The blood–brain barrier (BBB) is an important target to suppress brain damage and also promote brain repair in stroke. After stroke onset, the initial phase comprises leakage and exacerbation of brain damage. But during the delayed phase, endogenous mechanisms of barrier genesis and repair may also occur. Three recent articles define promising new mechanisms that may contribute to this balance initial injury and subsequent repair.

Several deleterious factors/cascades for stroke-induced BBB damage have been reported. However, the mechanisms of early BBB disruption after stroke are poorly understood. Gelatinase B/matrix metalloproteinase-9 (MMP-9) is well known to mediate ischemia-induced BBB disruption by degrading endothelial junction proteins and basal lamina, but Shi et al (Rapid endothelial cytoskeletal reorganization enables early blood-brain barrier disruption and long-term ischaemic reperfusion brain injury. Nat Commun. 2016;7:10523. doi: 10.1038/ncomms10523.) demonstrated that early/subtle BBB leakage within 30 to 60 minutes after ischemia–reperfusion injury was independent of MMP-9 activities. Instead, this study focused on the roles of actin-depolymerizing factor, which suppresses actin polymerization. By analyzing transgenic mice with endothelial cell–specific overexpression of constitutively active mutant actin-depolymerizing factor after 60-minute transient middle cerebral artery occlusion, the authors proposed that novel mechanisms that enhanced actin polymerization by ischemic stress might play a critical role in early BBB impairment, which eventually leads to MMP-9–dependent late-onset BBB damage as well as histological/neurological deficits. Because early and subtle increase in BBB permeability after ischemic stress may be partially reversible, actin-depolymerizing factor would be an attractive therapeutic target to protect BBB and to reduce brain damage in patients with stroke.

Angiopoietin-1 (Ang-1) and Ang-2 are secreted growth factors, and both of them modulate the signaling cascade of Tie2 receptor tyrosine kinase. Tie2 receptor is predominantly expressed in endothelial cells, and Ang-1 phospholipid and activates the Tie2 receptor to stabilize vessels. On the contrary, Ang-2 prevents the receptor phosphorylation of Tie2, which leads to vessel destabilization. Therefore, under the acute phase of stroke, Ang-1 and Ang-2 may show opposite effects on BBB function. A recent article by Gurnik et al (Angiopoietin-2-induced blood-brain barrier compromise and increased stroke size are rescued by VE-PTP-dependent restoration of Tie2 signaling. Acta Neuropathol. 2016;131:753–773. doi: 10.1007/s00401-016-1551-3.) demonstrated how Ang-2 contributed to stroke-induced BBB dysfunction. In this study, the authors used Ang-2 gain-of-function mice (Ang-2 Tet-OS: Tie1 tTA) to investigate the influence of endothelium-derived Ang-2 at the BBB. The Ang-2 gain-of-function mice exhibited decreased pericyte coverage of vessels and increased caveolae-like vesicles in endothelial cells, accompanied with increased permeability of BBB to 3 kDa dextran. In addition, after wild-type and Ang-2 gain-of-function mice were subjected to either permanent middle cerebral artery occlusion (distal model) or 60-minute transient middle cerebral artery occlusion (filament model), the Ang-2 gain-of-function mice showed larger infarcts and higher BBB permeability. Finally, Ang-2 expression was increased after stroke, and the vascular endothelial protein tyrosine phosphatase inhibitor AKB-9785 ameliorated those deficits in stroke animals. Therefore, Ang-2 would be a potential therapeutic target to protect BBB integrity in patients with stroke.

There may be some endogenous systems in brain to repair damaged BBB, but mechanisms as to how brains attempt to close the compromised BBB after injury remain mostly unknown. Lou et al (Purinergic receptor P2RY12-dependent microglial closure of the injured blood-brain barrier. Proc Natl Acad Sci USA. 2016;113:1074–1079. doi: 10.1073/pnas.1520398113.) revealed the novel role of juxtavascular microglial cells in terms of repairing damaged BBB under pathological conditions. The authors showed that in response to capillary injury by small focal lesions using 2-photon focused laser excitation, processes of microglia in the perivascular region were rapidly attracted to the site of the capillary lesion. This response of juxtavascular microglia may contribute to closure of the damaged BBB because electron microscopic analysis showed aggregation of densely packed processes, which ensheathed the site of injury in capillary. In addition, photoablation of microglial cells in the perivascular area abolished this rapid closure of BBB leakage. Within the neurovascular unit, microglia are the only cells that expressed detectable levels of the purinergic receptor P2Y12 (P2RY12), and the P2RY12-deficient mice failed in closing the laser-induced BBB opening. Therefore, juxtavascular microglia may play an important role in repairing damaged BBB after injury, through the P2RY12 receptor–mediated pathways.

These 3 studies demonstrate novel mechanisms of BBB damage and repair after brain damage. BBB compromise is one of the major hallmarks in stroke, and the acute BBB dysfunction would exacerbate brain damage thereafter. Therefore, further investigation into how we can protect BBB against ischemic damage or reseal stroke-induced BBB opening may eventually lead us develop effective therapeutic approaches to patients with stroke.

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