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EDITORIAL

Translational Stroke Research on Blood-Brain Barrier Damage: Challenges, Perspectives, and Goals

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Over the past few decades, basic and clinical research has identified numerous risk factors for the development of stroke and led to major improvements in health management in the USA. As a result of these efforts, the relative rate of stroke death dropped by 33.7 %, and the actual occurrence of stroke deaths fell by 18.2 % in the decade spanning from 2003 to 2013, according to the American Heart Association. Thus, stroke fell from the fourth to the fifth leading cause of death in 2013, behind heart disease, cancer, chronic lower respiratory diseases, and unintentional injuries. These improvements are largely attributed to superior control of hypertension, diabetes mellitus, high cholesterol, and tobacco use [1]. To date, the treatment of acute ischemic stroke is largely dependent on recanalization using recombinant tissue-type plasminogen activator (tPA) in the appropriate patient population [2, 3]. Encouragingly, recent clinical trials have demonstrated significant benefits for intra-arterial thrombectomy in a subset of acute stroke patients with intracranial large artery occlusion [4]. Despite these improvements in population health and stroke treatment, stroke still remains a leading cause of long-term disability and approximately 795,000 people experience a new or recurrent stroke every year [1]. Thus, basic and clinical investigations of the mechanisms underlying ischemic brain injury must remain an urgent priority in order to promote the discovery of novel therapeutic targets and improve the safety and efficacy of current tPA and thrombectomy treatments.

During and after ischemic stroke, loss of blood-brain barrier (BBB) integrity is a prominent pathological event that contributes to further evolution of the injury. BBB dysfunction is also a hallmark of intracerebral hemorrhage [5, 6]. Despite its obvious clinical relevance, BBB protection has received much less attention than is warranted. An impaired BBB not only facilitates the development of brain edema and neuroinflammation, but also increases the risk of lethal hemorrhagic transformation during thrombolysis, thereby limiting the use of tPA and leading to poor patient outcomes [7, 8]. Recent advances in stroke telemedicine provide an effective and promising method to increase the use of tPA therapy [9], which, together with the growing application of thrombectomy, is likely to improve post-ischemia reperfusion in a larger population of stroke patients in the near future. As this treatment method works better when the BBB remains intact, therapeutic strategies aimed at neurovascular unit protection and prevention of BBB damage after ischemia/reperfusion (I/R) need to be better prioritized in stroke research.

In earlier reports, it was widely held that all forms of BBB rupture after I/R were the direct consequence of matrix metalloproteinase (MMP)-mediated degradation of endothelial intercellular junctions and basal lamina [10–14]. However, recent animal models of stroke have revealed a complex, biphasic temporal profile of BBB breakdown, with an immediate phase of early BBB hyperpermeability 4–6 h after stroke, followed by a delayed opening of the BBB 48–72 h after stroke. In recent years, the availability of advanced imaging techniques and novel transgenic animal models have greatly facilitated research on BBB dysfunction after stroke, with

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an increasing focus on the initiation of the early breach at the level of the endothelial cell. Unexpectedly, studies have shown that the degradation of tight junctional proteins—generally held responsible for BBB opening after stroke—occurs much later than the pathological hyperpermeability of the BBB [15]. Enhanced transendothelial vesicle trafficking has been reported instead, which may represent an important mechanism neglected in older studies [16, 17]. A recent study revealed additional, subtle microarchitectural changes in the cytoskeleton of brain microvascular endothelial cells, which occur well before the frank degradation of endothelial junctions and basement membrane by the MMPs [18]. For example, I/R-enhanced actin polymerization in endothelial cells is a driving force for increased paracellular permeability and renders the BBB much more susceptible to further attack by infiltrating peripheral immune components [18]. The actin cytoskeleton and tight junctions are physically linked and cytoskeletal changes may impact BBB function without the overt loss of tight junction proteins [18, 19]. Together, these studies have lent greater insight into early pathophysiological changes in the BBB immediately after I/R and shed new light on components of this injury. Endothelial cell-targeted interventions have also begun to tackle a fundamentally important question: is early impairment of the BBB one of the causes, rather than only a consequence of brain parenchymal injury in stroke? In this scenario, BBB destruction and parenchymal injury likely exacerbate each other in a feed-forward or self-amplifying spiral. If this hypothesis continues to garner support from further studies, maintenance of the BBB immediately after stroke onset might be expected to brake the downstream progression of ischemic brain injury, improve neurological outcomes, and perhaps even save lives.

In addition to the actin cytoskeleton, emerging evidence also supports a critical role for other BBB cell components, such as astrocytes and pericytes, in the regulation of BBB stability [20–22]. Besides their participation in the development and maintenance of normal BBB integrity [23], these cells are thought to contribute to post-injury BBB repair. Brain vascular pericytes, for example, appear to acquire multipotent stem cell activity following ischemia and become capable of differentiating into cells of neural or vascular lineage, thereby reconstructing the neurovascular unit [24]. Furthermore, astrocytes possess end-feet that envelop brain capillaries and become swollen after stroke injury, perhaps serving to limit the entry of plasma factors and blood into the parenchyma of the brain [25]. Other cells in the neurovascular unit, including oligodendrocyte precursor cells [26] and microglia [27], also influence BBB function via secreted factors and are likely to engage in crosstalk [28]. How different cell types and cell type-specific mechanisms contribute to BBB dysfunction remains poorly studied and warrants deeper investigation; cell-specific gene-targeting strategies are especially powerful in this regard. The choice of appropriate tracers to assess the permeability of the BBB also cannot be understated, as different tracers use distinct pathways to diffuse across the BBB, through paracellular or trans-endothelial mechanisms [16, 29, 30]. There also remains a need to develop advanced molecular imaging techniques to detect BBB penetration of tracers during early stages of I/R. This might enable early detection of BBB dysfunction in the clinical setting, which would offer the distinct advantage of targeting thrombolysis to the appropriate patient population. Furthermore, we need to improve our understanding of the context dependency of the mechanisms underlying BBB breakdown, as there might be unique changes in different cell types at various stages of injury development.

As the major point of separation of brain parenchyma from circulating blood, the BBB also serves as a dynamic neuroimmune interface where multicellular interactions transpire. The neuroinflammatory responses to I/R include the following: (1) parenchymal inflammation, which is primarily attributed to I/R-activated endothelial cells, (2) subsequent release of various pro-inflammatory meditators such as cytokines and chemokines, and (3) peripheral immune changes such as leukocyte-endothelial interactions via selectins, adhesion molecules, and chemokines/chemokine receptors [31]. Whereas the severely injured BBB freely permits the infiltration of peripheral immune cells, blocking early BBB damage ameliorates secondary injuries caused by pro-inflammatory responses, blocks a self-amplifying cascade of tissue destruction, and offers persistent histological and functional protection [18]. Aside from deleterious actions, some immune responses also actively promote the reestablishment of BBB integrity following injury, as might be expected from the primary role of the immune system in self-repair and healing [32, 33]. Fine-tuning these immune responses to achieve homeostasis at the neuroimmune interface is an important research topic for the restoration of BBB function.

There are several important directions for future preclinical studies on the BBB. First, employment of translatable model systems is essential, e.g., use of an embolic stroke model that encompasses tPA-induced reperfusion [34, 35]. Future studies are warranted to determine whether early BBB impairment might predict the risk of hemorrhagic transformation upon tPA recanalization and influence stroke prognosis. Second, we need to target our treatments to different cell types at distinct stages of injury, because different mechanisms may dominate specific stages of stroke injury. Third, the pathophysiology of BBB disruption must be evaluated

in the context of age, gender, and comorbid conditions such as hypertension, hyperglycemia, and high cholesterol [1, 36, 37]. These variables likely promote the clinically heterogeneous profiles of stroke. Finally, attention should be given not only to acute protection against BBB damage but also to structural and functional restoration of the BBB, such as repair of tight junctions, in order to ensure a profound and sustained improvement in long-term neurological outcomes. Such approaches might also reduce the risk of stroke recurrence where there may be proinflammatory changes in the cerebral endothelium.

In conclusion, a fruitful collaboration between scientific researchers and the medical establishment is partly responsible for recent improvements in health outcomes and significant reductions in mortality after stroke. A new research emphasis on restoring the neurovascular unit now raises hope of long-lasting protection of the BBB after stroke [38]. If parenchymal injury lies downstream of early BBB damage, or even if they only exacerbate each other in a feed-forward loop, finding the therapeutic means to restore BBB integrity is expected to pay large dividends, given the current use of thrombolysis and interventional recanalization and the risk for hemorrhagic transformation. Success in this arena may provide the necessary momentum for continued improvements in stroke outcomes over the next few decades so that the recent positive trajectories in mortality reduction do not flag.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

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