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Update article

Pericyte function in the physiological central nervous system

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ABSTRACT

Damage to the central nervous system (CNS) leads to disruption of the vascular network, causing vascular dysfunction. Vascular dysfunction is the major event in the pathogenesis of CNS diseases and is closely associated with the severity of neuronal dysfunction. The suppression of vascular dysfunction has been considered a promising avenue to limit damage to the CNS, leading to efforts to clarify the cellular and molecular basis of vascular homeostasis maintenance. A reduction of trophic support and oxygen delivery due to circulatory insufficiency has long been regarded as a major cause of vascular damage. Moreover, recent studies provide a new perspective on the importance of the structural stability of blood vessels in CNS diseases. This updated article discusses emerging information on the key role of vascular integrity in CNS diseases, specially focusing on pericyte function.

1. Vascular dysfunction is associated with the severity of neuronal dysfunction in CNS disease

During embryogenesis, a primary capillary plexus formed by angioblasts of the mesoderm undergoes extensive vascular development, known as vasculogenesis, and develops into a hierarchical vascular branching network. In the adult, blood vessels possess a mature phenotype, and they remain a highly quiescent tissue. However, vascular dysfunction, which usually begins with the rupture of capillaries and associated hemorrhage, occurs in several neurological diseases, including multiple sclerosis (Minagar and Alexander, 2003), brain tumors (Lee et al., 2006), epilepsy (Marchi et al., 2012), and stroke (Yang and Rosenberg, 2011). Abnormalities in the vascular system coincided with endothelial cell apoptosis (Winn and Harlan, 2005) are considered to contribute to disease onset and/or progression of neurodegenerative event (Grammas, 2000). In the context of circulatory function, vascular rupture results in oxygen debt and nutrient starvation, leading to neurodegeneration. Thus, protecting the vasculature during CNS damage is believed to mediate the prevention and/or mitigation of neurological deterioration followed by neurodegeneration. In addition to acting as a circulatory system, recent studies have begun to focus on the vasculature from the point of view of its structural alterations and their relevance to pathological processes in the CNS (Fig. 1).

Vascular barrier disruption is a major anatomical change occurring in the pathological CNS vasculature. Blood–CNS vascular barriers normally effectively isolate the CNS from systemic influences and prevent entry of circulating blood cells, serum proteins, and blood-derived vasculotoxic and neurotoxic macromolecules into the brain. Damage to the CNS impairs the integrity of vascular barriers, causing an increase in bulk flow transcytosis. Since it is well established that blood-borne molecules exert toxic activity (Mhatre et al., 2004; Chen et al., 2010; Paul et al., 2007; Zhong et al., 2008), the disruption of vascular barriers amplifies microvascular degeneration and enhances the development of vascular-mediated neurodegeneration. Studies in recent decades have revealed that the formation and maintenance of vascular barriers requires cell–cell interactions within the vasculature. In this update article, we summarize recent progress in investigating the role of cell–cell interactions on vascular barrier homeostasis in the CNS, specially focusing on pericyte function.

2. The neurovascular unit is associated with vascular barrier function

The circulation through the brain and spinal cord differs from the circulation through most peripheral tissues, in that the brain's capillary bed does not produce ultrafiltrate. This lack of leakage is a

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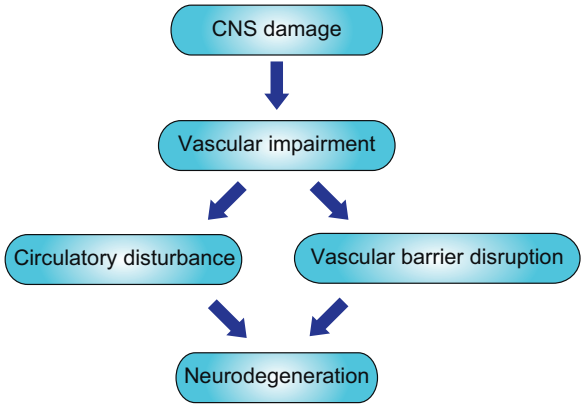

Fig. 1. Vascular dysfunction is associated with the severity of neurological impairments. Damage to the central nervous system (CNS) leads to disruption of blood vessels, causing vascular dysfunction. Flowchart diagram depicting vascular dysfunction leading to circulatory dysfunction and disruption of the vascular barrier, causing neurodegeneration.

major factor contributing to the concept of the blood–brain barrier (BBB) and blood–spinal cord barrier (BSCB). The first experimental evidence of this vascular barrier was described by studies in the late 19th century, which found that water-soluble dyes injected into the circulatory system did not stain the brain or spinal cord (Ehrlich, 1885). The dyes were prevented from entering the brain because they bound tightly to albumin in the blood, and a barrier prevented the transfer of albumin from blood to brain. Further work has clarified the nature of the vascular barrier, which can be identified as a tangible interface comprised of capillary endothelial cells. The endothelial cells of the CNS are anatomically different from capillary endothelial cells of the periphery, and are characterized by a lack of fenestration, the presence of only a few pinocytotic vesicles, and tight junctions in the interendothelial cleft. It is now widely accepted that tight junctions are intricate complexes of transmembrane (junctional adhesion molecule-1, occludin, and claudins) and cytoplasmic (zonula occludens-1 and -2, cingulin, AF-6, and 7H6) proteins linked to the actin cytoskeleton. These proteins cement adjacent brain endothelial cells together to form physical barriers (Huber et al., 2001). In addition to the presence of a physical barrier within the CNS, a selective transport barrier also exists that facilitates the entry of required nutrients while excluding or removing potentially harmful components (Begley and Brightman, 2003). Furthermore, a combination of intracellular and extracellular enzymes provides a metabolic barrier that protects functions of the vascular barrier (Ghersi-Egea et al., 1988). These characters at the capillary bed are observed throughout the CNS, excepting some circumventricular organs such as the area postrema, median eminence, neural lobe of the pituitary, pineal gland, and hypophysis (Johansson, 1990).

The barrier function of endothelial cells is known to be enhanced by crosstalk between endothelial cells and other cell types, such as neurons, pericytes, and astrocytes, and the extracellular matrix. These cells integrate into a cellular complex called the neurovascular unit (NVU), which is recognized as being essential to the expression of vascular barrier-like enforced tight junctions and the induction of specific enzymes, as well as in promoting multidrug resistance within the cerebral endothelium. For example, astrocytes can enhance vascular barrier properties, leading to formation of tight junctions, through upregulation of the expression and polarized localization of transporters, including Pgp (Schinkel, 1999) and GLUT1 (McAllister et al., 2001), and specialized enzyme systems (Abbott et al., 2006). A significant loss of neuronal activity is observed in neurological diseases and is thought to lead to an impairment of blood flow. This alteration of blood flow is closely associated with vascular permeability, suggesting that neuronal activity is also required for vascular barrier homeostasis. Recently, studies have particularly focused on the rapidly evolving role of CNS pericytes in the formation and maintenance of vascular barrier function.

3. Pericytes are essential for maintaining vascular barrier function

Pericytes and endothelial cells are ensheathed by the basal lamina, a membrane 30–40 nm thick that is composed of collagen type IV, heparin sulfate proteoglycans, laminin, fibronectin, and other extracellular matrix proteins (Farkas and Luiten, 2001). Despite the normally low level of pericyte turnover, the proliferation of pericytes that are derived from bone marrow pericyte progenitor cells (Hess et al., 2004) and pre-existing pericyte pools around the vessel (Ozerdem and Stallcup, 2003) increases in response to a pathological stimulus. Because CNS vessels possess high degree of pericyte coverage, the extent of pericyte coverage in CNS vessels has been thought to correlate with CNS-specific vascular features (Shepro and Morel, 1993). Thus far, pericytes have been confirmed to play a role in the regulation of neurovascular parameters including capillary diameter (Hamilton et al., 2010), blood flow (Kutcher and Herman, 2009), and vascular barrier formation.

The first evidence that pericytes play a functional role in the vascular barrier was provided by analysis of platelet-derived growth factor (PDGF)-β-deficient mice. Pericytes express PDGF receptors and respond to PDGF by upregulating their migration activity *in vitro* (Bernstein et al., 1982; D'Amore and Smith, 1993). PDGF-β-deficient mice exhibit a lack of pericytes and show ruptured blood vessels at late gestation, suggesting that pericytes are required for the formation of the vascular barrier (Lindahl et al., 1997). This finding is supported by subsequent analysis of mice with null and hypomorphic alleles of *Pdgfrb*, which have defects in pericyte generation (Daneman et al., 2010). These mice lack pericytes, a deficit that is correlated with an increased permeability of the vascular barriers during embryogenesis. Molecular characterization has shown not only that pericytes are necessary for the formation of the vascular barrier genes, but also that an absence of pericytes increases the expression of genes related to vascular permeability, including Angpt2, Plvap, and leukocyte adhesion molecules (LAMs). These studies indicate that pericyte–endothelial interactions are critical for the regulation of the vascular barrier during development.

The role of pericytes in regulating vascular barrier integrity was expanded following the observation of BBB disruption in mice with genetically disrupted Pdgfrb signaling during adulthood (Armulik et al., 2010). Pdgfrb signaling-deficient mice showed reduced pericyte densities with increased vessel diameter and reduced vessel density. BBB integrity in these mice was assessed by the accumulation of intravenously injected tracers; tracer accumulation in mutant brain parenchyma was increased in a time-dependent fashion. These experiments establish a close connection between pericyte density and the permeability of the vascular barrier in the adult CNS. There was no significant difference in the expression of tight junction protein in adult pericyte-deficient mutants compared with controls; however, mutants displayed focally increased junctional width and undulation. These abnormalities in the ultrastructure of endothelial junctions are believed to contribute to dysfunction of the vascular barrier in the adult CNS. The current belief regarding pericyte function states that they are required for suppressing the leaky phenotype of brain vascular endothelial cells in both the developing and adult CNS (Fig. 2).

The protective role of pericytes on CNS homeostasis is supported by evidence showing that vascular damage in pericyte-deficient

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