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Short Review

Brain Endothelial Cells as Potential Therapeutic Targets in Neurological Diseases

Adriana Jiménez[1], Neptali Gutiérrez de la Cruz[2], Marco Antonio Vargas-Hernández[2] and Enrique Estudillo[3]*

[1]División de Investigación, Hospital Juárez de México, Mexico City 07760, Mexico

[2]Escuela Militar de Graduados de Sanidad, Secretaría de la Defensa Nacional, Batalla de Celaya 202, Lomas de Sotelo, Miguel Hidalgo, 11200 Ciudad de México, México

[3]Laboratorio de Reprogramación Celular, Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez, Mexico City 14269, Mexico

Brain homeostasis highly depends on Blood Brain Barrier (BBB) function and integrity. BBB displays some changes as individuals age, and brain endothelium damage has a key role in the pathology of neurological diseases such as ischemic stroke and neurodegenerative disorders [1]. Brain Endothelial Cells (BECs) form a highly impermeable barrier between the blood and brain parenchyma that selectively restricts the movement of molecules and cells. BECs not only play a key role in BBB permeability, but also maintain BBB integrity as they are closely associated with pericytes, astrocytes and neurons, and can respond to peripheral inflammatory mediators. Recently, we discussed the participation of BECs in the pathology of Alzheimer Disease (AD) and the relevance of their study as therapeutic targets in neurodegenerative diseases rather than as a barrier that prevents the entry of therapeutic drugs into the brain [2].

Neurological diseases such as AD and other dementias are associated with aging; interestingly, the brain endothelium display changes with age, for example, vessels rarefaction, increased string vessels and impaired vasodilation are observed in the aging brain of humans and animals, which lead to a decrease in the blood flow of the brain [3]. The single-cell RNA sequencing analysis of brain cells from C57BL/6 mice identified a population of 10% senescent endothelial cells in old mice [4]. Moreover, single-cell RNA sequencing of mouse hippocampal BECs showed that capillary BECs are more susceptible to change their transcriptomic profile in response to aging than arterial and venous BECs; surprisingly, young endothelial cells were able to respond to aged plasma by adopting the transcriptomic profile similar to aged BECs [5].

Transport through BECs is also affected by age, glucose transport in the brain decreases with aging while glucose metabolism also decreases, furthermore GLUT1 expression is reduced in brain-derived endothelial cells from AD patients which is an age-related disease [6]. In the same way, the large neutral amino acid transporter (LAT-1), p-glycoprotein (P-gp) and low-density lipoprotein receptor-related protein-1 (LRP-1) are impaired with age [7]. Notably, LRP-1, P-gp and Receptor for Advanced Glycation Endproducts (RAGE) are key regulators of beta amyloid peptide clearance, which deregulation is associated with AD [2]. Pituitary adenylate cyclase-activating polypeptide (PACAP) transport across BBB was also reduced in SAMP8 mice, which are a model of age-related cognitive decline; the reduction of PACAP transport was higher in the olfactory bulb, hippocampus and hypothalamus [8,9].

BECs are tightly joined by claudins and occludin, these interactions can be affected with age and brain damage. Senescent endothelial cells were found close to areas of leaky vasculature in the APP/PS1 and APP23 mice models of AD. Senescent BECs were characterized by decreased expression of VE-Cadherin and claudin 5, and were observed even before the formation of senile plaques, suggesting that premature BECs senescence may contribute to AD [10]. During brain damage the increase of VEGF-A downregulates claudin 5 and occludin causing BBB permeability, conversely VEGF-A inhibition reduces BBB damage and neuroinflammation in mice [11]. Restoration of tight junctions has been shown to be beneficial in depression and cognitive decline. In mice models, the chronic treatment with antidepressants improved depression-like behaviors which was associated with increased claudin 5 expression, this effect was also observed by the inhibition of HDAC1 which activates FOXO1, a negative regulator of claudin 5. Additionally, increased ZO-1 expression by silencing of miR-501-3p rescued BBB disruption and reduced cognitive impairment [12]. Recently, Gorick and cols. developed a computational model of BECs signaling to predict therapeutic targets for neurological diseases. VEGF-A, BDNF, NGF, cathepsin D and Wnt signaling pathways were upregulated in gliomas, while in AD, VEGF-A and cathepsin D were downregulated; finally, in brain ischemia cathepsin D and BDNF were low and VEGF-A and Wnt increased [13].

BBB impairment leads to peripheral immune cells infiltration and the release of central and peripheral proinflammatory molecules causing neuroinflammation. The role of BECs in cellular infiltration has been widely described in experimental autoimmune encephalomyelitis and multiple sclerosis, in which MCAM expression increases in BECs and promotes T_H1 and T_H17 lymphocyte penetration into the brain parenchyma; notably, the luminal expression of MCAM in BECs is very low under physiological conditions [14], suggesting MCAM as a potential therapeutic target for autoimmune neuroinflammation.

***Corresponding author:** Enrique Estudillo, Laboratorio de Reprogramación Celular, Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez, Mexico City 14269, Mexico, E-mail: jestudillo@innn.edu.mx

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During immune cell infiltration into the brain parenchyma, BECs must interact with leukocytes through adhesion molecules, therefore blocking this process could reduce neuroinflammation. The humanized antibody Natalizumab targets α4-integrin to block its interaction with VCAM-1 and shows beneficial results by reducing disability progression and relapse rate in multiple sclerosis. In addition, inhibitory small molecules that block the binding of α4β1-integrin to VCAM-1, fibronectin or ICAM-1 such as TBC 3486 and statins can reduce the severity of disease in experimental autoimmune encephalomyelitis. However, other antibodies such as Rovelizumab directed against αLβ2-integrin and Enlimomab which targets ICAM-1, did not show beneficial effects in clinical trials for multiple sclerosis and ischemic stroke, respectively [15].

Peripheral and central inflammation cause BBB dysfunction mediated by proinflammatory cytokines such as TNF-α and IL-6, which negatively correlate with ZO-1, claudin 5 and VE-cadherin expression in BECs [1]. Conversely, TNF-α inhibition improve BBB integrity in a mice model of depression, nevertheless, other authors did not find a negative effect of TNF-α in tight junction protein levels at the BBB [11]. TNF-α and IL-6 can also induce ROS production in BECs by activating NADPH Oxidase (NOX) proteins, whose inhibition by N-acetylcisteine rescues the expression of VE-cadherin and claudin 5 [1]. Additionally, oxidative stress induced by NOX4 and NOX5 promotes immune cell infiltration into brain parenchyma [11].

On the other hand, BECs can secrete proinflammatory factors such as thrombin, IL-1β, IL-6, TNF-α, monocyte chemoattractant protein-1 (MCP-1), ROS and nitric oxide, also contributing to neuronal damage. This secretory action of BECs was proposed as the endothelial-mediated neurotoxicity hypothesis in AD, in which systemic inflammation in AD patients activates BECs to secrete these proinflammatory factors leading to neurodegeneration [2]. Furthermore, it has been proposed that senescent cerebrovascular cells change their secretory phenotype to release proinflammatory factors such as VCAM-1, TNF-α, IL-1β and VEGF that induce chronic neuroinflammation, tight junction degradation, ROS, and impaired nitric oxide synthesis, thus leading to neurovascular uncoupling and BBB damage [16]. All the previous information highlights the relevance of BECs in the development of neurological diseases and aging, therefore, further investigation of these cells must be carried out as a potential therapeutic target and not only as an obstacle for the delivery of drugs to the CNS.

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Conflict of Interest

The authors declare no conflict of interest.

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