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REVIEW ARTICLE

The Stroke-Induced Blood-Brain Barrier Disruption: Current Progress of Inspection Technique, Mechanism, and Therapeutic Target

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Abstract: Stroke is one of the leading causes of mortality and morbidity worldwide. The blood-brain barrier (BBB) is a characteristic structure of microvessel within the brain. Under normal physiological conditions, the BBB plays a role in the prevention of harmful substances entering into the brain parenchyma within the central nervous system. However, stroke stimuli induce the breakdown of BBB leading to the influx of cytotoxic substances, vasogenic brain edema, and hemorrhagic transformation. Therefore, BBB disruption is a major complication, which needs to be addressed in order to improve clinical outcomes in stroke. In this review, we first discuss the structure and function of the BBB. Next, we discuss the progress of the techniques utilized to study BBB breakdown in *in-vitro* and *in-vivo* studies, along with biomarkers and imaging techniques in clinical settings. Lastly, we highlight the mechanisms of stroke-induced neuroinflammation and apoptotic process of endothelial cells causing BBB breakdown, and the potential therapeutic targets to protect BBB integrity after stroke. Secondary products arising from stroke-induced tissue damage provide transformation of myeloid cells such as microglia and macrophages to pro-inflammatory phenotype followed by further BBB disruption *via* neuroinflammation and apoptosis of endothelial cells. In contrast, these myeloid cells are also polarized to anti-inflammatory phenotype, repairing compromised BBB. Therefore, therapeutic strategies to induce anti-inflammatory phenotypes of the myeloid cells may protect BBB in order to improve clinical outcomes of stroke patients.

Keywords: Blood-brain barrier, macrophage, microglia, neuroinflammation, programmed cell death, stroke, tight junction.

1. INTRODUCTION

Despite recent advances in clinical care and management, stroke is still one of the leading causes of mortality and morbidity worldwide [1, 2], and costs an estimated 33.9 billion dollars each year in the US [2]. Stroke is a huge public health concern in both human and financial resources. Therefore, further diagnostic techniques and novel treatments are required to improve outcomes of both ischemic and hemorrhagic strokes.

The blood-brain barrier (BBB) is a characteristic structure of microvessels within the brain and maintains a homeostatic environment in the central nervous system (CNS). The BBB also works as an essential physical and chemical barrier to protect the brain tissue from exposure to potentially toxic or harmful substances by restricting transduction [3, 4]. The BBB can be disrupted by ischemic and hemorrhagic stroke, which can lead to influx of water molecules and blood components into the brain extracellular space resulting in serious clinical consequences such as vasogenic brain edema and hemorrhagic transformation [5-8]. In clinical settings, brain edema was an independent risk factor for mortality and adverse outcomes in both ischemic and hemorrhagic stroke patients, particularly within the first week following onset [9, 10], and the increasing microvascular permeability predicted the development of delayed cerebral ischemia in patients with aneurysmal subarachnoid hemorrhage (SAH) [11]. In contrast, hemorrhagic transformation is a major risk in post-ischemic stroke patients treated with thrombolytic therapy and thrombectomy [12-15]. A risk of hemorrhagic transformation reached 2.4−8.8% following the use of tissue plasminogen activator (t-PA) [16, 17], and 8−9.9% following mechanical angioplasty along with thrombolytic therapy [18,

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19]. BBB disruption is a key factor to predict the risk of hemorrhagic transformation following thrombolytic therapy and thrombectomy. Therefore, the diagnostic technique to predict comprised BBB prior to these treatments would be useful to reduce the risk of hemorrhagic transformation in patients with acute ischemic stroke, and may change the time window for these therapies from the current fixed time to tailored time depending on a patient's status [12-15, 20]. Furthermore, enhanced BBB permeability also allows macrophages and neutrophils in plasma to migrate into the brain parenchyma, and exacerbates neuroinflammation and brain injuries [21-24]. BBB disruption was also associated with abnormal brain function, specifically with hypersynchronized activity and seizures [25-33]. Thus, BBB disruption is considered as a major factor to determine functional outcome and an important therapeutic target to prevent further brain injury in acute stroke.

In this review, we focus on BBB disruption after stroke. First, we discuss the structure and function of cells forming the BBB. Secondly, we identify techniques to measure the integrity of the BBB in *in-vitro* and *in-vivo* studies, and biomarkers as well as imaging techniques for clinical evaluation. Finally, we discuss mechanisms of post-stroke BBB breakdown *via* neuroinflammation as well as apoptosis and potential therapeutic target to preserve the BBB integrity after stroke.

2. THE STRUCTURE AND FUNCTION OF BBB

The innermost layer of the BBB is composed of endothelial cells forming a junction complex. The endothelial cells are surrounded by the basement membrane or basal lamina (BM) [34]. Structurally, the BM is classified into endothelial BM and parenchymal BM (which are separated by pericytes) [35]. Moreover, astrocytic end-feet embrace the BM, which further strengthens the BBB and helps maintain the environment (Fig. **1**) [3, 36-42].

The junction complex forms the tight and the adherens junctions between endothelial cells to restrict paracellular transport [43-47]. The main components of tight junction proteins are transmembrane adhesion proteins such as

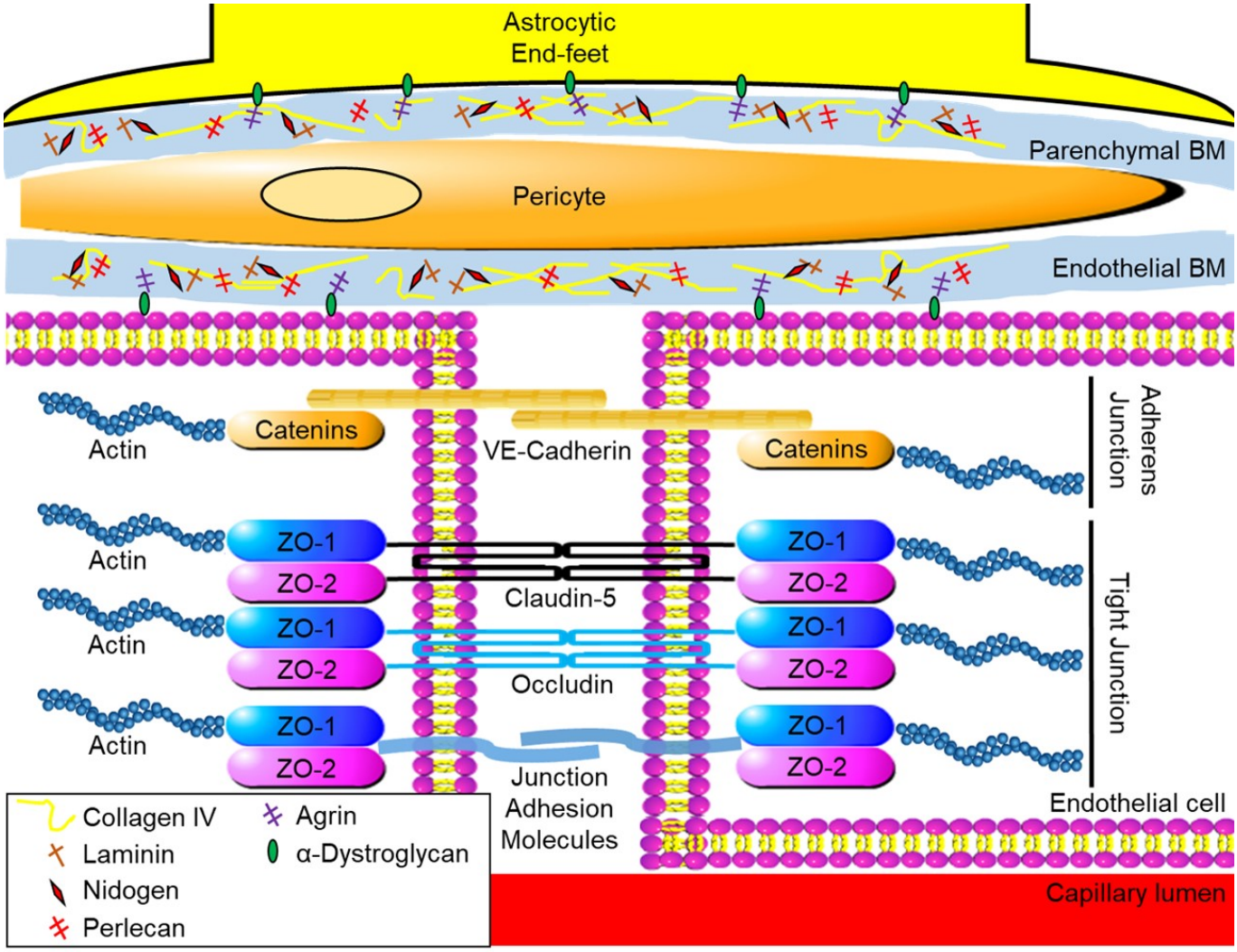

Fig. (1). Physical structure of blood-brain barrier of brain capillary. BM: basement membrane, VE-cadherin: vascular endothelial- cadherin, ZO: zonula occludens. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

claudin-5, occludin, and junction adhesion molecules and cytoplasmic accessory proteins such as zonula occludens (ZO)-1 and -2 [45, 48-50]. The transmembrane adhesion proteins connect with the proteins on adjacent cells and occlude the intercellular space [45]. Cytoplasmic accessory proteins provide a foundation for the transmembrane adhesion proteins with actin cytoskeleton in intracellular space [43, 45]. Meanwhile, adherens junction proteins are located at the basolateral side of the intercellular space. The main components of adherens junction proteins consist of transmembrane vascular endothelial (VE)-cadherin and cytoplasmic accessory proteins such as α-, β-, and γ-catenin [45]. The cytoplasmic accessory proteins in adherens junctions also provide physical support *via* the actin cytoskeleton. The function of tight junctions are to serve both as physical and biochemical barriers and transporter systems [45, 48, 51-53]. In addition, brain endothelial cells have no fenestration within the cells [3]. All of these characteristics of brain capillary lead to a very low vascular permeability. Lipid-soluble small molecules up to 500 Da can pass the tight junction transcellularly, while water-soluble small molecules can overcome the tight junction paracellularly [48]. However, large molecules over 1000 Da cannot cross the BBB through the pathways or junctions [3, 54]. The endothelium also has a couple of transportation routes to cross the BBB such as carrier-mediated transcellular transport (transcytosis), receptor-mediated transcytosis, and adsorptive-mediated transcytosis [55]. Small endogenous molecules such as amino acids, glucose, and ketones are transported across the BBB *via* transport proteins through the carrier-mediated transcytosis [56, 57]. According to this carrier function, selective nutrients can enter the brain parenchyma and maintain the environment in the brain [48]. Endogenous larger molecules, including insulin and transferrin, are recognized by receptors located on the endothelial cell surface, and transported to get passed the BBB [56, 57]. Adsorptive-mediated transcytosis is a pathway for a positively charged large plasma protein such as albumin, which binds to a negatively charged area on the endothelial cell surface to be absorbed into the brain parenchyma by endocytosis [56, 57]. In experimental models of stroke, tight junction breakdown has been commonly examined by measuring the expression of ZO-1, claudin-5, occludin, and other junction proteins [45, 58]. The adherens junction protein, VE-cadherin, was also suppressed in post-stroke models [58-60]. However, VE-cadherin and β-catenin can work as a temporary barrier to restrict the extravasation of large molecules prior to the reappearance of transmembrane adhesion proteins of tight junction [61].

The BM is mainly composed of extracellular matrix (ECM) proteins including collagen IV, fibronectin, laminin, nidogen, and heparin sulfate proteoglycan such as perlecan and agrin [35, 47]. These proteins provide structural support as well as signaling transduction [45, 51-53]. Collagen IV is composed of trimeric protein containing six kinds of α-chains (COL4A1–6), and the most abundant in the BM [35, 62-65]. Collagen IV is secreted by endothelial cells, astrocytes, and pericytes, and plays roles in retaining laminin, nidogen, and perlecan [52, 66]. COL4A1 and 2 were highly expressed in BMs and ablation of COL4A1 and 2 resulted in embryonic death due to abnormal BM structure as well as fragile vessels [35, 66]. Missense mutations of COL4A1 and 2 resulted in brain malformation and occurrence of intracerebral hemorrhage (ICH) in mice [67-69]. Collagen IV expression may be decreased after stroke, but may be upregulated in later repairing phases of BBB [70, 71].

Fibronectin is a group of glycoproteins with disulfide-linked dimer. Two types of fibronectin exist: soluble plasma fibronectin and insoluble cellular fibronectin. The latter form is a major component of ECM and is produced by fibroblasts in the BM [51, 72-74]. Fibronectin provides cell adhesion, migration, and cytoskeletal organization [75]. In an *in-vitro* study, fibronectin promoted survival and proliferation of endothelial cells in the CNS, suggesting angiogenic effects [76]. Fibronectin-inactivated mice resulted in embryonic death due to notochord and somite absence as well as heart and embryonic vessel deformities [77]. Fibronectin is an indispensable factor for cerebral vascular development and integrity [78-80].

Laminin is a trimeric protein which consists of a combination of α, β and γ chains forming 15 different isoforms [81-85]. The major laminin isoforms in the BBB are laminin-111 (α1β1γ1), -211 (α2β1γ1), -411 (α4β1γ1), and -511 (α5β1γ1). Brain microvascular endothelial cells release laminin-411 and -511, which are mainly located in endothelial BM, while astrocytes solely produce laminin-111 and -211, which are predominantly found in the parenchymal BM [86-90]. Laminin organizes BM structure as well as barrier function of the BBB [85, 91]. Deletion of the laminin failed to organize collagen IV and perlecan during developing embryoid bodies [92]. Laminin α4 knockout mice resulted in the lack of vasculature followed by occurrence of ICH [41, 93]. Null mutation of LAMC1 gene coding for laminin γ1 in mice lacked BMs resulting in embryonic death leading to leaky vasculature causing ICH [92, 94]. Other mutations in laminin subunits such as α1 and β1 also led to BMs disorganization [95-98]. In adult mice, ablation of astrocytic laminin led to the disruption of BMs and vascular smooth muscle cells, resulting in ICH [93]. Laminin provides adult angiogenesis, while fibronectin contributes to embryonic angiogenesis [78, 99]. Laminin is also involved in tissue repair after stroke. Laminin expression including laminin-111, -211 -411, and -511 was upregulated in the area of ischemic penumbra after transient ischemia and promoted subsequent neurogenesis and angiogenesis *via* integrin signaling pathways [100-102], while endothelial laminin expression in the ischemic core region was downregulated due to loss of vascular component [103]. Laminin provided vascular scaffolds *via* β1 integrin, promoting neuronal migration toward damaged area on 18 days after ischemic stroke [104-106]. An *in-vitro* study demonstrated that cerebral endothelial cell-induced laminin promoted neurite outgrowth [107, 108].

Nidogen (enactin) is composed of two isoforms: nidogen-1 and -2, which are produced by endothelial cells and astrocytes, respectively [109]. The function of nidogen is to link collagen IV and laminin to provide BM stabilization [35, 52]. In particular, nidogen-1 synthesis may be a key regulator for adhesive properties of astrocyte to BM [109]. Knockout of either nidogen-1 or -2 in mice was still able to form functionally normal BMs, although its expression level was downregulated in cerebral vessels [110-112]. However, deletion of both nidogen-1 and -2 resulted in perinatal death due

to severe BM defects [113-115]. Nidogen-1 null mice promote upregulation and redistribution of nidogen-2, while nitrogen-2 null mice do not change expressions of nidogen-1 [116, 117]. Therefore, nidogen-2 possibly compensates the expression of nidogen-1.

Perlecan and agrin are heparan sulfate proteoglycans found in the BM [118, 119]. Perlecan is also known as heparan sulfate proteoglycan 2 [119]. Perlecan has five different domains (domain I-V) and three glycosaminoglycan chains with NH_2 terminal, which interact with a large number of molecules such as ECM proteins and heparin-binding growth factors to mediate a variety of cell signaling to control migration, proliferation, and differentiation [120-123]. Perlecan is an indispensable factor to organize BMs and promote cerebral angiogenesis during embryonic period similar to fibronectin [124, 125]. Deletion of perlecan during the embryonic stages in mice resulted in death [35, 124-126]. Lacking of perlecan only in the BM causes microvessels to bleed and dilate in mice [82]. In experimental ischemic stroke, a perlecan level was downregulated by 43–63% within 2 h from onset [127, 128]. In contrast, post-stroke perlecan domain V treatment promoted brain angiogenesis *via* the induction of vascular endothelial growth factor (VEGF) from brain endothelial cells [129]. Treatment with exogenous recombinant domain V of human perlecan after ischemic stroke exerted neuroprotective effect as well as infarction volume reduction in both wild-type mice and perlecan-deficient mice [127, 130]. Endogenous perlecan also seems to be actively processed into potentially beneficial protein fragments such as the C-terminal fragment of domain V after stroke [131]. The fragment promoted recovery of BBB injury after ischemic stroke [132]. Perlecan may be an important factor for BBB development as well as BBB reformation after the breakdown. Agrin has multiple isoforms by alternative splicing [133, 134]. Agrin in the BM consists of isoforms without a peptide insert at site B/z (B/z-negative form) [135]. During development, appearance of agrin in BM had the same time window as that of BBB formation [136]. Agrin binds to α-dystroglycan located on astrocytic end-feet or endothelial cells and acts as an anchor to connect endothelial cells and astrocytes to the BM [137]. Agrin also plays a role in the maintenance of BBB properties by polarizing astrocytes, clustering aquaporin-4 into orthogonal arrays of particles, expressing claudin-5 as well as occludin, and suppressing potential harmful matricellular protein tenascin-C [138, 139].

Perivascular cells (pericytes and astrocytes) also have a role in regulating BBB function, forming the neurovascular unit [56, 140-143]. Pericytes are involved in physical support and maintenance of endothelial cells as well as paracrine signaling to the endothelium for stabilization of the BBB [57, 72, 144-152]. Lack of pericytes showed an increase in endothelial transcytosis, failure of tight junction formation, and induction of genes related to increased vascular permeability in mice [153]. The detachment of pericytes was enhanced by VEGF, leading to production of matrix metalloproteinase (MMP)-9 as well as induction of leaky BBB especially in the brain cortex, striatum, and hippocampus in both *in-vivo* and *in-vitro* studies [148, 154-161]. VEGF is a glycoprotein regulating vascular permeability and angiogenesis during embryonic angiogenesis mainly *via* VEGF receptor (VEGFR) 2 located on endothelial cells [162]. VEGF enhanced BBB permeability in both adult mice with normal physiological conditions and inflammatory diseases [162]. Some studies demonstrated that VEGF signaling pathways included potentially detrimental endothelial nitric oxide synthase and matricellular protein tenascin-C [162, 163]. VEGF and VEGFR2 expressions were significantly increased at 24 h post-SAH [162], and a VEGF inhibitor exerted neuroprotective effects *via* protection of the BBB after SAH [154, 162]. However, when it comes to ICH and CI, elevation of serum VEGF was correlated with positive outcomes in clinical settings [164, 165]. The findings may be related to endothelial cell regeneration and angiogenesis by VEGF [166]. Astrocytes are the most abundant glial cells and are responsible for maintaining the environment in the brain [56, 167, 168]. Astrocytic end-feet are responsible for 90% of the BMs, which form the outermost layer of BBB, and control BBB integrity, cellular link to neurons, and ion and water transport [47, 57, 93, 152, 169-172]. An *in-vivo* study showed that lack of astrocytes by 3-chloropropanediol treatment caused microvascular damage, resulting in BBB breakdown without neuroinflammation [173]. Mice lacking glial fibrillary acidic protein, an astrocyte-specific filament protein, also showed an increase in infarction size in both permanent and transient focal ischemia compared to wild-type mice [174]. On the other hand, in post-ischemic stroke and inflammatory diseases in the CNS, astrocytes were reported to activate immune cell infiltration and release VEGF and MMPs to degrade tight junction proteins (claudin-5 and occludin) as well as the ECM in both *in-vivo* and *in-vitro* study, causing BBB disruption [163, 175-178].

3. ASSESSMENT OF BBB PERMEABILITY

3.1. Assessment of BBB Permeability in *In-Vitro* and *In-Vivo* Studies

Transendothelial electrical resistance (TEER) would be the most common technique to evaluate the integrity of tight junction in cell culture models of endothelial monolayers [48, 179, 180]. BBB function in TEER is examined by measuring electrical resistance across a cellular monolayer. Representative setup for TEER measurement is equipped with endothelial cell lines, porous membrane, tracer compounds, and electrodes (Fig. **2**). Some brain endothelial cell lines such as rat RBE4, rat GP8, and human cerebral microvascular endothelial cells (hCMEC/D3) express appropriate BBB protein characteristics [37]. Other cell types regulating BBB integrity such as pericytes, and astrocytes have also been tested in co-culture with brain endothelial cells [181]. The models using hCMEC/D3 in co-culture with astrocytes showed significant increases in TEER values as well as decreases in the passage of permeability tracers through the endothelial monolayer [182-184]. Brain endothelial cells produced from human pluripotent stem cells can provide cell lines that have highly accurate and repetitive structure of BBB in terms of permeability for small molecules, expression of nutrient transporters, and polarized efflux transporter activity [185]. Endothelial cells are grown on cell culture medium with porous membrane, which separates the compartments between luminal side and abluminal side. The

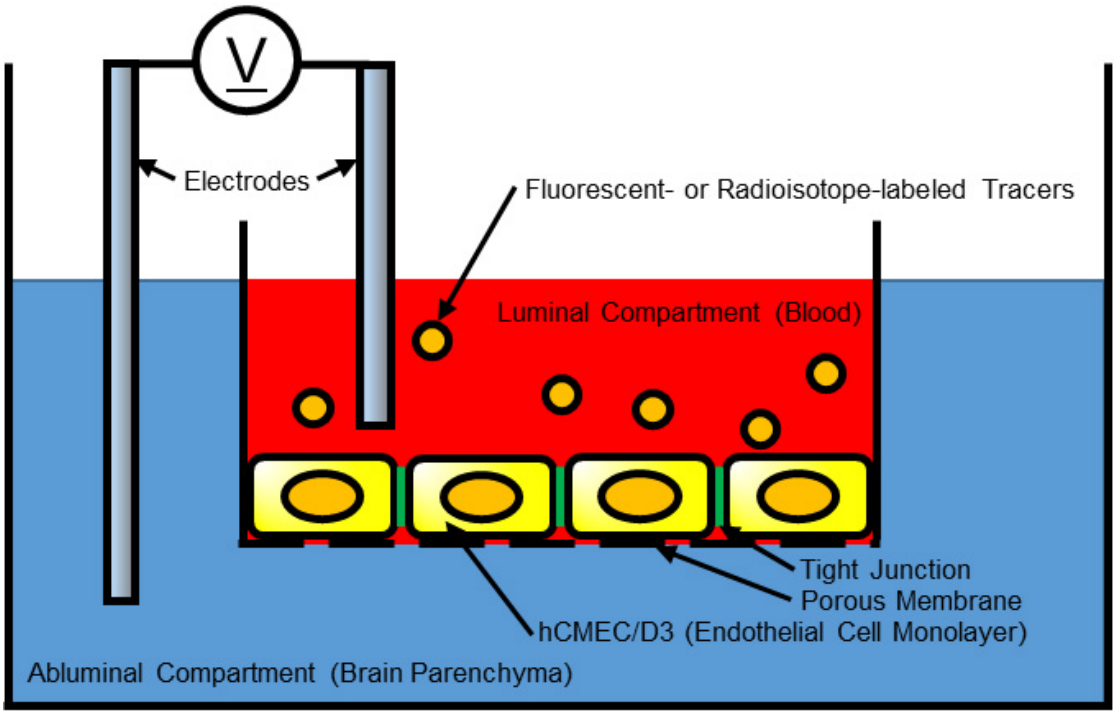

Fig. (2). Transendothelial electrical resistance system to determine the blood-brain barrier integrity in *in-vitro* study. Monolayer endothelial cells, human cerebral microvascular endothelial cells (hCMEC)/D3 grown on porous membrane are separating the luminal compartment from the abluminal compartment. The resistance of tracers to pass through tight junction is measured by electrodes located in both compartments. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

tracer compounds generally consist of either fluorescent- or radioisotope- tagged molecules (Table **1**). Tracer permeability *via* porous membrane is measured using different sized tracer compounds [45]. Electrodes are placed in both compartments and are used to monitor the electrical resistance to pass through the endothelial cells *via* transcellular and paracellular pathways [179]. The electrical resistance through transcellular pathway is primarily defined by individual cell and membrane, while the paracellular electrical resistance is based on formation of the tight junctions with adjacent cells [186]. Tracer compounds in the luminal side pass through endothelial cells and pericyte layers, and permeability is measured by the concentration of tracers in the abluminal side after a given period of time and is expressed by endothelial permeability coefficient Pe (cm/s) [187]. Overall, the TEER value reflects the integrity and permeability of endothelial cells in culture [188, 189]. The main advantage of the TEER is a non-invasive method and is able to monitor live cells continuously in various stages from BBB disruption to repair after stroke [48].

Alternatively, the recent advances of BBB organoids are useful for the permeability assay and drug pharmacokinetics researches [190]. An organoid is an *in-vitro* and 3-dimensional artificial miniature organ showing realistic micro-anatomy. BBB organoids consist of human primary brain endothelial cells, pericytes, and astrocytes, providing better characteristics of BBB integrity including tight junctions and adherens junctions, as well as more realistic function associated with molecular transporters and drug efflux pumps expression compared to conventional static culture systems [190].

In *in-vivo* studies, the measurement of extravasated Evans blue dye is widely accepted to evaluate the BBB disruption. Evans blue is a water-soluble molecule in blue with molecular weight of 960.8 Da, and binds strongly to endoge-

Table 1. The tracers used for *in-vitro* measurement of blood-brain barrier permeability.

Tracer	Molecular Weight (Da)
Radioisotope-labeled marker	-
^{14}C-α-aminoisobutyric acid	103
^{14}C-mannitol	180
^{14}C-sucrose	342
^{14}C-methotrexate	455
^{14}C-inulin	5k
^{14}C-labeled dextran	70k
Fluorescence-labeled marker	-
Sodium fluorescein	376
Lucifer yellow	444
Horseradish peroxidase	40k
Fluorescein isothiocynate-dextran	62k
Fluorescein isothiocynate-albumin	67k

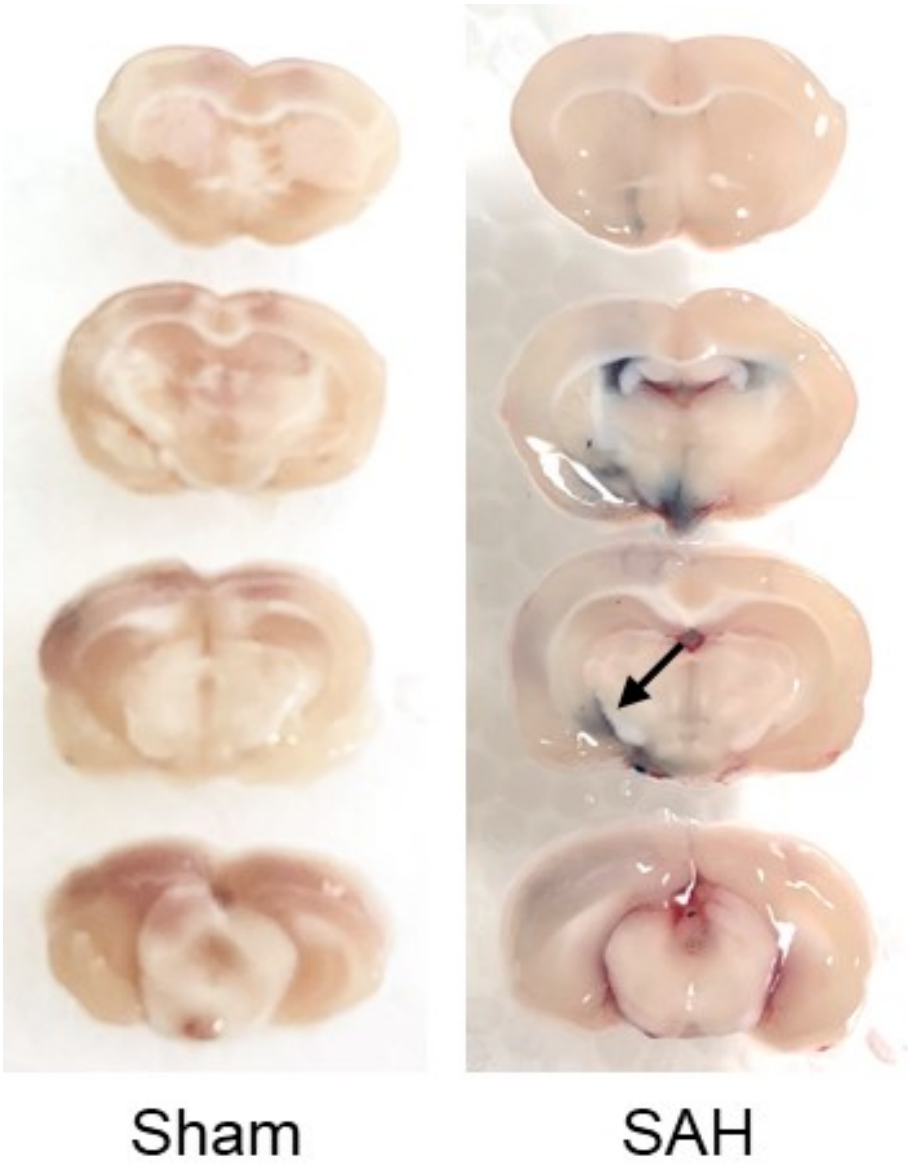

Fig. (3). Evans blue dye test at 24 h after subarachnoid hemorrhage (SAH) induction in rats. Four % Evans blue was injected intraperitoneally at 2 h before brain harvesting. Extravasated Evans blue complex is shown in a SAH-operated rat (arrow). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

nous albumin following an intravenous injection [4]. This forms a large molecular complex with a molecular weight of 60,000 Da, and the BBB breakdown leads to the leakage of this large complex from the intravascular area to brain parenchyma [4]. Extravasated Evans blue-albumin complex is identified macroscopically and as red fluorescence microscopically (Fig. **3**), and is measured by colorimetric and spectrophotometric methods [191]. The advantage of this method is cost-effective as well as to be able to assess the BBB disruption quantitatively. However, data acquisition is limited to only a single time point due to the methods requiring animal sacrifice. In addition, it may not reflect the active BBB disruption because the result shows total extravasation of Evans blue-albumin complex from stroke onset to the sacrificed time point. Moreover, the spatial information identifying compromised BBB is inferior to immunohistochemical or immunofluorescence staining techniques.

Another *in-vivo* study to assess BBB disruption is immunohistochemical or immunofluorescence staining of blood components. This method measures the leakage of blood components from the intravascular area into the brain parenchyma [192]. Currently, albumin, fibrinogen, and immunoglobulins (Igs; IgG and IgM) staining are used for this method [192]. Extravasated these blood components are identified microscopically (Fig. **4**). The advantage is that this method is capable of evaluating the BBB disruption without administration of any exogenous tracers cost-effectively and semi-quantitatively [45, 193]. In addition, spatially visualized information is obtained. However, as is the case with Evans blue dye method, animal sacrifice is required for data acquisition and only the total extravasation can be obtained since stroke induction. In addition, slight BBB disruption may fail to be detected due to the generally huge size of blood components [192].

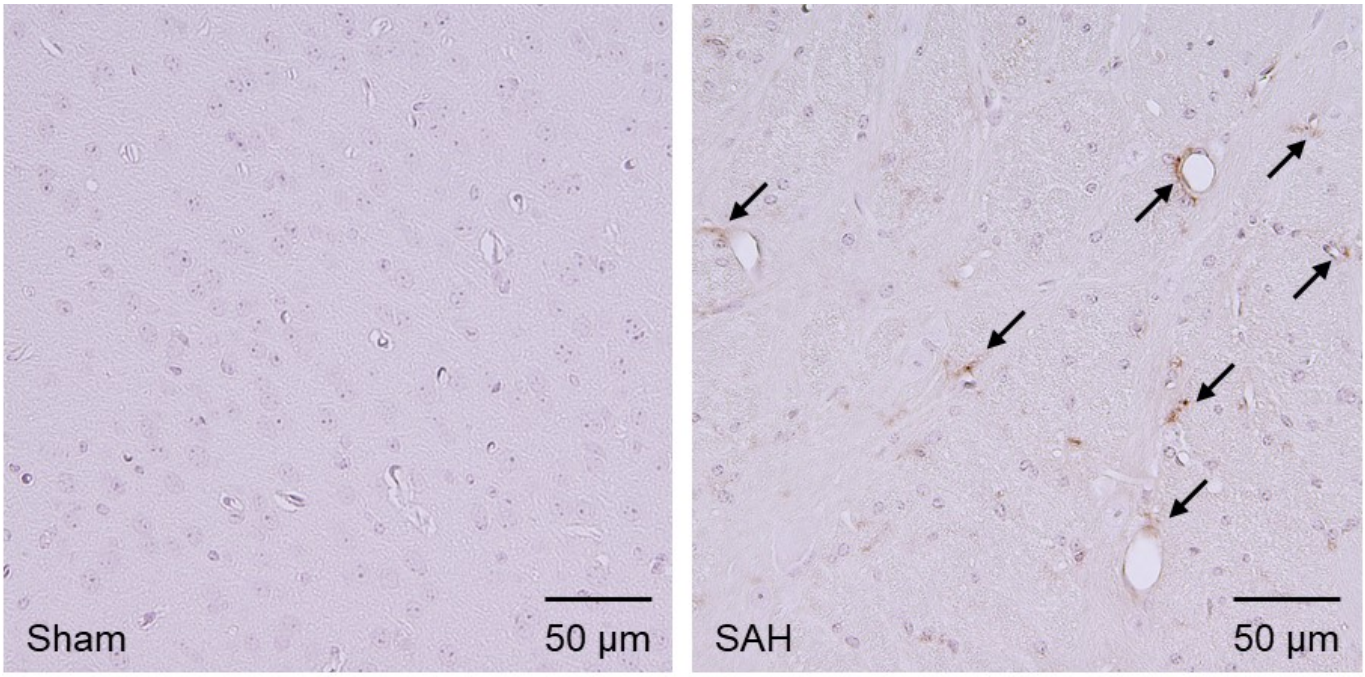

Fig. (4). Immunohistochemical staining for immunoglobulin G (IgG) in the left temporal cortex at 1.0 mm posterior to the bregma at 24 hours after subarachnoid hemorrhage (SAH) induction in mice. Compared with sham-operated mice, extravasated IgG is stained in SAH-operated mice (arrows). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Transendothelial leukocyte migration is also a technique for evaluation of BBB disruption in both *in-vivo* and *in-vitro* studies [45, 194]. This method can show the severity of brain injury after stroke as well as BBB disruption because leukocyte infiltration causes neuroinflammation in the brain following stroke [195, 196]. However, leukocytes require several steps to migrate into parenchyma such as leukocytes endothelial adhesion, activation and crawling at the endothelial cells, and transmigration [197]. Therefore, this method may be influenced depending on the function of leukocyte to cross into the brain parenchyma [194, 198]. As another *in-vivo* method, the leakage of radioisotope-labeled sucrose and inulin has been measured to evaluate the BBB disruption because these carbohydrates also do not cross the BBB in normal physiological conditions and are stable metabolically [199, 200].

3.2. Identifying Clinical Biomarkers of BBB Breakdown

Currently, the most widely accepted clinical biomarkers to evaluate BBB integrity are the cerebrospinal fluid (CSF) albumin or IgG per serum albumin or IgG ratio measurement [201-205]. Serum albumin and IgG are hardly transported within CSF in normal conditions of the BBB. However, these proteins easily enter into the brain parenchyma and CSF under the compromised BBB, resulting in an increase in the CSF per serum ratio when the serum and CSF samples are collected simultaneously. However, this technique is not commonly performed in clinical settings because the acquisition of CSF data requires invasive technique such as lumber puncture.

Previous clinical studies to identify clinical biomarkers of the BBB breakdown are limited. Evaluation of BBB integrity would be useful to estimate the risk of hemorrhagic transformation after thrombolytic therapy and thrombectomy in ischemic stroke [170]. Therefore, some clinical studies focused on the relationships between serum biomarkers and hemorrhagic transformation following ischemic stroke. A study demonstrated that serum levels of tight junction proteins occludin and S100 on admission were significantly elevated in patients with hemorrhagic infarction compared to those without post-stroke hemorrhagic complications, suggesting that it can be potential clinical biomarkers to identify BBB disruption attributed to the hemorrhagic transformation following cerebral infarction (CI) [206]. In addition, patients with hemorrhagic infarction showed an increase of serum claudin-5 per ZO-1 ratio based on the data on admission, and a decrease of serum VEGF levels compared to patients without hemorrhagic transformation [206]. Serum S100B was also a good biomarker to predict BBB damage in traumatic brain injury [205]. S100B is an abundant protein in the brain expressed in astrocytes, though it is not specific [207]. Therefore, this protein is considered as one of the candidates to detect BBB damage caused by compromised astrocytes. Another study showed that plasma levels of cellular fibronectin and MMP-9 were correlated with hemorrhagic transformation after thrombolytic therapy in CI [208, 209]. The cellular fibronectin is predominantly expressed in BM and one of the essential components of BBB [51, 72-74]. MMP-9 is known as a proteolytic enzyme induced by inflammatory cytokines as well as reactive oxygen species (ROS), and degrades the ECM of cerebral microvessel BM [210, 211]. Therefore, elevation levels of cellular fibronectin and MMP-9 suggest the degradation of microvessel components leading to BBB disruption after ischemic injury *via* the inflammatory response [208, 209]. CSF MMP-9 expression

could be increased following stroke as well. A clinical study showed that blood and CSF levels of MMP-9 correlated with each other, and that higher MMP-9 levels in the CSF within 14 days post-SAH were associated with worse 3-month clinical outcomes [212]. Neutrophils may be an important source of MMP-9 in the CSF [7, 212, 213]. On the other hand, post-traumatic BBB dysfunction as measured by albumin CSF per serum ratio was correlated with serum ubiquitin C-terminal hydrolase L1 (UCH-L1) elevation between 12 and 24 h after trauma [205]. UCH-L1 is used as a brain-specific biomarker because it is a neuron-specific protein and abundant in neuronal soma [205]. Thus, recent studies have expanded clinical biomarkers to assess BBB integrity. However, none of them is still less than the ideal biomarkers, which provide accurate results and is capable of simple and prompt measurement [170].

3.3. Imaging Techniques Measuring BBB Permeability in Clinical Settings

A number of imaging techniques for evaluating BBB permeability have been used in clinical settings. Dynamic contrast-enhanced computed tomography (DCE-CT) scan has been used to assess the post-stroke BBB disruption [14, 214-216]. Images are acquired by scanning during an intravenous injection of an iodinated contrast agent, which cannot pass the intact BBB. The major advantage of DCE-CT for the purpose of BBB permeability imaging is to be able to scan faster than other imaging modalities, and therefore it may be applicable to post-stroke patients who are unable to tolerate the longer scan due to disturbance of consciousness or requirement of immediate interventions. Disadvantages of DCE-CT scan include risks related to radiation, and adverse reactions due to an injection of iodinated contrast agent. The resolution of imaging is inferior to that acquired by dynamic contrast enhanced magnetic resonance (MR) imaging (DCE-MRI) scan [22]. Besides, the extent of BBB damage evaluated by DCE-CT scan may fluctuate depending on the cerebral blood flow, and therefore BBB disruption cannot be detected in severe ischemic region because of the insufficient blood supply [20].

DCE-MRI scan is the most widely adopted minimally invasive imaging technique for evaluating and measuring BBB breakdown [26, 33, 217-219]. This method commonly uses contrast agents containing gadolinium, which is a MR-visible tracer and does not cross the normal BBB. The MR images acquired by dynamic T1-weighted imaging (T1WI) following a contrast agent injection reflect the quantitative extravasation caused by the BBB breakdown [220, 221]. BBB permeability is calculated by evaluating the differences of intensity on MRI before and after an injection of a contrast agent [222]. A previous study showed that parenchymal enhancement on MRI T1WI after 2 h from thrombolytic therapy predicted the subsequent hemorrhagic transformation [13]. Another study demonstrated that delayed gadolinium enhancement of CSF space on fluid-attenuated inversion recovery images was also associated with hemorrhagic transformation and poor clinical outcome following focal CI [223]. The advantage of DCE-MRI is that non-iodine contrast agents can reduce risks for adverse reactions, and that high contrast as well as resolution images can be obtained [218]. Disadvantage of DCE-MRI includes longer scanning time [22]. It takes up to 1 h for processing full brain permeability by DCE-MRI scans [224]. The time-consuming nature may be a critical factor that leads to worse clinical outcomes in patients with acute ischemic or hemorrhagic stroke before intervention. Other limitations include potential artifacts as a major concern, and that this method is still difficult to detect slight BBB injury [20, 225-227]. In contrast, recent studies showed that arterial spin labeling (ASL) techniques of MRI could be used for evaluation of BBB integrity based on the different diffusion or transverse relaxations by separating the intravascular and extravascular signaling [228]. ASL technique does not require contrast agents containing gadolinium, but reliable areas to measure barrier function are currently limited to gray matter and white matter [228].

Single photon emitting computed tomography (SPECT) has also been used to measure BBB permeability [229, 230]. ^{99m}Tc-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) brain scintigraphy is the common technique for the assessment of BBB integrity [229]. ^{99m}Tc-DTPA is a non-diffusible tracer and its uptake takes place at the site of severe tissue damage [229]. DTPA-SPECT has been used in the past to detect the BBB injury due to infection, trauma, brain metastasis, and stroke [229, 231-234]. BBB intensity as measured by ^{99m}Tc-DTPA uptake was also correlated with post-stroke seizures as well as neurologic poor outcomes [229, 230]. Advantage of ^{99m}Tc-DTPA SPECT is more cost-effective compared with DCE-MRI [229]. However, the low anatomical resolution and ionizing agent are disadvantages of DTPA-SPECT. Alternatively, ^{68}Ga ethylenediaminetetraacetic acid (^{68}Ga EDTA) tracer in positron emission tomography is also used to obtain the image of subtle leakage [228]. However, due to the disadvantage including use of ionizing radiation, high costs, lack of available infrastructure, and low spatial information, this technique has been limited to studies related to cerebral small vessel diseases [228].

4. INFLAMMATORY RESPONSE AND PROGRAMMED CELL DEATH INVOLVED IN BBB DISRUPTION AND THE POTENTIAL THERAPEUTIC TARGETS IN STROKE

4.1. Pathophysiological Changes in the Acute Phase after Stroke

BBB disruption is initiated by various factors induced after stroke such as pro-inflammatory substances, ROS, and MMPs [235]. In ischemic stroke, insufficient blood flow leads to the lack of O_2 and glucose supply as well as depletion of adenosine triphosphate (ATP) [55, 236]. Dysfunction of ion transport arising from a shortage of ATP results in excessive releases of glutamate and intracellular Ca^{2+} overload [236]. Uptake of glutamate facilitates astrocyte swelling, leading to compression of vessels in the ischemic regions and further reduction of vascular blood flow [237]. Intracellular Ca^{2+} overload activates a variety of cytotoxic factors which cause dysfunction of mitochondria and endoplasmic reticulum as well as generation of ROS, resulting in cerebral tissue damage and releasing damage-associated molecular patterns (DAMPs) [238, 239]. ROS signaling includes apoptotic factors such as p53, caspases-3 and -9, causing BBB disruption [23]. DAMPs are endogenous mole-

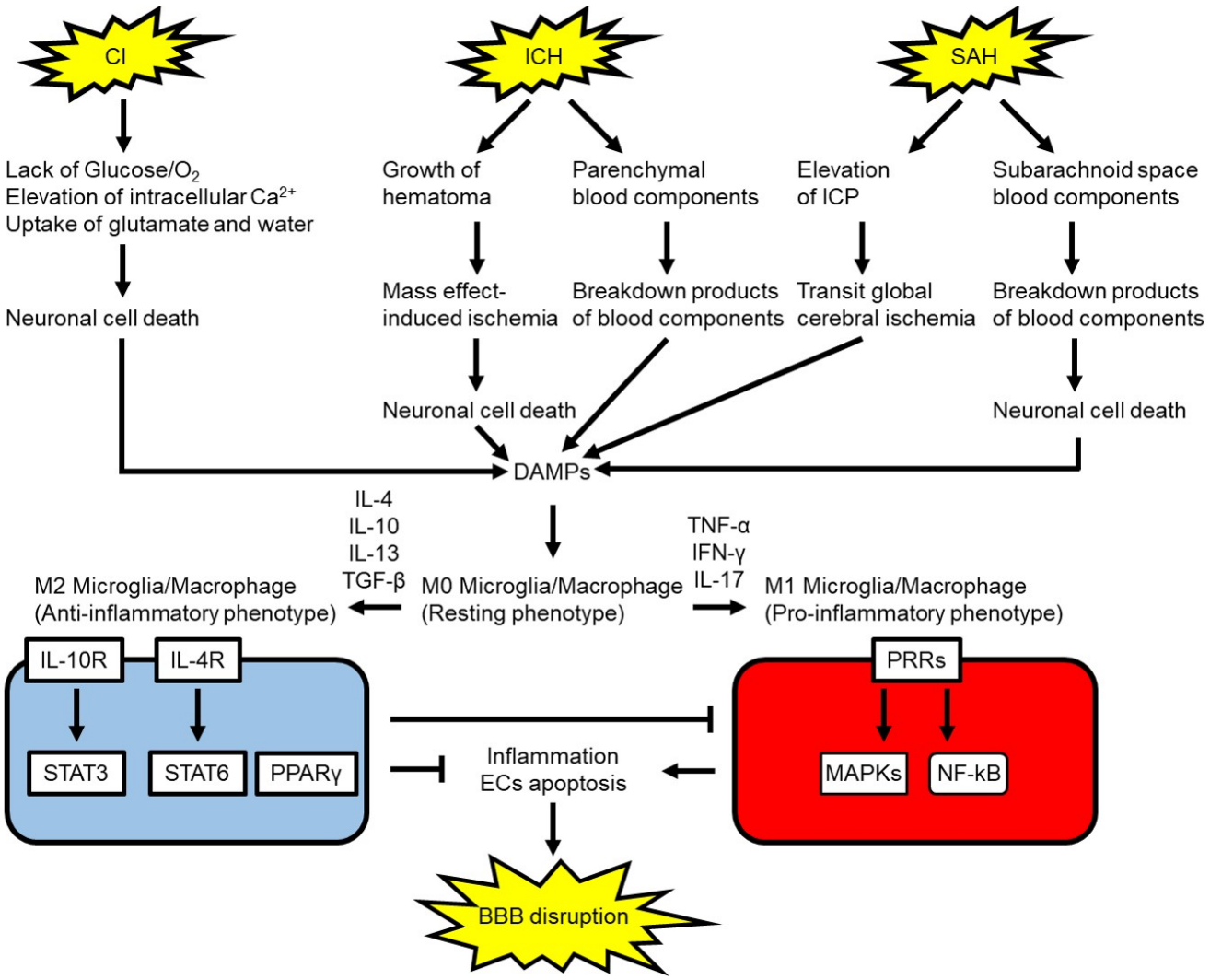

Fig. (5). Possible microglia/macrophages polarization signaling following stroke and response to blood-brain barrier (BBB). CI: cerebral infarction, DAMP: damage-associated molecular pattern, ECs: endothelial cells, ICH: intracerebral hemorrhage, ICP: intracranial pressure, IFN-γ: interferon-γ, IL: interleukin, IL-4R: IL-4 receptor, IL-10R: IL-10 receptor, MAPK: mitogen-activated protein kinase, NF-κB: nuclear factor-κB, PPARγ: peroxisome proliferator activated receptor γ, PRR: pattern recognition receptor, SAH: subarachnoid hemorrhage, STAT: signal transducer and activator of transcription, TGF-β: transforming growth factor-β, TNF-α: tumor necrosis factor-α. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

cules released as a result of tissue damage or secondary products arising from blood components breakdown. These DAMPs include heme, fibrinogen, high-mobility group box 1 (HMGB1), S100P, heat shock proteins, and matricellular proteins such as tenascin-C and galectin-3 [240, 241]. ICH can cause secondary ischemia by the hematoma mass effect as well as increased intracranial pressure (ICP) [142]. ICH-induced ischemia destroys cerebral tissues and releases DAMPs [242]. In addition, the extravasated blood components within brain parenchyma are also processed and cause DAMPs production [55]. When it comes to SAH, a ruptured intracranial aneurysm leads to transient global cerebral ischemia due to immediate ICP elevation in a hyper-acute phase and releases a variety of cytotoxic factors including ROS, hemoglobin degradation products including iron, and other DAMPs into the subarachnoid space [10, 210, 243-246]. In the most severe cases, arterial bleeding causes persistent elevated ICP and global cerebral ischemia leading to brain death [247]. In surviving SAH cases, the subsequent processes cause delayed cerebral ischemia due to cerebral vasospasm, neuroinflammation, apoptosis of endothelial cells and so on (Fig. **5**) [10, 210, 243-247].

4.2. Time Window of BBB Opening after Stroke

In experimental models of ischemic stroke, the BBB was undamaged up to 2 h following onset [248]. BBB disruption was observed 6 h after reperfusion in experimental models of transient focal cerebral ischemia [248, 249]. Clinically, BBB breakdown occurs within 48-72 h after ischemic stroke [229, 248]. In contrast, blood injection models of ICH enhanced BBB permeability within 12 to 24 h, while BBB disruption was detected within 5 h in a collagenase injection model of ICH [45]. Expressions of the tight junction markers, ZO-1, claudin-5, and occludin were downregulated 1 to 3 days

from onset in both collagenase and blood injection models of ICH [250-258]. Clinically, BBB permeability in patients with ICH increases after 24 h of onset [55]. Perihematomal vasogenic edema peaked at around 72 h in experimental animal models of ICH, while 10 days in ICH patients [55, 259]. On the other hand, BBB disruption associated with SAH occurred as early as 10 min and prolonged up to 7 days after onset in experimental rodent models [195, 260]. Another study demonstrated a biphasic opening of BBB with a peak at 3 and 72 h in rat endovascular perforation models of SAH [261]. This biphasic pattern possibly arises from BBB breakdown caused by ICP elevation in a super-acute phase and the subsequent cytotoxic factors because these peaks coincided with the reduction of cerebral blood flow [261]. Clinically, SAH-induced global brain edema is found in 8–67% of patients at admission, while late-onset brain edema took place in 12% of SAH patients within 2 weeks of onset [244].

4.3. Polarization of Myeloid Cells to Inflammatory Phenotype after Stroke

Inflammatory responses following stroke originate from myeloid cells: that is, microglia/macrophage activation and leukocyte infiltration [262-266]. Microglia/macrophages are polarized following occurrence of stroke, transforming into pro-inflammatory or anti-inflammatory phenotypes (Fig. **5**) [267-271]. Resting microglia/macrophages (M0 phenotype) stimulated with DAMPs are polarized to pro-inflammatory microglia/macrophages (M1 phenotype) under the presence of tumor necrosis factor (TNF)-α, interferon (IFN)-γ, and interleukin (IL)-17. Microglia/macrophage were activated by 4 h and prolonged for at least 4 weeks in an ICH model produced by an intracerebral blood injection in rats [272]. Activated microglia induce pro-inflammatory mediators and cytokines *via* activation of pattern recognition receptors (PRRs) which include Toll-like receptors (TLRs), nucleotide-binding oligomerization domain-like receptors (NLRs), and receptors for advanced glycation end products (RAGEs) [273-275]. Pro-inflammatory cytokines and mediators induce specific cell adhesion molecules on endothelial cells, causing neuroinflammation, degradation of BM and tight junction proteins in brain capillary leading to BBB disruption, and apoptosis of various cells including caspase-dependent endothelial cell apoptosis [210, 244, 245, 276]. Apoptosis of ECs was increased following stroke, leading to enhancement of the BBB permeability [245]. Caspase-3 positive human brain microvascular endothelial cells were also increased in oxygen-glucose deprivation administration models of ischemic stroke [277]. *In-vivo* studies in hemorrhagic stroke demonstrated that cell death in endothelial cells of microvessels was increased after SAH as well as in the perihematomal area in a collagenase model of ICH [277]. In addition, both apoptosis and autophagy of endothelial cells were induced in the hippocampus after SAH [277]. Moreover compromised BBB allows macrophages and leucocytes into brain parenchyma, leading to further inflammatory responses [275]. The transmigration and infiltration of leukocytes were enhanced with BBB permeability and caused further induction of cytokines as well as MMPs after ICH [278-281].

4.4. The Involvement of PPRs in an Acute Phase after Stroke

TLRs are cell surface receptors involved in innate immunity and inflammatory response. Among TLR family members, TLR4 plays the most important role after stroke and has been researched extensively [275]. DAMPs bind to TLR4, which in turn activates transcriptional factor nuclear factor-κB (NF-κB) as well as mitogen-activated protein kinases (MAPKs) *via* myeloid differentiation primary response protein 88 and toll receptor–associated activator of interferon dependent signaling pathway leading to the release of pro-inflammatory cytokines and mediators such as IL-1β, IL-6, IL-8, IL-12, TNF-α, and MMPs into the brain tissue [244, 275]. Therefore, TLR4 is possibly one of good therapeutic targets to prevent BBB disruption following stroke. Our recent study showed that selective TLR4 antagonists attenuated post-SAH neurobehavioral impairments as well as BBB disruption *via* inactivation of MAPK c-Jun N-terminal kinases and MMP-9 in mice [282]. Post-ischemic BBB disruption was also improved by Tanshinone II A *via* suppression of TLR4, RAGE, HMGB1, and NF-κB expression [283]. On the other hand, NLRs signaling is also known as one of the innate immune system [284]. Currently, four NLR family members have been described, and NLRP3 inflammasome has been studied most [285, 286]. NLRP3 inflammasome is a cytosolic receptor and no direct ligand has been known. However, some non-protein DAMPs such as ATP and uric acid activate NLRP3 inflammasome indirectly in response to stroke stimuli [287]. ATP binds to P2X7 receptor (P2X7R) located on cell surface of neurons and glial cells, and leads to activation of the downstream signaling NLRP3 inflammasome and MAPKs followed by production of pro-inflammatory substances resulting in BBB injury [288-295]. Uric acid also activates NLRP3 inflammasome although the exact mechanisms have not been revealed [241, 296]. A P2X7 antagonist BBG inhibited MAPK p38 activation as well as NLPR3 inflammasome, and alleviated inflammation-associated neurologic deficits as well as neuronal apoptosis following SAH [293, 297]. In contrast, a selective NLRP3 antagonist MCC950 improved post-SAH neurological impairments *via* the reduction of BBB disruption as measured by albumin levels in the brain tissues as well as suppression of the release of pro-inflammatory cytokines such as TNF-α, IL-1ß, and IL-6 and MMP-9 in SAH [298]. In addition, ruscogenin, a major bioactive steroid sapogeni, attenuated cerebral ischemia-induced BBB disruption *via* inactivation of NLRP3 inflammasome and MAPKs [299]. Post-ICH BBB disruption was also ameliorated by selective NLRP3 inflammasome antagonist MCC950 [300]. RAGE is a cell surface receptor expressed on various CNS cells including myeloid cells. RAGE is activated by DAMPs such as HMGB1 and S100, and induces activation of NF-κB as well as MAPKs *via* Ras activation [301-306]. The soluble form of RAGE (sRAGE) has been used for the treatment targeting RAGE because it shows competitive antagonistic blocking against full-length RAGE [307]. Post-SAH sRAGE treatment reduced neuronal cell death *via* suppression of inflammation in rats [307].

4.5. The Involvement of MMPs towards BBB Disruption after Stroke

MMPs are key mediators of BBB breakdown, endothelial upregulation of adhesion molecules, and infiltration of inflammatory cells in stroke [47, 196, 266, 308-310]. MMP-2 is found in CSF, astrocytes, microglia, macrophages, and is upregulated with hypoxia-inducible factor-1α (HIF-1α) [310, 311], while MMP-3 is produced by microglia, macrophage, and neurons [210, 211, 311-314]. HIF-1α is a dimeric protein complex, which is induced *via* responses to growth factors as well as hypoxic state, and enhances vascular permeability and the expression of VEGF [315, 316]. A HIF-1α inhibiter, YC-1, suppressed MMP-2 as well as VEGF and prevented BBB injury in ischemic stroke [310]. Knockout of HIF-1α only in endothelial cells reduced BBB damage and infarct size after transient occlusion of middle cerebral artery in mice with diabetes, although diabetes was associated with BBB disruption [315]. In contrast, MMP-9 is induced by neutrophils, microglia, and macrophages with ROS as well as inflammatory cytokines such as TNF-α and IL-1β [210, 211, 312-314].

MMPs are potential therapeutic targets to block BBB injury, oxidative stress, and inflammatory responses [317-324]. The pan-MMP inhibitors GM6001 and BB-1101 as well as genetic deletion of MMP-12 improved post-ICH brain injury [325-328]. Clinically, minocycline reduced MMPs induction and exerted anti-inflammatory effects [329]. Treatment with minocycline also showed better neurological outcomes in patients with multiple sclerosis mainly *via* BBB-protection effects [330]. However, other studies have found that MMP inhibition following stroke has detrimental effects. A pan-MMP inhibitor BB-1101 blocked an increase in brain MMP-2 levels, but it did not have any effect on infarct size at 48 h after focal ischemia and had significant adverse effects on neurologic function in rats after 3 to 4 weeks of onset [321]. Another pan-MMP inhibitor BB-94 exacerbated brain injury after ICH [331]. This may be because the function of MMPs differs depending on the subtype, and the angiogenetic effect shows both protective and detrimental responses at different phases, severity, and types of stroke. MMP-2 induced early degradation of tight junction proteins within several hours in animal models with reperfusion injury after transient ischemia, while MMP-3 as well as MMP-9 lead to delayed opening of BBB *via* neuroinflammation at 24 to 72 h after onset [311, 317, 321, 322]. However, the action of MMP-2 towards BBB injury and neuronal death after stroke is controversial [47]. MMP-2 is upregulated in peripheral blood and CSF as well as perihematomal tissues in ICH models [314, 332, 333], while some studies have shown no obvious increase in MMP-2 expression after ischemic stroke [334-336]. Effects of ischemia-induced MMP-2 seem to depend on the reperfusion time as well as the severity of stroke [47]. Some studies demonstrated that MMP-2 induced proteolytic effects on endothelial cells after CI [311, 317, 322, 337], and that MMP-2−deficient mice subjected to transient focal ischemia display smaller ischemic lesions, less edema, and hemorrhagic volumes than wild-type mice [338, 339]. However, another study showed that MMP-2 knockout mice provided upregulation of MMP-9 and no significant improvement of ischemic lesion size compared with wild-type mice in both transient focal ischemia and permanent ischemia models [340]. A clinical study reported that plasma MMP-2 was increased only in patients with lacunar stroke within 12 h and was correlated with stable or recovering symptoms. In contrast, plasma MMP-9 was increased in patients with severe stroke after 7 days of onset and was associated with worse clinical outcomes [321]. MMP-9 is a proteolytic enzyme which plays critical roles in regard to BBB disruption due to the effects degrading ECM proteins in cerebral microvessel BM such as collagen IV, laminin, and fibronectin as well as endothelial tight junction proteins such as ZO-1 [210, 211, 243, 317]. In patients with ischemic stroke, MMP-9 in infarcted brain tissue is increased at least by 48 h from onset [341]. In addition, serum levels of MMP-9 were associated with hemorrhagic transformation in patients with ischemic stroke [208, 209]. In contrast, knockout of MMP-9 significantly suppressed brain edema as well as BBB disruption in transient focal ischemic models in mice [340]. MMP-9 was also upregulated in blood, CSF and perihematomal tissues in animal ICH models [314, 332, 333]. In both clinical and experimental studies, MMP-9 concentrations correlated with neurological deterioration, hematoma expansion, and perihematomal edema [332, 342]. MMP-9 was suppressed by depletion of circulating blood neutrophils, which inhibited neuroinflammation as well as BBB disruption after ICH in rats [280]. In addition, MMP-9 inhibitor SB-3CT also reduced SAH-induced brain edema [211]. Knockout of MMP-9 in mice showed better neurological recovery, less brain swelling, and mortality compared with wild-type animals after SAH [321]. MMPs are potential targets to be addressed in order to protect BBB integrity after stroke. However, further experimental studies would be required before clinical studies because extended and broad inhibition of MMPs might be detrimental rather than protective [321].

4.6. Polarization of Myeloid Cells to Anti-Inflammatory Phenotype after Stroke

A number of studies have shown that acute inhibition of microglia reduces BBB disruption after stroke [265, 266, 281, 343]. However, microglia can have beneficial as well as detrimental effects [45, 265, 266]. IL-4, IL-10, and transforming growth factor (TGF)-β induce alternative anti-inflammatory microglia/macrophages (M2 phenotype), which provide inhibition of M1 phenotype functions as well as inflammation resolution by releasing anti-inflammatory cytokine such as IL-4, IL-10, and TGF-β *via* mainly STAT3, STAT6 and peroxisome proliferator activated receptor (PPAR)γ (Fig. **5**) [237, 242, 344-346]. In addition, M2 microglia-induced Ym1/2, IL-10, and TGF-β improved stroke outcome *via* induction of angiogenesis, and suppression of BBB injury [347]. Furthermore, macrophages absorb cytotoxic substances including DAMPs and digest them by lysosomes *via* degradative endocytic pathways [348]. Therefore, these myeloid cells are considered to play an essential role in debris removal, hematoma phagocytosis in hemorrhagic stroke, and repair of tissues including endothelial cells [265, 266].

When M1 phenotype microglia predominate at damaged tissues, M2 phenotype microglia are decreased [349]. How-

ever, it is not well understood when and why the proinflammatory M1 phenotype is switched to the anti-inflammatory M2 phenotype, and microglia can express both M1 and M2 phenotypes simultaneously [349]. The expression levels of cytokines such as Ym1/2, IL-10, and TGF-β produced by M2 phenotypes were increased between 1 and 3 days with a peak at 3 to 5 days after CI, returning to normal levels within 14 days [347]. M1 phenotype markers such as TNF-α, IL-6 and IL-1β increased from days 3 to 14 after ischemia [347]. An AMPK activator, metformin, provided functional recovery and tissue repair by promoting the polarization of microglia toward a M2 phenotype *via* the suppression of NF-κB-mediated inflammatory signaling after ischemic stroke in mice [350]. Some experimental studies demonstrated that PPARγ agonists induced the polarization of M2 phenotype in microglia and showed neuroprotective effects after ICH [264, 351, 352]. The synthetic PPAR agonist HU-211 also suppressed the BBB disruption and production of cytokines in traumatic brain injury [353]. On the other hand, promoting BBB repair may play a role in detrimental effects because compromised BBB helps clearance of cytotoxic substances from brain parenchyma [45]. Thus, tailored treatments depending on severity of stroke and the time window of treatment should be considered in the future studies.

4.7. Roles of Pericytes and Astrocytes in BBB Disruption after Stroke

Pericytes are potentially involved in both BBB protection and damage after stroke depending on the situations [160]. Pericytes protected BBB function *via* maintaining endothelial cells and tight junctions under *in-vitro* hypoxic damage [354, 355]. In contrast, ischemia induces microvessels contraction by pericytes, followed by the degeneration [356]. Pericytes were detached from brain microvessels within 2 h after cerebral ischemia and weakened the intercellular contacts and signaling interactions between endothelial cells and pericytes [156, 158, 357, 358]. The detachment of pericytes promoted BBB disruption as well as leukocyte infiltration, resulting in further neuronal damage after stroke [160, 359]. On the other hand, viable pericytes may release proinflammatory substances by the stimulation of DAMPs and inflammatory cytokines, resulting in BBB dysfunction [160]. In addition, pericytes may transform into microglia to be involved in inflammation and inflammation-mediated tissue damages [160]. However, in a later phase, pericytes migrated into the peripheral region of ischemic core and acted as vessel coverage in middle cerebral artery occlusion in mice, suggesting a compensatory mechanism to limit BBB breakdown [360, 361].

Astrocyte also regulates BBB function, and astrocyte-induced factors may have both beneficial and detrimental effects on BBB after stroke. Selective knockout of the astrocytic Na^+/H^+ exchanger isoform 1 attenuated astrogliosis and BBB disruption after ischemic stroke in mice [362]. Pyr3, a specific transient receptor potential canonical channel 3 inhibitor, suppressed the pathological activation of astrocytes and prevented BBB breakdown after ICH in rats [363]. In contrast, astrocyte-derived angiopoietin-1 (ANG-1), sonic hedgehog, glial-derived neurotrophic factor, retinoic acid, insulin-like growth factor-1, and apolipoprotein E protected apoptosis of endothelial cells and induced tight junction repair. In addition, these factors also decreased endothelial cell adhesion molecules and reduced leukocyte infiltration [364]. Lower plasma ANG-1 levels were associated with poor outcomes after ischemic stroke [365], while higher serum ANG-1 resulted in good outcome in patients with intracerebral hemorrhage [165]. On the other hand, astrocyte-derived VEGFs, MMPs, nitric oxides, and endothelins are involved in endothelial cell apoptosis and downregulation of tight junction proteins, as well as upregulation of endothelial cell adhesion molecules, which induced leukocyte transmigration [364].

4.8. Alternative Potential Therapeutic Options against BBB Disruption after Stroke

Another potential target to prevent BBB disruption following stroke is matricellular proteins. Matricellular proteins are inducible and secretory non-structural proteins belonging to the ECM proteins [366]. Matricellular proteins are induced by various stimuli including stroke and are associated with aggravation or improvement of BBB disruption in stroke [244, 367]. Our recent studies showed that the expression of matricellular proteins including tenascin-C, periostin, and galectin-3 was enhanced after SAH and lead to BBB disruption *via* MAPKs and MMP-9 activation in mice [368-371]. A galectin-3 inhibitor, citrus pectin, attenuated BBB disruption *via* inactivation of TLR4 as well as MMP-9 [372, 373]. Tenascin-C and periostin enhanced the expression each other, resulting in BBB disruption *via* activation of MAPKs signaling pathway [374]. Treatment with neutralizing antibody against periostin suppressed tenascin-C induction as well as BBB disruption after SAH [369]. In contrast, another matricellular protein osteopontin was expressed in reactive astrocytes as well as capillary endothelial cells, and protected BBB integrity *via* inactivating MAPKs and NF-κB [244, 375]. Osteopontin induced by macrophages also seems to promote the repair of the compromised BBB associated with phagocytosis of fragmented cell debris, formation of connective tissue matrix, and resolution of damaged brain tissues after stroke [376]. Osteopontin knockout failed to repair the ischemia-induced damage of neurovascular unit in mice, resulting in incomplete coverage by perivascular astrocytic end-feet and persistently leaky compromised BBB [377]. On the other hand, ischemia-induced BBB disruption was ameliorated by aperin-13 and salidroside, which exerted anti-apoptotic effect *via* activation of phosphatidylinositol 3-kinase/Akt signaling pathways [324]. Inhibitors of cyclooxgyenases-2 reduced delayed BBB damage arising from neuroinflammation in experimental models of stroke [311]. Non-invasive vagus nerve stimulation also could suppressed BBB injury as well as infarct size by inhibiting MMP-2 and MMP-9 in ischemic stroke [378]. Alternatively, hypertonic saline prevented BBB dysfunction in ischemic stroke models *via* regulating VEGF and VEGFR2 as well as aquaporin-4 [379, 380]. Aquaporin-4 is a water channel protein widely expressed throughout the CNS including astrocytic end-feet [381]. Aquaporin-4 deficiency alleviated ischemia-induced brain edema, while it played a role in repairing compromised BBB in a delayed phase of stroke [237, 382]. Therefore, aquaporin-4-targeted therapy is possibly required to match the

time window for treatment to obtain beneficial effects towards BBB protection.

CONCLUSION

BBB disruption is a pathological change causing brain edema, hemorrhagic transformation, and neuroinflammation after stroke. Stroke-induced neuroinflammation and apoptosis of endothelial cells are involved in BBB disruption. Therefore, a multitude of therapies to address these pathophysiological changes have been proposed in both experimental and clinical studies, but currently the clinical benefits for patients with stroke still remain insufficient. On the other hand, BBB disruption may also exert beneficial effects for clearance of cytotoxic substances from brain parenchyma. Thus, further studies to capture BBB disruption and to determine appropriate treatments depending on patients' status would be needed to improve clinical outcomes of stroke patients.

LIST OF ABBREVIATIONS

^{68}Ga EDTA	=	^{68}Ga ethylenediaminetetraacetic acid
^{99m}Tc-DTPA	=	^{99m}Tc-diethylenetriaminepentaacetic acid
ASL	=	arterial spin labeling
ATP	=	adenosine triphosphate
BBB	=	blood-brain barrier
BM	=	basement membrane
CI	=	cerebral infarction
CNS	=	central nervous system
CSF	=	cerebrospinal fluid
DAMP	=	damage-associated molecular pattern
DCE-CT	=	dynamic contrast-enhanced computed tomography
DCE-MRI	=	dynamic contrast enhanced magnetic resonance imaging
EC	=	endothelial cell
ECM	=	extracellular matrix
GFAP	=	glial fibrillary acidic protein
hCMEC	=	human cerebral microvascular endothelial cell
HIF-1α	=	hypoxia-inducible factor-1α
HMGB1	=	high-mobility group box 1
ICH	=	intracerebral hemorrhage
ICP	=	intracranial pressure
IFN-γ	=	interferon-γ
Ig	=	immunoglobulin
IL	=	interleukin
IL-10R	=	IL-10 receptor
IL-4R	=	IL-4 receptor
MAPK	=	mitogen-activated protein kinase
MMP	=	matrix metalloproteinase
MR	=	magnetic resonance
NF-κB	=	nuclear factor-κB
NLR	=	nucleotide-binding oligomerization domain-like receptor
P2X7R	=	P2X7 receptor
PPARγ	=	peroxisome proliferator activated receptor γ
PRR	=	pattern recognition receptor
RAGE	=	receptors for advanced glycation end product
ROS	=	reactive oxygen species
SAH	=	subarachnoid hemorrhage
SPECT	=	single photo-emitting computed tomography
sRAGE	=	soluble form of RAGE
STAT	=	signal transducer and activator of transcription
T1WI	=	T1-weighted imaging
TEER	=	transendothelial electrical resistance
TGF-β	=	transforming growth factor-β
TIMPs	=	tissue inhibitor of metalloproteinases
TLR	=	toll-like receptors
TNF-α	=	tumor necrosis factor α
t-PA	=	tissue plasminogen activator
UCH-L1	=	ubiquitin C-terminal hydrolase L1
VE-cadherin	=	vascular endothelial- cadherin
VEGF	=	vascular endothelial growth factor
VEGFR	=	VEGF receptor
ZO	=	zonula occludens

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CONFLICT OF INTEREST

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