Pericytes in Epilepsy

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Pericytes are a component of the blood–brain barrier (BBB) neurovascular unit, in which they play a crucial role in BBB integrity and are also implicated in neuroinflammation. The association between pericytes, BBB dysfunction, and the pathophysiology of epilepsy has been investigated, and links between epilepsy and pericytes have been identified. Here, we review current knowledge about the role of pericytes in epilepsy. Clinical evidence has shown an accumulation of pericytes with altered morphology in the cerebral vascular territories of patients with intractable epilepsy. In vitro, proinflammatory cytokines, including IL-1β, TNFα, and IL-6, cause morphological changes in human-derived pericytes, where IL-6 leads to cell damage.

pericytes mural cells cytokine blood-brain barrier neuroinflammation

1. Introduction

Accumulating evidence has demonstrated that the pathogenesis of epilepsy is linked to neuroinflammation and cerebrovascular dysfunction [1][2][3][4][5][6]. Traditionally, microglia had been considered to be responsible for the cytokine-centered immune response in the central nervous system (CNS); however, brain pericytes can respond to inflammatory signals, such as circulating cytokines, and convey this information to surrounding cells through chemokine and cytokine secretions [7][8][9][10]. Recent studies have demonstrated that pericytes may act as sensors for the inflammatory response in the CNS, as pericytes react intensely to proinflammatory cytokines when compared to other cell types (e.g., microglia) that constitute the CNS and factor-induced reactive pericytes can also activate microglia in vitro [9][11][12][13].

Pericytes provide physical support to the blood–brain barrier (BBB) and play an integral role in CNS homeostasis and BBB function [14]. Pericyte degeneration and/or dysfunction contribute to the loss of BBB integrity, which is an early hallmark of several neurodegenerative and inflammatory conditions [8][15][16]. Another notable feature of pericytes is their ability to regulate the migration of leukocytes across the brain microvascular endothelial cell (BMVEC) barrier, which secretes key molecules that support the BBB barrier [17][18]. Recent research on the pathogenesis of epilepsy has begun to elucidate the mechanisms mediating peripheral-to-CNS cell infiltration in human and mouse models [19][20]. Pericytes may contribute to the mechanisms, while emerging research is investigating the extent of peripheral immune cell involvement in the inflammatory pathology of epilepsy.

The various functions of pericytes and their involvement in CNS diseases, including ischemic stroke [21], spinal cord injury [22], brain injury [23], and multiple sclerosis [24], has been reported.

The association between pericytes and epilepsy has attracted attention, while several recent studies have illustrated the contributions of pericytes to the pathogenesis of epilepsy [2][25][26][27][28][29][30][31][32]. These studies suggested that pericytes might participate in the pathogenesis of epilepsy, consisting of neuroinflammation and BBB damage and the interaction between peripheral and central immunity. Thus, evidence on the relationship between pericytes and the pathogenesis of epilepsy is gradually accumulating. Therefore, this study aimed to investigate the pathogenesis of epilepsy and pericytes because none of the review articles focused on this, even though therapeutic targets for pericytes in neurological disorders were investigated [17][33][34].

2. Pericytes and Neuroinflammation

Evidence accumulated from experimental models and human samples implicates immunological processes in the pathogenesis of epilepsy [1][4]. The involvement of pericytes in the CNS immune responses has attracted significant attention. Pericytes present heterogeneous signals to the surrounding cells and actively modulate inflammatory responses in a tissue- and context-dependent manner. The expression of various pattern-recognition receptors (PRRs), including toll-like receptors (TLRs) and nucleotide-binding and oligomerization domain (NOD)-like receptor families, has been detected in brain pericytes [35]. Given the abundance of surface receptors, pericytes can respond to inflammatory mediators, such as monocyte chemoattractant protein-1 (MCP-1/CCL2) and tumor necrosis factor (TNF)-α, which in turn induce the secretion of CCL2, nitric oxide (NO), and several cytokines [7][8][9][36]. Pericytes act as promoters of both the innate and adaptive immune system [37]. In the CNS, microglia are a hallmark of the immune response, which produce cytokines such as interleukin (IL)-1β, TNF-α, IL-6, and various other chemokines [38], and related effector pathways, including cyclooxygenase-2 (COX-2)/prostaglandin (PGE2) and complement factors [39]. The rapid activation of microglia impairs neuronal function by inducing inflammatory mediators, such as NO, reactive oxygen species (ROS), and proinflammatory cytokines [40][41].

Pericytes have been shown to be more sensitive to proinflammatory cytokines compared to other cells in the NVU [9][11][12][13]. Specifically, cytokine and chemokine release profiles from brain pericytes in response to TNF-α are distinct to those of other cell types comprising the NVU, and TNF-α-stimulated pericytes release macrophage inflammatory protein (MIP)-1α and IL-6. Among BBB cells, pericytes stimulated with TNF-α induced the highest levels of *iNOS* and IL-1β mRNA expression, which indicates the activation of BV-2 microglia [9]. The mechanism underlying TNF-α-induced IL-6 release involves the inhibitor kappa B (IκB)-nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) and the Janus family of tyrosine kinase (JAK)-signal transducer and activator of transcription (STAT) 3 pathways [13]. NFκB plays a key role in inflammation, immune, and stress-related responses, as well as in the regulation of cell survival and in the growth of neural processes in developing peripheral and central neurons [42]. These findings indicate that the activated brain pericytes trigger the development of uncoordinated NVU function, including glial activation, and may act as sensors at the BBB in TNF-α-mediated brain inflammation.

Pericytes also release anti-inflammatory factors, highlighting their involvement in regeneration and protection [7][43][44]. Pericytes respond to lipopolysaccharide (LPS), secrete anti-inflammatory cytokines such as IL-10 and IL-13 [45], and produce neurotrophins such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF),

which regulate neuronal development [46][47]. Pericytes upregulate neurotrophin-3 production in response to hypoxia, resulting in increased NGF production in astrocytes, thereby protecting neurons from hypoxia-induced apoptosis [47]. These actions highlight the neuroprotective functions of pericytes under pathological conditions.

3. Blood-Brain Barrier Disruption in the Pathogenesis of Epilepsy

Experimental evidence of BBB impairment in the pathogenesis of epilepsy has been demonstrated in patients and animal models [48][49][50][51], which is a hallmark of epilepsy. BBB disruption can also directly induce seizure activity and exacerbate epileptogenesis; the relationship between epilepsy and BBB breakdown is bidirectional [48][49].

BBB dysfunction and subsequent infiltration of serum albumin into the brain leads to changes in epileptogenesis, including astrocyte changes, neuroinflammation, excitatory synapse formation, and pathological plasticity [52][53]. These BBB alterations are not only due to leakage, as demonstrated by Evans Blue staining [49]. There is involvement of various inflammatory mediators as nondisruptive changes at the molecular level of pericytes are also involved in the changes of the BBB; specifically, they secrete various mediators as follows: IL-1β, TNF-α, IFN-γ, matrix metalloproteinases (MMPs), ROS/reactive nitrogen species (RNS), (NO), and prostaglandin E2 (PGE2). Pericyte-derived MMP-9 upregulation in the cerebral microvasculature can cause endothelial dysfunction through degradation of tight junctions and extracellular matrices, resulting in subsequent pericyte loss from the microvasculature and BBB disruption [11][37]. Moreover, the secretion of ROS/RNS, NO, and PGE2 lead to vasodilation and breaching of the BBB [9]. Epileptic seizures can cause pericytes surrounding the blood vessels to rearrange [2] and morphologically alter, which is facilitated by the inflammatory mediators [29][30]. These series of alterations are thought to be linked to the pathogenesis of epilepsy, although further details are warranted.

4. Leukocyte Recruitment and Peripheral-to-Central Infiltration

Pericytes regulate the migration of leukocytes across the BMVEC barrier and secrete key molecules that support the BBB [17][18]. Chemokines (CCL2, CXCL1, CXCL8, and CXCL10) secreted by pericytes in both basal and inflammatory states recruit peripheral immune cells, including monocytes, B and T cells, and neutrophils, to the CNS parenchyma via upregulation of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) on the endothelium [7][8][9][54]. Although the human brain is considered an immune-privileged area [52][55], this is not preserved during inflammatory conditions. Analysis of brain parenchyma in patients with epilepsy showed that there have been both positive [56][57] and negative [58] reports on the occurrence of infiltration of peripheral leukocytes into the brain tissue. Recent experimental research demonstrated that peripheral-to-CNS cell infiltration, particularly monocytes, occurs in the status epilepticus (SE) model, without evidence of infections or immune disorders [20][59][60]. The possibility of classifying peripheral monocytes and indigenous microglia, which have been considered difficult to differentiate, has been increased using genetic engineering [59][61][62].

In chemokine receptor 2 (CCR2)-knockout mice, the CCL2 receptor, which blocks peripheral monocyte invasion into the brain tissue, attenuated neuronal damage in SE models [59]. Analysis of the brain tissue from pediatric patients with drug-resistant epilepsy (DRE) revealed that seizure frequency was correlated with the number of infiltrating peripherally activated CD3+ T cells and monocytes, but not microglia [19]. Current analysis of pediatric patients with DRE also demonstrated a correlation between the number of seizures and intracellular IL-1β levels in monocytes [63], while experimental data and human research attributed seizure-induced neuronal death to the activation of resident microglia [62][64]. Whether the peripheral monocytes or the resident microglia are the primary triggers of epilepsy, as well as the extent to which the infiltrated cells are significant, remains to be determined; nevertheless, the combination of the roles of the pericytes in maintaining the BBB integrity, producing inflammatory mediators, and recruiting leukocytes indicate that the pericytes could be intimately involved in the pathogenesis of epilepsy.

5. Clinical Evidence Links Pericytes to Epilepsy

The disarray of the pericyte-basal lamina interface in patients with epilepsy was first described in 1990 [65]. Evidence of pericyte degeneration with basement membrane unit thickness and cytoplasmic density has also been reported in most of the spiking area microvessels in human brain tissues of intractable complex partial seizures using an electron microscope [65].

With the advent of PDGFRβ, though a nonspecific CNS pericyte marker, the immunostaining reports of the presence of PDGFRβ+ cells have emerged in the brain specimens of patients with intractable epilepsy in focal cortical dysplasia (FCD) and temporal lobe seizures (TLE) [2][25][29]. In tissues from patients with refractory TLE and hippocampal sclerosis (HS), the presence of PDGFRβ+ cells associated with blood vessels and parenchyma was observed, although findings were heterogenous [2]. Indeed, the highest perivascular PDGFRβ immunoreactivity was detected in patients with TLE-HS, specifically in the microvasculature [2]. Tissue from patients with cryptogenic epilepsy has exhibited a similar immune response pattern, although to a lesser extent than that of FCD. Increased perivascular PDGFRβ immunoreactivity was associated with increased hippocampal vascularization in the cells of patients with TLE-HS [25].

Another study of TLE and FCD specimens revealed robust PDGFRβ-positive cell pericyte immunoreactivity surrounding the blood vessels, particularly in TLE with HS specimens, with aggregation of IBA1/HLA microglial cells and pericyte-microglia outlining the capillary wall [29]. The morphological changes in pericytes were induced by proinflammatory cytokines, including IL-1β, TNFα, and IL-6; in particular, IL-6 exposure was drastically associated with apoptosis, suggesting pericyte damage [29].

Collectively, the accumulation of pericytes (PDGFRβ-positive cells) in the cerebral vascular regions was consistently observed in patients with refractory epilepsy [2][25][29]. The degree of accumulation correlates to some extent with the clinical picture [25][29], and morphological changes of the pericytes might be due to proinflammatory cytokines [29]. In addition, the amount of angiogenesis, which is associated with epileptogenesis, was related to the

number of PDGFRβ-positive cells [25], suggesting a relationship between PDGFRβ-positive cells and the pathogenesis of epilepsy.

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