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•Commentary•

Commentary: brain endothelial GSDMD as a novel target for brain disorders associated with BBB damage

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The blood-brain barrier (BBB) is a highly selective and critical interface between the blood and the central nervous system (CNS), essential for maintaining the microenvironment necessary for normal brain function and homeostasis [1]. The BBB is primarily formed by brain endothelial cells (bECs), pericytes, and astrocytes, and it operates in concert with microglia/macrophages and neurons [2, 3] to constitute the neurovascular unit (Fig. 1). Disruption of the BBB or the presence of systemic inflammation can precipitate or exacerbate various CNS pathologies, including Alzheimer's disease [4], amyotrophic lateral sclerosis [5], Huntington's disease [6] and multiple sclerosis. Several mechanisms contribute to BBB disruption under pathological conditions: (1) reactive oxygen species (ROS) can directly damage neurons [7] or the endothelial cells of the BBB, leading to edema; (2) activated microglia, astrocytes, and infiltrating leukocytes, especially neutrophils, release matrix metalloproteinases (MMPs) [1, 8], which further degrade the BBB. Additionally, significant BBB breakdown occurs during Gram-negative bacterial infections or systemic inflammation, permitting the entry of inflammatory mediators and neurotoxic substances into the brain and thereby exacerbating sepsis-associated encephalopathy. However, the exact mechanisms of BBB compromise in these contexts remain unclear. Therefore, investigating the mechanisms of BBB disruption under inflammatory conditions is crucial for providing a theoretical foundation for developing effective clinical treatments.

In the article entitled "Brain endothelial GSDMD activation mediates inflammatory BBB breakdown" recently published in *Nature*, researchers found that LPS stimulation conditions activates the caspase-4/11-GSDMD signaling pathway in brain endothelial cells, leading to inflammatory disruption of the BBB [9]. The study involved administering a single intraperitoneal injection of LPS to mice, which induced BBB breakdown in wild-type (WT) mice. However, this effect was significantly reduced in TLR4$^{-/-}$, Casp-11$^{-/-}$, and Gsdmd$^{-/-}$ mice. Given that the expression of caspase-11 in mice is influenced by transcriptional regulation mediated by the TLR family of pattern recognition receptors, the researchers proposed a hypothesis that TLR4-mediated transcriptional activation of caspase-11, rather than the up-regulation of inflammatory factors mediated by TLR4, may be involved in LPS-induced BBB disruption. To verify this hypothesis, the researchers pre-injected poly (I∶C), an agonist for TLR3, into the abdominal cavity of mice to induce the expression of caspase-11 in a way that was independent of TLR4. The results showed that even TLR4$^{-/-}$ mice showed significant BBB breakdown in response to LPS after this pretreatment, whereas Casp11$^{-/-}$ or Gsdmd$^{-/-}$ mice did not exhibit similar BBB disruption. Single-cell RNA sequencing confirmed GSDMD expression in brain endothelial cells. Furthermore, LPS-induced activation of caspase-4/11 and subsequent GSDMD cleavage were detected in both primary mouse brain endothelial cells and immortalized human brain microvascular endothelial cells (hBMECs). In particular, hBMEC displayed significant material exchange upon the induction of the GSDMD *N*-terminus, which occurred before cell lysis or pyroptosis. This finding suggests that a sufficient quantity of the GSDMD *N*-terminus can create pores in the cell membrane, altering the permeability of brain endothelial cells without causing cell death. These results indicate that inhibiting GSDMD activation in brain endothelial cells may be

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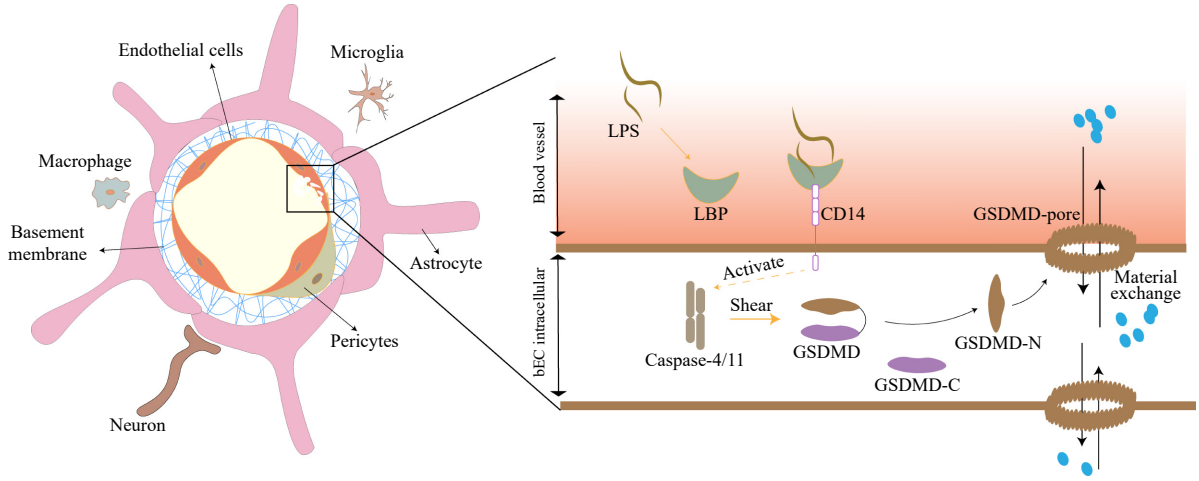

Fig. 1 Structure of blood-brain barrier and molecular mechanism of GSDMD activation in brain endothelial cells.

an effective strategy to maintain the integrity of the BBB.

Given the variety of blood vessels in the brain, including arteries, capillaries, and veins [10], and the observation that LPS-induced BBB rupture occurs throughout the brain parenchyma with higher concentrations near the meninges, it is important to investigate whether this pattern is related to different types of blood vessels.

The study confirms that under inflammatory conditions, LPS is internalized into endothelial cells *via* the LBP-CD14 axis, activating caspase-4/11, which in turn cleaves GSDMD, leading to BBB breakdown (Fig. 1). This finding opens up the potential for designing targeted inhibitors of GSDMD to regulate BBB permeability, thereby facilitating the delivery of therapeutic drugs for CNS diseases. Moreover, traditional Chinese medicine has historically been used to treat various conditions related to BBB disruption [8, 11]. Screening the active ingredients of these herbal remedies for their effects on GSDMD regulation could provide a more rational basis for their clinical efficacy. In conclusion, this study not only deepens our understanding of BBB regulatory mechanisms but also identifies a new therapeutic target for the clinical treatment of brain disorders associated with BBB damage.

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