The blood–brain barrier (BBB) protects the brain from pathogens, toxins, and encephalitogenic immune cells. BBB disruption is a common feature in several central nervous system (CNS) diseases including stroke, but the cellular and molecular mechanisms involved still remain mostly unknown. Three recent studies suggest novel mechanisms for BBB damage under pathological conditions.

Bittner et al (Endothelial TWIK-related potassium channel-1 [TREK1] regulates immune-cell trafficking into the CNS. Nat Med. 2013;19:1161–1165) analyzed the roles of ion channels of endothelial cells in immune cell trafficking into inflamed CNS. Ion channels have attracted attention as effective targets for CNS diseases, and in this study, the authors focused on TREK1 (TWIK-related potassium channel-1, encoded by KCNK2), which is a member of the 2-pore domain potassium channel family. In in vitro cell culture systems, inflammatory stimulation (interferon-γ or tumor necrosis factor-α) downregulated the TREK1 expression in endothelial cells. Blocking TREK1 in endothelial cells by the TREK1-specific antagonist spadin increased the leukocyte (CD4+ T cells or CD8+ T cells) migration, which was at least partly mediated by reduction of extracellular signal-regulated kinase phosphorylation. In vivo, the authors analyzed TREK1-deficient (Kcnk2−/−) mice and reported that the transgenic mice showed an upregulation of cellular adhesion molecules in the brain endothelium. To show the clinical relevance of these findings, the authors subjected the mice to experimental autoimmune encephalomyelitis (mouse model of multiple sclerosis) by immunization with a myelin-oligodendrocyte-protein peptide 35–55. The TREK1-deficient mice showed higher experimental autoimmune encephalomyelitis severity scores with increased immune cell infiltration into the CNS, which were attenuated by a diet enriched with the TREK1 activating omega-3 fatty acid α-linolenic acid. Taken together, the TREK-1 ion channel can be a potential therapeutic target for CNS diseases by reducing BBB dysfunction.

Recently, another potential target to stabilize BBB integrity in multiple sclerosis was also reported. Lanz et al (Protein kinase Cβ as a therapeutic target stabilizing blood-brain barrier disruption in experimental autoimmune encephalomyelitis. Proc Natl Acad Sci U S A. 2013;110:14735–14740) used mouse models of multiple sclerosis (ie, experimental autoimmune encephalomyelitis) to test the efficacy of LY-317615, a synthetic bisindolylmaleimide and inhibitor of protein kinase Cβ, on BBB dysfunction in the pathophysiological conditions. LY-317615 was clinically under investigation for the treatment of cancer (it failed a phase III clinical trial for lymphoma in 2013). Maintaining the integrity of the BBB requires a complex network of tight junction proteins between endothelial cells. In autoimmune neuroinflammation, deficiency or downregulation of tight junction proteins results in increased permeability followed by infiltration of encephalitogenic T cells. The authors demonstrated that LY-317615 ameliorated the inflammation, demyelination, axonal damage, and clinical symptoms in the model mice. These protective effects were mainly mediated by the stabilization of BBB and suppression of the transmigration of encephalitogenic T cells: (1) LY-317615 upregulated claudin-5, a tight junction–associated protein, in endothelium both in vitro and in vivo; (2) macroscopic (Evans Blue) and microscopic (2-photon microscopy) analyses showed that LY-317615 reduced the BBB breakdown in vivo; and (3) LY-317615-pretreated endothelial cells showed less transendothelial migration of T cells in vitro. Therefore, endothelial protein kinase Cβ can be a drug target for stabilizing BBB integrity.

BBB dysfunction is also seen in genetic diseases. Mayes et al (Nf1 Loss and Ras hyperactivation in oligodendrocytes induce NOS-driven defects in myelin and vasculature. Cell Rep. 2013;4:1197–1212) analyzed mouse models of Rasopathies that are inherited disorders, in which individuals have mutations in Ras signaling pathway genes. The authors prepared 2 mouse models of Rasopathy: (1) PlpCre;Nf1 fl/fl mice
(NF1 loss in oligodendrocytes) that is a model for so-called neurofibromatosis type 1 (NF1) patient, and (2) CNP-HRasG12V mice (Ras-GTP is constitutively expressed primarily in the white matter) that is a model for Costello syndrome. As seen in patients with NF1 Rasopathy, these transgenic mice showed altered white matter structure (e.g., white matter enlargement and aberrant myelin) and hyperactive locomotion. Unexpectedly, after NF1 loss or HRasG12V expression, noncell-autonomous defects in the BBB also developed (e.g., tight junctions in endothelium contained gaps in the transgenic mice). As cellular mechanisms for the BBB dysfunction, the authors demonstrated that in the model mice, oligodendrocytic reactive oxygen species production was increased through the upregulation of nitric oxide synthase proteins. Because the nitric oxide synthase inhibitor NG-nitro-l-arginine methyl ester or the antioxidant N-acetyl cysteine showed some efficacy in the vascular dysfunction, future studies may be warranted to assess the therapeutic potential of antioxidant for Rasopathy patients.

The molecular and cellular mechanisms of BBB dysfunction may be conserved in stroke and other CNS diseases. Therefore, although these 3 studies did not use animal models of stroke, testing the novel therapeutic targets introduced above in stroke models will be important subjects for future studies.