce permeability and increase vascular permeability (Kolarova et al., 2021). According to the traditional Starling model, two opposite forces passing through the endothelial cell layer maintain fluid distribution balance, which is determined by four factors: capillary pressure, tissue fluid hydrostatic pressure, plasma colloid osmotic pressure, and tissue fluid colloid osmotic pressure (Starling, 1896). In recent years, the discovery of microvascular barrier functions has questioned this notion, suggesting that the structural net consisting of the endothelial glycocalyx binds with the endothelial cell membrane of blood vessels and forms the endothelial surface layer, which bears the blood vessel barrier. The resulting osmotic pressure of the transendothelial PG protein colloid is the main determining factor of the internal and external flow of fluid in capillaries (Michel, 1997). A schematic diagram of the physiological functions of glycocalyx is shown in Figure 2.

The Role of Glycocalyx in Inflammation

The vascular response is the central part of the inflammatory response. Lipowsky et al. (2011) observed that, in a mouse model of inflammation, after the vascular endothelial glycocalyx structure is destroyed, vascular endothelial cell intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) make it easier for leukocytes in the blood circulation to adhere to the vascular endothelial cells, which in turn cause a series of inflammation and pathological changes (Mulivor and Lipowsky, 2004; Devaraj et al., 2009; Mulivor and Lipowsky, 2009; Schmidt et al., 2012; Lipowsky and Lescanic, 2013). Therefore, glycocalyx shedding is the response of vascular endothelial cells to inflammatory mediators. In an inflammatory state, the glycocalyx of vascular endothelial cells falls off, but it also plays an important role in regulating the occurrence and development of inflammation. HS is the main component of the vascular endothelial glycocalyx and exists on the surface and matrix of cerebrovascular cells (Bernfield et al., 1999). A series of in vitro cell experiments confirmed that HS is a potential ligand of P and L-selectin, which binds to pro-inflammatory chemokines and promotes the transmembrane transport of chemokines (Hoogewerf et al., 1997; Koenig et al., 1998). Vascular endothelial HS participates in and regulates multiple stages of an inflammatory response, but its exact role in the process of inflammatory response is not fully understood.

The Role of the Glycocalyx in the Anticoagulant Process

Glycocalyx’s dense and bush-like structure can hide coagulation-related molecules. Under physiological conditions, direct contact between endothelial cells and blood cells can be avoided, thereby avoiding thrombosis. In addition, glycocalyx can also achieve anticoagulant effects by interacting with antithrombin III, thrombomodulin, and tissue factor pathway inhibitor (TFPI). The main mechanisms of actions include (Bell et al., 2017; Lupu et al., 2020): (1) PECAM is exposed by the shed glycocalyx; (2) Antithrombin III binds to HS in the glycocalyx to enhance its anticoagulant effect; (3) Thrombomodulin can bind to CS to convert thrombin into the protein C activator of the pathway, thereby forming the anticoagulation pathway; (4) TFPI is an effective inhibitor of FVIIa and FXa in the coagulation pathway, and the anticoagulation effect is achieved mainly through the interaction of TFPI and glycocalyx (Kozar and Pati, 2015).

The Glycocalyx as a Signal Sensor

The glycocalyx can sense changes in blood flow shear force and transmit it to endothelial cells, which induces corresponding morphological and functional responses, such as the release of endogenous vasoactive substances and nitric oxide (NO) and cytoskeleton changes (Lyu et al., 2020). In the rat blood vessel model, the amount of NO produced by blood vessels was detected after HS enzymatically degraded under changes of blood flow.
FIGURE 2 | The intact glycocalyx can maintain the permeability of the blood-brain barrier. Damage to the glycocalyx will increase the permeability of the blood-brain barrier (for example, albumin exudation). The CAMs and PECAM hidden in the glycocalyx are exposed due to the shedding of the glycocalyx, causing the aggregation of leukocytes and platelets. CAMs, endothelial cell adhesion molecules. PECAM, platelet/endothelial cell adhesion molecule.

Shear force. Researchers have found that the production of nitric oxide is significantly reduced (Yen et al., 2015). However, not all components of the glycocalyx can mediate shear-induced NO release. Anne Marie W Bartosch et al. (2017) used atomic force microscopy (AFM) to selectively apply forces onto glycocalyx components, including PGs and GAGs, to observe how each component individually promotes force-induced NO production. They concluded that HS and the glypican-1, not syndecan-1, CD44, and HA, are the main mechanical sensors for shear-induced NO production (Bartosch et al., 2017). According to the report of Eno E Ebong, core protein syndecan-1 of HS mediates flow-induced endothelial cells elongation and alignment because SDC1 is linked to the cytoskeleton which impacts cell shape (Ebong et al., 2014). Kang et al. (2021) found that 24-h shear exposure increased the average maximum infiltration distance of low-density lipoprotein and enhanced endothelial cells apoptosis and that both of these effects were inhibited by HAase, indicating that the glycocalyx of endothelial cells can also serve as shearing mechanical sensors regulate endothelial cell apoptosis, thereby affecting leaky connections and regulating low-density lipoprotein transport.

The Effect of the Endothelial Glyocalyx in Cerebrovascular Micro-Homeostasis

The BBB is a unique structure that is mainly composed of pericytes, endothelial cells, the glycocalyx, basement membranes, and astrocytes (Kutuzov et al., 2018). Glyocalyx plays an irreplaceable role in maintaining the barrier function of cerebral blood vessels. Through EB and IgG extravasation assays, Zhu et al. (2018) found that in the group with integral glycocalyx structure, EB and IgG did not leak into the hippocampus. However, upon treatment with heparanase (HPSE), leakage was obvious (Zhu et al., 2018). The glycocalyx can prevent some molecules from passing through the BBB. Kutuzov et al. (2018) used a two-photon microscopy to observe the transport of four different sizes of molecules, i.e., fluorescein sodium (376 Da), Alexa Fluor (643 Da), 40-kDa dextran, and 150-kDa dextran from blood to the brain tissue in the cortical capillaries of anesthetized mice. Fluorescein and Alexa penetrate almost the entire glycocalyx structure layer, while the penetration rate of dextran is less than 60% of the volume. This indicates that glycocalyx can block large molecules in the BBB very well, but the ability to prevent small molecules from infiltrating is limited (Kutuzov et al., 2018). In the rat cardiac arrest/cardiopulmonary resuscitation model, the degree of glycocalyx destruction caused by HAase treatment was related to the high BBB permeability and aggravation of cerebral edema after circulation recovery and perfusion, as well as the decrease in survival rate at day 7 and poor nervous system-related prognosis (Zhu et al., 2018). The mechanisms by which the glycocalyx maintains the permeability of the BBB mainly include the following. First, the dense bush-like structure can play a physical isolation effect (Kutuzov et al., 2018). Second, HS and CS in the side chain of GAGs carry negative charges. Therefore, glycocalyx can prevent negatively charged molecules such as albumin from passing through the BBB due to charge repulsion (Deen et al., 2001). And third, after damage to the endothelial glycocalyx, the levels of inflammatory molecules and matrix metalloproteinases (MMPs) increase, resulting in disruption of the close interactions that form the BBB and further increasing vascular permeability.

In addition to regulating the permeability of the blood-brain barrier (BBB), glycocalyx is also involved in cerebrovascular coagulation and neuroinflammatory processes (Lupu et al., 2020). Delayed cerebral ischemia is a common complication of aneurysmal subarachnoid hemorrhage, but the specific mechanism is not clear. Bell et al. (2017) study on patients with aneurysmal subarachnoid hemorrhage found that in patients with delayed cerebral ischemia, specific markers of glycocalyx damage, including SDC-1, were significantly elevated and that this elevation of syndecan-1 expression was related to vascular adhesion protein-1 in the plasma and endothelial cell adhesion molecules (CAMs) in the cerebrospinal fluid. This indicates
that the breakdown of cerebrovascular glycocalyx integrity may be related to ischemic brain diseases (Bell et al., 2017). Moreover, the endothelial adhesion molecules ICAM-1 and VCAM-1 within the glycocalyx are exposed after glycocalyx degradation (Simard et al., 2012). This adhesion molecules are known as the central mediators of leukocyte adhesion to and
transmigration across BBB (Schnoor et al., 2015). Upregulation of proinflammatory cytokines as a response to leakage of leukocytes further contributes to the subsequent increased neuronal excitability (Rana and Musto, 2018). Kim et al. found that after glycocalyx degradation, ICAM-1 and NF-kB not only increase leukocyte adhesion, but also up-regulate the expression of iNOS and COX-2 (Kim et al., 2013). Inflammatory factors such as TNF-α and oxygen free radicals increase the production of MMPs, which in turn damage brain tissue. The function, shedding enzyme and strategies of glycocalyx protection are summarized in Table 1.

### Major Shedding Enzyme Responsible for Glycocalyx Damage

The glycocalyx is degraded via inflammatory mechanisms such as MMPs, HPSE, and HAase. These sheddases are activated by reactive oxygen species and pro-inflammatory cytokines such as tumor necrosis factor alpha and interleukin-1beta (Iba and Levy, 2019; Uchimido et al., 2019). Several studies have determined that MMPs are the primary molecule responsible for glycocalyx degradation (Song et al., 2015). MMP-2, MMP-7, and MMP-9 directly cleave CS, MMP-1 cleaves syndecan-1, and MMP-9 is the main shedding enzyme of syndecan-4 (Endo et al., 2003; Reine et al., 2019). ADAM17 also participates in glycocalyx degradation by removing the extracellular domain of syndecan-4 (Pipeříková et al., 2016). In addition, studies have confirmed that ADAM15 causes vascular BBB dysfunction by inducing glycocalyx degradation. The underlying mechanism includes ADAM15-mediated CD44 cleavage and the release of the extracellular domain (HA) into the circulation, thereby promoting hyperpermeability of blood vessels and BBB destruction (Yang et al., 2018). Therefore, blocking ADAM15 may be a potential strategy to maintain the integrity of the glycocalyx. MMP is regulated by the activity of histone deacetylase (HDAC) inhibitors. When HDAC is up-regulated under stimulation, the expression of tissue inhibitors of matrix metalloproteinases (TIMPs) decreases and the expression of MMP increases, leading to accelerated glycocalyx degradation in endothelial cells (Ali et al., 2019). Ischemia and hypoxia can induce the activation of mast cells, so that the HPSE stored in the mast cells is released into the extracellular space, resulting in cleavage of HS from the endothelial glycocalyx (Becker et al., 2010b). HPSE is the only enzyme known to cleave HS and is another important factor that promotes the shedding of the glycocalyx (Becker et al., 2015). Research on HPSE has helped elucidate the catabolic processes involved in the decomposition of HS. Methylation of the HPSE promoter may regulate HPSE expression (Shteper et al., 2003). Recently, the transcription factor SMAD4, a key protein in the TGF-β signaling pathway, was found to inhibit HPSE by binding to the HPSE promoter region (Qu et al., 2016; Zheng et al., 2016). The inhibitory effect of p53 combined with the promoter on HPSE expression also resulted in the decrease of HPSE activity, indicating p53 is an effective regulator of HPSE expression (Baraz et al., 2006). Enzyme that promotes the shedding of HA is HAase.

HAase cracks HA. Atherosclerosis and HAase activity is related (Nieuwdorp et al., 2007). Volume overload is encountered during neurosurgery. Volume overload will cause an increase in the release of natriuretic peptides. Experiments showed that A-, B-, and C-type natriuretic peptides have the ability to promote glycocalyx shedding (Jacob et al., 2013). A summary of the mechanism of damage to glycocalyx shedding is shown in Figure 3.

### Potential Strategies of Clinical Protection

The physiological function of the BBB is inseparable from the complete glycocalyx structure. The search for measures to protect the glycocalyx from degradation has always been a research hotspot. Glucocorticoid can stabilize mast cells, inhibit the activation of white blood cells, relieve the downstream inflammatory response, and protect glycocalyx, but its clinical application is limited by the adverse complications of immunosuppression caused by large doses (Cui et al., 2015; Yu et al., 2019). Antithrombin agents can stabilize its structure by combining with endothelial glycocalyx, thereby reducing the enzymatic decomposition of glycocalyx. However, the use of antithrombin during neurosurgery will affect the coagulation function of patients and cause adverse events of postoperative massive bleeding (Chappell et al., 2009a,b). The protective mechanism of albumin is similar to that of antithrombin, but excessive use of albumin will increase the cost of hospitalization for patients, and albumin is an allogeneic source, which will increase the risk of allergy in patients (Becker et al., 2015; Aldecoa et al., 2020). TNF-α inhibitor etanercept has been reported to have a protective effect, but the effect needs to be further studied (Nieuwdorp et al., 2009). Sulodexide has anti-inflammatory, anticoagulant and vascular protection effects, which may be achieved by inhibiting HPSE and MMP activities to reduce glycocalyx shedding (Mannello and Raffetto, 2011; van Haare et al., 2017). Doxycycline and batimastat, all rather non-selective inhibitors of MMPs, can attenuate syndecan and glycanshedding (Lipowsky et al., 2011; Lipowsky and Lescanic, 2013). In addition, sevoflurane has been shown to have a certain protective effect on the glycocalyx. The application of sevoflurane anesthesia in neurosurgery may be more beneficial to the protection of the BBB function (Annecke et al., 2010; Fang et al., 2021).

### CONCLUSION AND FUTURE DIRECTIONS OF RESEARCH

Vascular endothelial glycocalyx plays an indispensable role in BBB, such as inflammation, vascular permeability, blood coagulation, and vascular tone. However, it is not clear whether the glycocalyx in the BBB is different from the glycocalyx in the general vascular structure. Reviewing the relevant literature, details on the neuro-specific contributions of the glycocalyx are still lacking. In addition, the structural and functional relationships between glycocalyx and pericytes are also worth exploring. The therapeutic strategies for glycocalyx...
also need further research because the drugs reported in the current research will inevitably have some adverse reactions or application limitations. Therefore, innovative strategies in this emerging field of experimental medicine are desperately needed.

**AUTHOR CONTRIBUTIONS**

JC and XW were involved in the study design. WG, HC, and JW provided and prepared the samples. JJ and FF wrote the manuscript. All authors contributed to the article and approved the submitted version.

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