EDITORIAL

Blood-brain Barrier Dysfunction in Cerebrovascular Diseases

Cerebrovascular diseases are one of the leading causes of death and adult disability worldwide and most common types of this diseases are ischemic stroke and hemorrhagic stroke. Blood-brain barrier (BBB) plays a vital role in regulating the trafficking of fluid, solutes and cells at the blood-brain interface and maintaining the homeostatic microenvironment of the central nervous system. Disruption of BBB has been proved closely related to the development of brain edema and neuronal cell death in cerebrovascular diseases. Recently, major efforts have been made to investigate the pathological mechanisms of BBB dysfunction, and develop pharmacological agents which would be able maintain BBB function after pathological events. In this Special Issue on BBB dysfunction in Current Neuropharmacology, the authors provide the latest review on cellular and molecular basis of BBB dysfunction, bring new insights into BBB protection, and point toward potential translation of preclinical studies to improve the treatment of cerebrovascular diseases.

In this special issue, Okada and colleagues presented a panoramic view of current studies on BBB dysfunctions after cerebrovascular diseases, including structure and function of BBB, techniques utilized to study BBB breakdown, biomarkers and imaging techniques in clinical settings, as well as pathological mechanisms and therapeutic targets [1]. They illustrated that phenotypic transformation of myeloid cells such as macrophages and microglia regulates the initiation, evolution, and resolution of inflammation, which compromise the integrity of BBB. Another group, Kang *et al* presented an in-depth discussion on the diversity of microglia phenotypic polarizations and the communication between microglia and endothelial cells after stroke. They concluded that the time pattern of microglia polarization may determine the therapeutic effect of pharmacological agents [2]. The crosstalk between inflammation and BBB dysfunction was eloquently elucidated by Ziping Han's team [3]. They reviewed how the dynamic and bidirectional crosstalk between inflammation and BBB during stroke occurs, and proposed personalized medicine for the treatment of stroke. The contribution from Shen and Ma represent an important advance in the role of miRNAs in the modulation of BBB functions after ischemic stroke and highlight the role of several miRNAs which are implicated in the pathogenesis of neonatal hypoxic-ischemic brain injury [4]. As there is a significant physiological difference between the developing and mature brain, more studies are needed to further determine the protective effect of miRNAs in hypoxic-ischemic brain injury in neonates.

In subarachnoid hemorrhage (SAH) patients, BBB disruption is a critical contributor to the development of early brain injury [5]. The disruption is highly associated with increased mortality and poor prognosis. Li and colleagues summarized the molecular mechanisms of BBB disruption after SAH, and stated that the apoptosis of endothelial cells and loss of tight junction proteins are the two major causes responsible for BBB broken after SAH [6]. They suggested, therefore, therapeutic strategies against these two factors should be further explored in the future. Furthermore, Chen *et al*. addressed the recent clinical trials on neuroprotection of SAH patients, including pharmacological and non- pharmacological approaches [7]. The authors indicated that intraventricular nimodipine shows the exciting result to achieve better clinical efficacy and fewer side effects. They also considered that imaging techniques are promising tools to detect the abnormality of BBB and to predict the outcome in clinical setting.

Angiogenesis is an important defense mechanism for the restoration of blood supply and re-organization of the neuronal circuit following ischemic stroke [8]. However, there is compelling concern that the therapeutic angiogenesis in vascular remodeling after stroke accompanied with abnormally increased BBB permeability. Yang and Torbey presented an elegant work in which they demonstrated that the abnormally high BBB permeability in peri-infarct areas is caused by a lack of major tight junction proteins in endothelial cells in newly build vessels, and pericytes play a key role in tight junction formation during angiogenesis [9]. They recommended defining and optimizing restorative therapies by characterizing the cellular and molecular mechanisms to facilitate functional BBB restoration without exacerbating brain edema and inflammation during treatment of ischemic stroke. Given the prosperity of stem cell therapy in recent years, Gao *et al*. extensively illustrated the effects and underlying mechanisms of cell therapy on the BBB permeability in ischemic stroke [10]. There is still a great gap between preclinical and clinical applications of stem cells, and some teething problems such as safety and ethical concerns need to be ironed out.

Collectively, this Special Issue highlights several issues that are at the forefront of the BBB dysfunction in cerebral diseases. A better understanding of these mechanisms will contribute to the identification of therapeutic targets and promote the translational research of BBB protection.

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