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Review Article

The cerebral endothelial cell as a key regulator of inflammatory processes in sterile inflammation

Peter Ludewig*, Jack Winneberger, Tim Magnus

Department of Neurology at the University Medical Center Hamburg- Eppendorf, Hamburg, Germany

ABSTRACT

Cerebral endothelial cells accomplish numerous tasks connected to the maintenance of homeostasis of the central nervous system. They create a barrier between the central nervous system and peripheral blood and regulate mechanotransduction, vascular permeability, rheology, thrombogenesis, and leukocyte adhesion. In pathophysiological conditions (e.g., stroke or ischemia-reperfusion injury) the endothelial functions are impaired, leading to increased vascular permeability, vascular inflammation, leukocyte-endothelium interactions, and transendothelial migration, driving CNS inflammation and neuronal destruction. This review describes the current knowledge on the regulatory roles of endothelial cells in neuroinflammatory processes.

1. Introduction

Brain endothelial cells are the crucial barrier separating the central nervous system (CNS) from the periphery, simultaneously ensuring an optimal nutrition supply and protection from harmful influences. Together with other cellular components such as pericytes, astrocytes, microglia, and neurons, the specialized brain endothelial cells form the multicellular blood-brain barrier (BBB). The BBB restricts plasma proteins, inflammatory molecules, and peripherally-derived immune cells to access the CNS uncontrolled and thereby maintains the homeostasis of the central nervous system. Breakdown of the BBB is one of the critical features of neuroinflammation leading to a detrimental inflammatory cascade. The inflammatory cascade in the CNS begins with the release of various danger-associated molecular patterns (DAMPs) and the recognition of these molecules by resident glial cells, e.g., microglia. Once activated, the glial cells release several inflammatory cytokines, such as TNF-α, which activates the endothelial cells further attracting leukocytes causing local inflammatory sites in the CNS. While over the last years most studies have focused on the infiltrating leukocytes, understanding the critical functions of endothelial cells in neuroinflammation draws more and more attention.

In this review, we summarize the current knowledge of the roles of endothelial cells during CNS inflammation and summarize the findings concerning therapeutic approaches to prevent or inhibit these processes.

2. Characteristics of the cerebral endothelial cells

Cerebral endothelial cells (CECs) feature special properties and differ from endothelial cells in other organs (Wolburg and Lippoldt, 2002). CECs form one of the tightest physical barriers in our body with high endothelial electrical resistance (TEER) and low paracellular permeability. The electrical resistance is in the range of 2000 $\Omega \times cm^2$ compared to 2–30 $\Omega \times cm^2$ in other tissues (Crone and Christensen,

Abbreviations: CEC, Cerebral endothelial cells; ESL, Endothelial surface layer; CNS, Central nervous system; BBB, Blood-brain barrier breakdown; TEER, Transendothelial electrical resistance; TJ, Tight junctions; AJ, Adherens junctions; PECAM1, Platelet endothelial cell adhesion molecule 1; CEACAM1, Carcinoembryonic antigen-related cell adhesion molecule 1; VE-cadherin, Vascular endothelial cadherin; JAM, Junction adhesion molecules; ZO, Zonula occludens; TEM, Transendothelial migration; DAMP, Danger-associated molecular patterns; PRR, Pattern recognition receptors; ROS, Reactive oxygen species; NADPH, Nicotinamide adenine dinucleotide phosphate; TNF, Tumor necrosis factor; IL, Interleukin; TLR, Toll-like receptors; NLR, NOD-like receptors; S1P, Sphingosin 1-phospate; VEGF, Vascular endothelial growth factor; LPS, Lipopolysaccharide; RhoA, Ras homolog gene family, member A; ROCK, Rho-associated, coiled-coil containing protein kinase 1; CCL, Chemokine (C−C motif) ligand; CXCR, CXC chemokine receptor; CXCL, Chemokine (C-X-C motif) ligand; ICAM, Intercellular adhesion molecules; VCAM, Vascular cell adhesion protein; PSGL-1, P-selectin glycoprotein ligand-1; VLA-4, Very Late Antigen-4, Integrin α4β1; LFA-1, Lymphocyte function-associated antigen 1; Rac1, Ras-related C3 botulinum toxin substrate 1; EAE, Experimental autoimmune encephalomyelitis; CVO, Circumventricular organs; ChP, Choroid Plexus; HPA, Hypothalamic-pituitary-adrenal axis; SCFA, Short chain fatty acids; NMDA, *N*-methyl-D-aspartate receptor; Aβ, Amyloid beta; NF-κB, Nuclear factor 'kappa-light-chain-enhancer' of activated B-cells

* Corresponding author at: University Medical Center Hamburg-Eppendorf, Department of Neurology, Martinistraße 52, 20246 Hamburg, Germany.
E-mail address: p.ludewig@uke.de (P. Ludewig).

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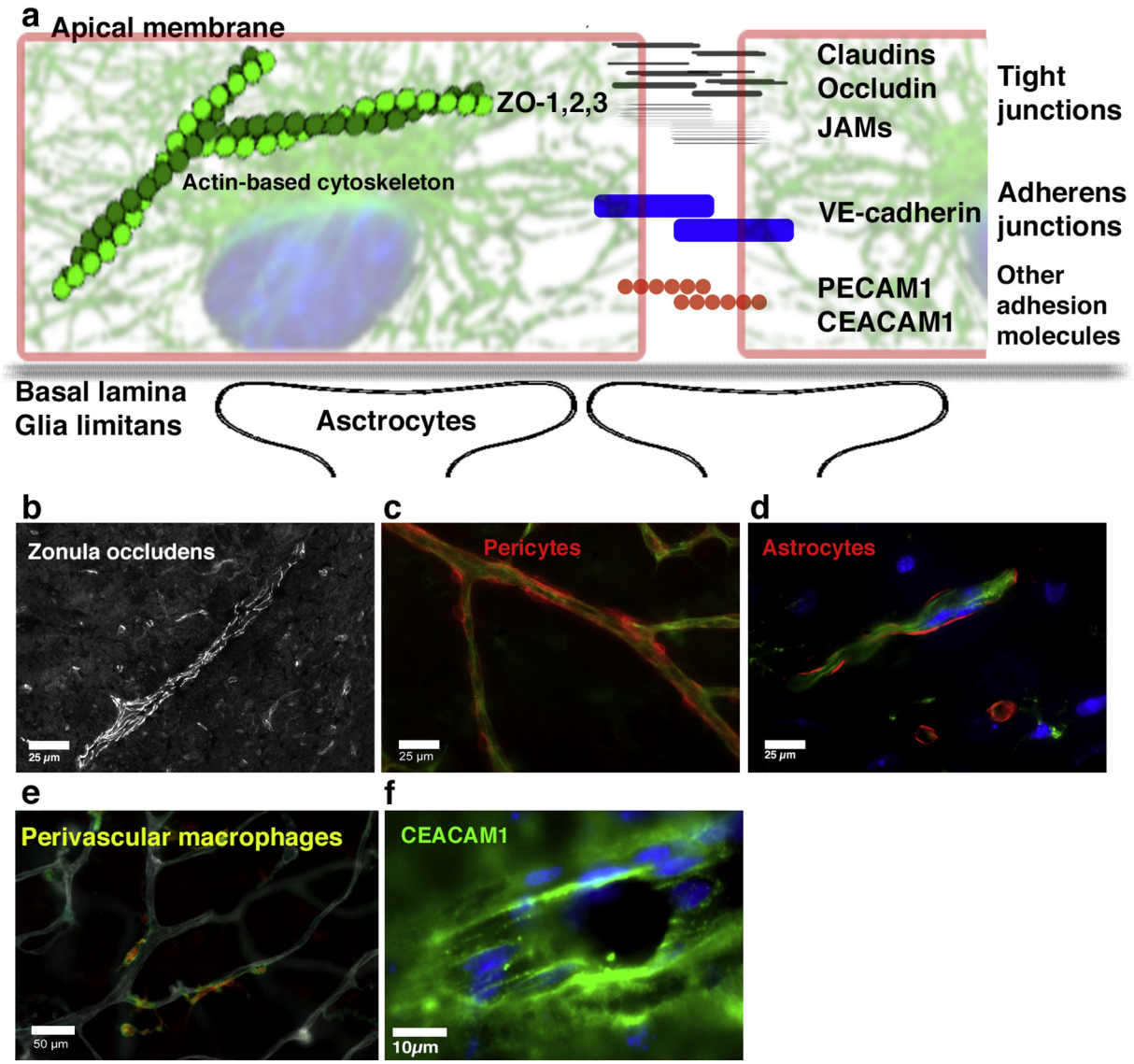

Fig. 1. Structure of the blood-brain barrier. Fig. 1a shows the main transmembrane proteins in endothelial cell-cell junctions, which enable vascular integrity, stability and decrease vascular permeability. Tight junctions and adherens junctions are indirectly linked to actin-cytoskeleton by a complex of proteins including ZO-1-3 (TJ), α-,β- and γ-catenins (AJ) and others. Different cell types such as astrocytes, perivascular macrophages, and pericytes, which form another physical barrier, the glia limitans, complete the anatomy of the blood-brain barrier. (B-f) show examples of the components of the blood-brain barrier: b: staining of cell-cell junctions (ZO-1 white); c: staining of pericytes (NG2, red) and endothelial cells (CD31, green); d: staining of astrocytes (aquaporin 4, red) and endothelial cells (CD31, green; DAPI, blue); e: staining of microglia (CD11b, green, IBA-1, red) associated to the vessels (CD31, white); f: staining of CEACAM1 (green), a cell adhesion molecule of the Ig-superfamily, shows intercellular localization. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

1981; Stamatovic et al., 2008), and restricts even the movement of small ions. The high TEER is mediated by a complex arrangement of endothelial cell-cell adhesions including tight junctions (TJ), adherens junctions (AJ), and a variety of other cell adhesion molecules (e.g., PECAM1 and CEACAM1 (Ludewig et al., 2013), see "Fig. 1"). Besides maintaining the adhesion between endothelial cells and the anatomic structure of vessels, the cell-cell junction molecules control vascular permeability and the migration of cells. The initial endothelial cell-cell contacts are mediated by the AJ molecule VE-cadherin, which gives mechanical support and stability to the vasculature. (Dejana et al., 2008) AJs are interconnected with TJs. TJs are formed by homophilic cell adhesion molecules, occludin, claudins, and junction adhesion molecules (JAMs). Whereas occludin and claudins are critical for the permeability and block diffusion of large macromolecules across the BBB (Haseloff et al., 2015), JAMs participate in leukocyte transendothelial migration (TEM) (Reglero-Real et al., 2016). The adhesion molecules are connected to the actin cytoskeleton via adaptor proteins (e.g. zonula occludens-1, ZO-2, ZO-3, catenins (Balda and Matter, 2016)), which further stabilizes the endothelial cell-cell contacts and allows participating in intracellular signaling. Especially small GTPases contribute to the composition of the TJ and AJ and interactions with the actin cytoskeleton (Cerutti and Ridley, 2017). The TJ also enable polarized properties of the CECs by separating the apical and basal domains of the cell membrane (Abbott et al., 2006). The polarity of the CECs is necessary for polarized transport functions, e.g., supplying the brain with nutrients via glucose carriers (McAllister et al., 2001). Together with these cell adhesion molecules, pericytes (Giannoni, 2018), perivascular macrophages (Faraco et al., 2017), and astrocytes (Sofroniew, 2015) complete the structure of the BBB. Especially astrocytes interact with the CECs via perivascular endfeet and form an additional barrier, the glial limiting membrane. The part of the glia limitans that encloses the parenchymal cerebral blood vessels is referred to

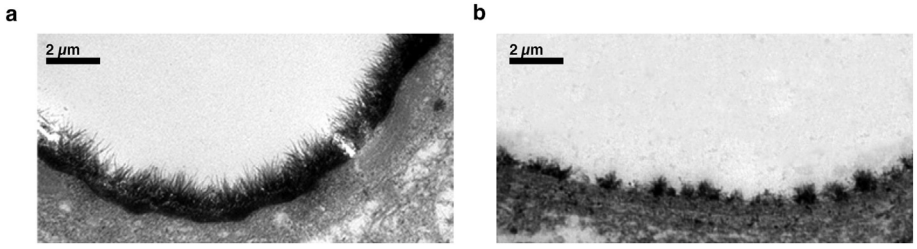

Fig. 2. Destruction of the glycocalyx in a murine model of ischemic stroke. The glycocalyx was stained with lanthanum and evaluated with electron microscopy. 2a shows the glycocalyx under normal condition. After induction of stroke (2b), this additional barrier gets destructed facilitating BBB breakdown and immune cell migration.

as the glia limitans perivascularis. The part of the glia limitans that covers the brain parenchyma and separates the neuropil from the pia mater is called glia limitans superficialis. Besides being an additional physical barrier, the glia limitans allows interactions between the cells of the neurovascular unit (Sofroniew, 2015; Wilson et al., 2010).

Whereas continuous capillaries characterize the blood-brain barrier, some regions of the brain contain fenestrated endothelium cells, like the choroid plexus (CP) and the circumventricular organs (CVO) (Gross et al., 1987; Joo, 1996). Emerging data show that these regions with fenestrated capillaries act as a critical signaling relay between the immune and nervous systems (Knoll et al., 2017; Shechter et al., 2013; Kunis et al., 2015; Miyata, 2015). Leukocytes can easily pass the fenestrated blood vessels leading to site-specific amplification of peripheral inflammatory signals and elevated chemokines in the cerebrospinal fluid, which can trigger inflammatory responses in deeper brain regions (Ge et al., 2017; Strominger et al., 2018; Benakis et al., 2018).

3. Cerebral endothelial cells - key orchestrators of neuroinflammation

The immune system protects the body from invading pathogens. In the case of noninfectious cell death, especially during development and tissue repair, the immune system can also respond with a sterile inflammatory response. However, the sterile inflammatory response can become pathological and detrimental. Cell death by necrosis, e.g., in ischemia-reperfusion injury after stroke, results in the release of alarmins or danger-associated molecular patterns (DAMPs) from neurons and glial cells (Gadani et al., 2015a; Gadani et al., 2015b). These DAMPs, their pattern recognition receptors (PRRs) and the signaling pathways alert the immune system and trigger an innate immune response (Kono et al., 2014). Besides immune effector cells such as microglia and astrocytes (Liddelow et al., 2017), CECs also expresses PRRs and are among the first cells to sense endogenous danger signals (El Kebir et al., 2009). CECs participate actively in CNS inflammation and recruit immune cells to the sites of tissue injury. Leukocytes cross the endothelium via a multistep cascade involving the activation of the endothelial cells. This results in the disruption of the CEC junctions, the loss of vascular integrity and increased permeability, as well as the disruption of the glycocalyx (Sieve et al., 2018), the expression of pro-inflammatory chemokines and cell adhesion molecules in CECs, followed by leukocyte capture, rolling, adhesion, and crawling on ECs, and finally leukocyte migration across the endothelium to the sites of inflammation.

4. CEC-glial crosstalk and activation of endothelial cells during inflammation

Under physiological conditions, leukocytes merely interact with resting CECs. However, in an inflammatory milieu CECs can change their phenotype rapidly to induce leukocyte recruitment to the inflammatory site. The close cell-cell interactions of glial cells and CECs suggest that they could induce specific features in the CECs (Davson and Oldendorf, 1967). Increasing evidence indicates that activated glial cells modulate the CEC phenotypes (Duport et al., 1998; Ramsauer et al., 2002; Schiera et al., 2003; Dohgu and Banks, 2013), and impaired endothelial-glial interactions result in impaired BBB functions (Abbott et al., 2006; da Fonseca et al., 2014; Abbott, 2002). When an injury occurs in the brain, microglia and astrocytes are capable of producing cytokines and chemokines and stimulate CECs. Microglia produces ROS through the action of NADPH oxidase, TNFα, and IL-1β, which impair BBB function by altering the expression of important molecules in the BBB integrity. Astrocytes secrete several substances regulating TJ expression and modulate the phenotype of CECs (Cheslow and Alvarez, 2016; Hayakawa et al., 2014). Furthermore, immunoregulatory loops between CECs and other glial cells exist and CECs can amplify inflammatory effects by acting back on glial cells (Didier et al., 2003).

Besides glial cells, platelets play a crucial role in neuroinflammation. Especially in stroke, where platelets often are the first cells to reach the site of vascular dysfunction, platelets can induce and exaggerate vascular inflammation, resulting in increased infarct volumes. (Carvalho-Tavares et al., 2000; Kleinschnitz et al., 2007)

The endothelial surface layer (ESL) of CEC consists of a glycocalyx, which is a complex layer of proteoglycans, glycoproteins, and glycolipids and presents the first barrier between the blood and the vessel wall (Van Teeffelen et al., 2007). Diseases such as atherosclerosis or ischemic stroke lead to ESL degradation (see “Fig. 2”). Damage to the ESL through ROS, released by microglia, or matrix-metalloproteinases, released by CEC or immune cells, during inflammation appears to be an initial step in endothelial dysfunction (Kurzelewski et al., 2005; Kutuzov et al., 2018). After glycocalyx degradation, the CEC becomes damaged and facilitates the adhesion and recruitment of inflammatory cells (Cancel et al., 2016).

Besides glycocalyx degradation, the pro-inflammatory stimuli immediately alter the composition of TJ and AJ in CECs and thereby increase the endothelial permeability, which is a prerequisite for transendothelial immune cell trafficking. CECs express several pro-inflammatory receptors, such as TNFRs (Lucas et al., 1998; Verma et al., 2006; Lopez-Ramirez et al., 2012) and pattern recognition receptors, such as TLRs (Nagyoszi et al., 2010) and NLRs (Nagyoszi et al., 2015). Activation of these receptors causes TJ/AJ disruption, whereas anti-inflammatory mediators, such as sphingosine 1-phosphate (S1P) or angiopoietin-1, decrease permeability. (Mehta and Malik, 2006) Pro-inflammatory molecules increase vascular permeability through either direct dismantling of the AJs and TJs via phosphorylation or changes to the associated cytoskeleton. Thrombin (Timmerman et al., 2012), TNFα (Nwariaku et al., 2002), VEGF (Wessel et al., 2014), and LPS (Yang et al., 2015) can phosphorylate AJ components and induce disassembly or internalization of the VE-cadherin complex resulting in increased permeability. A major mechanism, which has been described in sterile inflammation during cerebral ischemia (Gibson et al., 2014), is the activation of the small GTPase RhoA and its downstream target ROCK. TNFα phosphorylates claudins and occludins via ROCK1 and ROCK2, resulting in a loss of the TJ proteins at the junctions with increased permeability (Clark et al., 2015). ROCK also increases the actomyosin contractility. This results in a conformational change of the parallel actin bundles of the cytoskeleton to actin stress fibers, which impose an increased mechanical force on the junctions and disrupt their integrity (Hirano and Hirano, 2016).

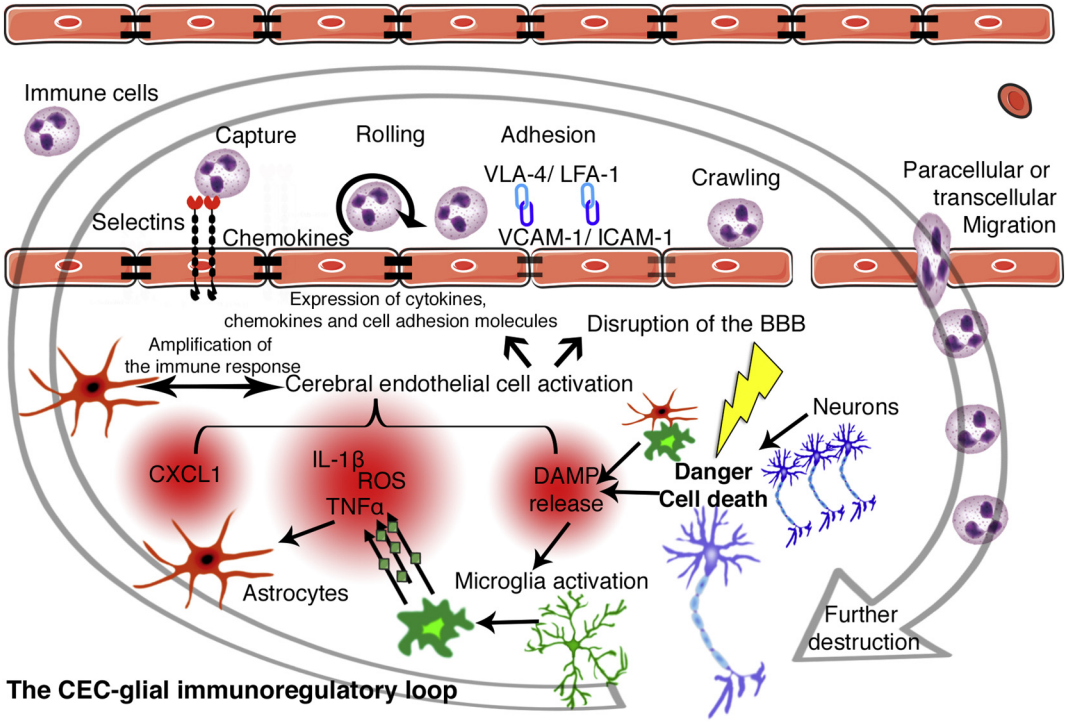

Fig. 3. Cerebral endothelial cells are key players in neuroinflammation. Endothelial activation in sterile inflammation after stroke or trauma leads to opening of the blood-brain barrier, the attraction of immune cells and disturbance of brain function. Danger-associated molecular patterns, released by necrotic neurons and glial cells, acts on microglia, astrocytes, and directly on cerebral endothelial cells. In glial cells, this triggers the production of TNFα, IL-1β, CXCL1, reactive oxygen species, and other cytokines or chemokines, all of which can activate cerebral endothelial cells. Upon activation, cerebral endothelial cells coordinate and regulate immune cell migration and further inflammatory processes. The inflammatory CECs present several cell adhesion molecules and chemokines on the cell surface, which initiate the immune cell diapedesis. In the first step, immune cells overcome the shear forces of the blood flow via interaction of PSGL-1 with selectins in the endothelial cells. Additionally, leukocytes bind chemokines presented on the endothelial luminal surface. The binding of chemokines leads to externalization of integrins such as VLA-4 and LFA-1 and their conformational change with increased avidity for the endothelial adhesion molecules ICAM-1 and VCAM-1 mediating the crawling and arrest of the immune cells on the endothelial cells. Transendothelial immune cell migration can occur in two different ways: the paracellular route involves migration across adjacent endothelial cells whereas in the transcellular route the leukocytes migrate through a single endothelial cell. Transmigrated immune cells then trigger further neuroinflammation.

5. CECs coordinate immune cell transendothelial migration

After weakening of the blood-brain barrier, leukocytes start crossing the endothelium (see "Fig. 3"). Chemokines and cell adhesion molecules expressed on endothelial cells, including selectins, integrin ligands, and adhesion molecules of the Ig-superfamily, contribute to the inflammatory immune responses and transendothelial migration (Ludewig et al., 2013; Reglero-Real et al., 2016; Nourshargh et al., 2010; Luscinskas et al., 2002).

The cascade starts with the expression of selectins on the CECs to mediate rolling and capturing of leukocytes. Integrins on the immune cells then cooperate with their endothelial ligands to induce slow rolling and leukocyte arrest. Endothelial chemokines bind to chemokine receptors to activate intracellular signaling events to enhance integrin affinity (Rossi et al., 2011). CECs express several chemokine receptors, such as CXCR2, which bind CXCL1 secreted by astrocytes. This is followed by a release of several chemokines, e.g., CCL2, CCL3, and interleukin 8, which regulate the trafficking of inflammatory cells (Wu et al., 2015; Ransohoff et al., 2007; Chui and Dorovini-Zis, 2010).

Next, intraluminal crawling of leukocytes in blood vessels occurs in an aMb2-integrin- and ICAM-1-dependent manner (Steiner et al., 2010). Finally, local VE-cadherin internalization and membrane proteins including PECAM-1, CD99, and JAMs promote the transendothelial migration of leukocytes (Schenkel et al., 2004). Interactions of VLA-4 and VCAM-1 during crawling actives small GTPases (Rac1), which produce intracellular reactive oxygen species by NADPH oxidases (Cook-Mills et al., 2004). ROS, in turn, activate tyrosine kinases (Mishra and Singh, 2014), which phosphorylate VE-Cadherin causing local loss of function of VE-cadherin and internalization, junction opening and increased transendothelial migration (van Buul et al., 2005).

There are different locations where leukocytes can migrate into the CNS. Immune cells can enter through the epithelial cells of the choroid plexus (Reboldi et al., 2009), through the meningeal blood vessels (Kivisakk et al., 2003), or through the postcapillary venules directly into the CNS parenchyma (Wilson et al., 2010; Zenaro et al., 2013).

Recently, lymphatic vessels have been described and offer a new pathway for immune cell migration and brain antigen presentation to the peripheral immune system (Louveau et al., 2015). This drainage system can have positive and negative implications within brain pathologies as multiple sclerosis, stroke or Alzheimer's disease. In experimental autoimmune encephalomyelitis (EAE), a murine model of multiple sclerosis, antigen presenting cells, as well as antigens, have been found in cervical lymph nodes inducing immune responses detrimental in a murine model of EAE (van Zwam et al., 2009). In models of stroke and Alzheimer's disease (AD), on the other hand, the clearance of interstitial fluid and antibodies through lymphatic structures is neuroprotective (Sun et al., 2018; Arbel-Ornath et al., 2013).

Additionally, there are different mechanisms to cross the CEC, either paracellular between the cell-cell junction, or transcellular through the CEC body (Muller, 2016; Sage and Carman, 2009). The choice of the route depends on the migrating cell type, the site of migration, and the type of endothelium (Heemskerk et al., 2016; Woodfin et al., 2011; Martinelli et al., 2014), but only a minority of cells use the transcellular pathway (Carman and Springer, 2004). Transcellular migration requires the lateral border recycling compartment (LBRC), a complex vesicular-tubule invagination of the endothelial plasma membrane.

PECAM1, CD99, and JAMs start the recruitment of the LBRC to the site of leukocyte interaction, which then surrounds the transmigrating immune cells for TEM (Sullivan et al., 2014; Mamdouh et al., 2009; Weber et al., 2015). The transmigrated immune cells initiate further intraparenchymal inflammatory processes, which can activate more glial cells and CECs and increase the neuronal damage.

6. Endothelial cells in physiological and pathological aging

Due to rising life expectancy and an aging population, age-related morbidities are rapidly increasing. Cerebrovascular dysfunctions are common among elderly persons. There is increasing evidence that dysfunction and senescence of the cerebral microvasculature play critical roles in these age-related brain pathologies (Yamazaki et al., 2016; Wilhelm et al., 2017). Endothelial function is dependent on the balance of pro- and anti-inflammatory, anti-thrombotic and antioxidant factors and moves towards a pro-inflammatory phenotype with progressing age (Donato et al., 2015). This leads to an endothelial dysfunction with impaired vessel dilatation (Donato et al., 2009), weaker angiogenic response (Zhuo et al., 2010) as well as increased vascular permeability (Blau et al., 2012). Inflammatory stimuli and ROS lead to activation of the NF-κB pathway, which increases the transcription of pro-inflammatory cytokines such as TNF-α and IL-1β and the endogenous production of ROS leading to a vicious cycle. ROS themselves reduce endothelial nitric oxide synthase activity and bioavailability of nitric oxide, thereby compromising normal endothelial function (Donato et al., 2015). As a result, several morphological and functional microvascular changes can be observed during aging, including a decrease in the number of mitochondria with lower metabolic rates (Tang et al., 2014; Chalmers et al., 2016; Ungvari et al., 2010), impaired angiogenesis and vessel rarefication (Ungvari et al., 2018), fibrosis, membrane thickening, loss of pericytes (Kisler et al., 2017), and finally microhemorrhages (Nezu et al., 2015). This leads to the dysregulation of cerebral blood flow and neurovascular uncoupling with reduced oxygen supply to the brain and metabolic stress. The neurovascular dysfunction leads to impaired neuronal excitability and neurodegenerative changes over time (Toth et al., 2017; Tarantini et al., 2017; Cai et al., 2017).

Therefore, endothelial cells also play a role in pathological aging as in Alzheimer's disease. Competing vascular and amyloid hypotheses have been proposed for explaining AD pathology, but may both be intertwined processes (Kelleher and Soiza, 2013). Vascular dysfunction leads to local hypoperfusion in the brain, damaging neurons and leading to accumulation of the amyloid beta peptide. Aβ-peptide itself, in turn, increases inflammatory cytokines, matrix metalloproteinases, integrins, ROS production and cytosolic calcium concentration leading to decreases of nitric oxide, junctional proteins and finally loss of endothelial functions and integrity, as well as neuronal damage (Canobbio et al., 2015; Wan et al., 2015; Zenaro et al., 2017).

7. Neuroinflammation and the gut microbiota

An interesting topic in brain immunology has developed in recent years, linking the gut microbiome to neuroinflammatory, neurodegenerative and neurobehavioral pathologies. Commensal bacteria and their metabolic products, e.g., short chain fatty acids (SCFA), have shown to have effects on cerebral endothelial cells, microglia cells and the hypothalamic-pituitary-adrenal axis (HPA) (Rea et al., 2016; Houser and Tansey, 2017). Germ-free mice display an increased permeability of the BBB due to downregulation of tight-junction proteins such as occludin and claudin-5 which could be alleviated by transfer of pathogen-free microbiota (Braniste et al., 2014). Furthermore, in a model of transient stroke modulation of the gut microbiota through antibiotic treatment could greatly reduce infarct volumes by inhibition of γδ T cells by the expansion of regulatory T cells (Benakis et al., 2016). In EAE the microbial metabolites of tryptophan could dampen microglial activation and NF-κB dependent pathways, suppressing a pro-inflammatory phenotype of astrocytes thereby ameliorating disease progression (Rothhammer et al., 2018). Microglial activation by microbiota can also influence the HPA axis and thereby neurobehavioral responses to stress (Forsythe et al., 2012). Presently the exact mechanisms and pathways allowing this gut-brain communication are not entirely understood and require further research.

8. Modulation of the BBB

BBB breakdown is a hallmark in many neurological disorders including ischemic stroke and epilepsy, negatively influencing disease progression. Contrarily the ability of locally loosening the BBB can offer possibilities of more effective administration of drugs to certain brain regions (Vazana et al., 2016). Glutamate and the corresponding NMDA receptor have been found to play a role in BBB opening in pathological conditions with inhibition of NMDA receptors ameliorating BBB leakage in murine epilepsy and stroke, as well as dampening expression of inflammatory cytokines such as TNF-α (Jander et al., 2000). Mechanistically, stimulation of NMDA receptors has shown to elevate intracellular calcium and nitrogen monoxide levels and lead to redistribution and phosphorylation of occludin, reducing junctional integrity (Andras et al., 2007; De Bock et al., 2013). Searching for ways to improve drug delivery to the brain, methods for local, controlled disruption of the BBB have been studied. Beyond approaches like vasoactive or hyperosmolar substances that open the BBB unselectively, methods such as focused ultrasound, photodynamic therapy, and photochemical internalization have the ability to increase permeability in a site-specific manner which is of great interest in the administration of drugs to brain tumors (Fang et al., 2014; Wu et al., 2018; Madsen and Hirschberg, 2010).

9. Summary

Sterile neuroinflammation and migration of leukocytes into the CNS occurs in many CNS diseases. Cerebral endothelial cells participate actively in the complex processes of CNS inflammation. Due to their location at the interface between the CNS and the periphery, CEC crosstalk with resident CNS cells and peripheral immune cells. Various molecules, especially DAMPs and cytokines released by glial cells such as microglia and astrocytes, are involved in the activation of CECs. Upon activation, CECs change their phenotype drastically and the composition of cell junction proteins, which results in an increased vascular permeability. Additionally, CECs begin to express various cell adhesion molecules and orchestrate the immune cell migration across the BBB to the sites of inflammation. Because of their importance and central role in neuroinflammation, targeting CEC activation could be a promising therapeutic target for various inflammatory CNS diseases. However, more research is needed to understand the specific role of endothelial cell activation in different CNS inflammatory disease models.

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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