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Breaking the fortress: a mechanistic review of meningitis-causing bacteria breaching tactics in blood brain barrier

Yingying Quan[1,2†], Yuxin Wang[1,2†], Shuji Gao[1,2], Shuo Yuan[1,2], Shenao Song[1,2], Baobao Liu[1,2*] and Yang Wang[1,2*]

Abstract

The blood-brain barrier is a physiological protective barrier around blood vessels in the brain. It prevents most bacteria and harmful substances from entering the brain through the blood. However, when bacterial meningitis occurs, bacteria enter the brain either from the circulation or by direct invasion from neighbouring structures, causing an inflammatory response that in severe cases may lead to death. High morbidity and mortality are prominent features of the disease. Many pathogenic bacteria can break through the blood-brain barrier and cause meningitis, such as *Streptococcus pneumoniae*, Group B *Streptococcus*, *Streptococcus suis*, *Neisseria meningitidis*, *meningitis-associated Escherichia coli*, etc. This article reviews the mechanisms by which these bacteria cross the blood-brain barrier when causing meningitis and the interactions between bacteria and host cells to help pathogens invade the brain. Clarifying the mechanism by which pathogens cross the blood-brain barrier can provide new ideas for developing effective treatments for bacterial meningitis.

Keywords Blood-brain barrier, Bacterial meningitis, Host-pathogen interaction, Bacterial invasion, Transcellular transport

Introduction

The "Global Roadmap to Overcome Meningitis by 2030" formulated by WHO, is the first resolution on meningitis adopted by the World Health Assembly in 2020 [1], and Member States have unanimously recognized the strategy. Meningitis is a disease caused by inflammation of the meningeal membrane (the membranous tissue covering the brain and spinal cord), which its typical symptoms include fever, severe headache, stiff neck, photophobia, disturbance of consciousness (such as confusion or drowsiness), seizures, and gastrointestinal reactions (such as nausea and vomiting) [2, 3]. Meningitis is a serious disease with a high mortality rate, and it may lead to serious long-term complications (sequelae), mostly caused by infectious causes (including bacteria, viruses, fungi, and other pathogenic microorganisms) [3]. It remains a serious global public health challenge [4], and bacterial meningitis is considered to be the most serious and urgent type, which can easily lead to acute death [4, 5].

Bacterial invasion of the meninges typically occurs primarily via hematogenous dissemination (bacteremia), less commonly through direct extension from adjacent

†Yingying Quan and Yuxin Wang contributed equally to this work.

*Correspondence:
Baobao Liu
bobbyliu515@163.com
Yang Wang
wangyocean@163.com
[1]College of Animal Science and Technology, Henan University of Science and Technology, Luoyang 471000, China
[2]Henan Provincial Engineering Research Center for Detection and Prevention and Control of Emerging Infectious Diseases in Livestock and Poultry, Luoyang 471003, China

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infectious foci (such as middle ear or paranasal sinus infections) or penetrating skull fractures, and can also be transported to the central nervous system (CNS) through peripheral nerves (such as the trigeminal or olfactory nerves) [6–8]. Therefore, the prerequisite for bacteria to enter the CNS is not always bacteremia. However, whether it is spreading to the brain from bacteremia or adjacent lesions, all bacteria need to break through the critical barrier between blood and nerve tissue to reach the CNS.

The barrier system of the CNS is heterogeneous in anatomy and function, mainly including the blood-brain barrier (BBB), the blood-cerebrospinal fluid barrier (BCSFB), and the arachnoid barrier. The BBB is mainly composed of cerebral capillary brain endothelial cells (BECs) and their tight junctions (TJs), selectively regulating the exchange of substances between the peripheral circulation and the CNS [9]. The BCSFB is located in the cortex of the choroid plexus (CP) and maintains the CNS homeostasis by secreting cerebrospinal fluid [10]. The arachnoid barrier is composed of multiple layers of tightly connected arachnoid cells that separate the dura mater and the subpial space, further blocking the invasion of pathogens [11, 12]. The synergy of these barriers renders the CNS a highly immune-privileged compartment, yet concurrently imposes multilayered challenges for pathogen invasion, as bacteria need to penetrate at least one barrier to cause meningeal infections.

In this review, we focus on the mechanisms determined by pathogenic bacteria at the level of breaking through the BBB and introduce the structure and function of the BBB and the research progress on some molecular mechanisms by which common pathogenic bacteria (*Streptococcus pneumoniae* (*S. pneumoniae*), Group B *Streptococcus* (GBS), *Streptococcus suis* (*S. suis*), *Neisseria meningitidis* (*N. meningitidis*), *Meningitis-associated Escherichia coli* (*Meningitis-associated E. coli*), etc.) interact with host cells when breaking through the BBB. Clarifying how these bacteria enter the CNS from the blood will help prevent bacterial meningitis disease, provide ideas for developing drugs that can be delivered into the CNS, and find better ways to treat it.

Blood-brain barrier

The physiological functions of the blood-brain barrier

The BBB is a critical interface for the bidirectional transport of biomaterials essential for the regulation of brain metabolic activity and neural function. Maintaining the structural and functional integrity of this specialised barrier is essential to protect the homeostatic microenvironment required for optimal brain physiology [13]. Evidence is now available to elucidate the multifaceted neuroprotective effects of the BBB [9, 14–17]. First, it maintains the fidelity of intercellular communication by precisely regulating neurotransmitter distribution in brain compartments. Secondly, its tight junction structure effectively restricts the paracellular diffusion of macromolecules while allowing the transcellular transport of essential micronutrients. In addition, through its selective permeability, the BBB not only facilitates the on-demand delivery of nutrients and oxygen to meet neuronal needs but also establishes strong protection against neurotoxic substances and pathogen invasion, thus creating an optimal environment for neuronal circuitry to operate. Together, these integrated mechanisms form the fundamental material basis for maintaining neurophysiological homeostasis and preventing chemically induced neuropathological changes.

The anatomical basis of the blood-brain barrier

The BBB is anatomically composed of three main types of cells, including BECs, pericytes and astrocytes [13] (Fig. 1). Its central anatomical element is the cerebral microvasculature formed by continuous, nonporous endothelial cells (ECs), which act as the first barrier of the CNS in direct contact with the bloodstream [17] and which exhibit unique morphological adaptations compared with the peripheral vascular system. These specialised ECs exhibit flattened morphology and are embodied with intercellular TJs that effectively restrict the movement of ions, macromolecules, and cells between the blood and the brain, while allowing selective transcellular transport, and are the embodiment of barrier properties [13]. Pericytes, an important component of cerebral capillaries, belong to the mural cells that wrap around the luminal side of the capillaries, showing extensive cytoplasmic protrusions wrapping around the ECs and sharing basement membranes with the ECs [18, 19]. Through N-calmodulin-mediated adhesion plaques and connexin-based gap junctions, these pericytes engage in bidirectional signalling with BECs [9, 13]. It has been noted that their indispensable role in BBB individual development has been demonstrated in mouse models [20] and that pericytes maintain BBB integrity, assist angiogenesis, and maintain vascular stability [21]. Astrocytes are the most important and largest of glial cells, and the most numerous cells in the CNS. They wrap neuronal processes or blood vessels [22, 23]. Astrocytes can induce barrier properties in the brain and other ECs and epithelial cells [23], so they are also believed to play a role in maintaining the barrier function of BECs. BECs, pericytes, and astrocytes promote the formation of the basement membrane by secreting extracellular matrix (ECM) molecules, which hold members of the neurovascular unit in place and regulate their cell-to-cell interactions [17].

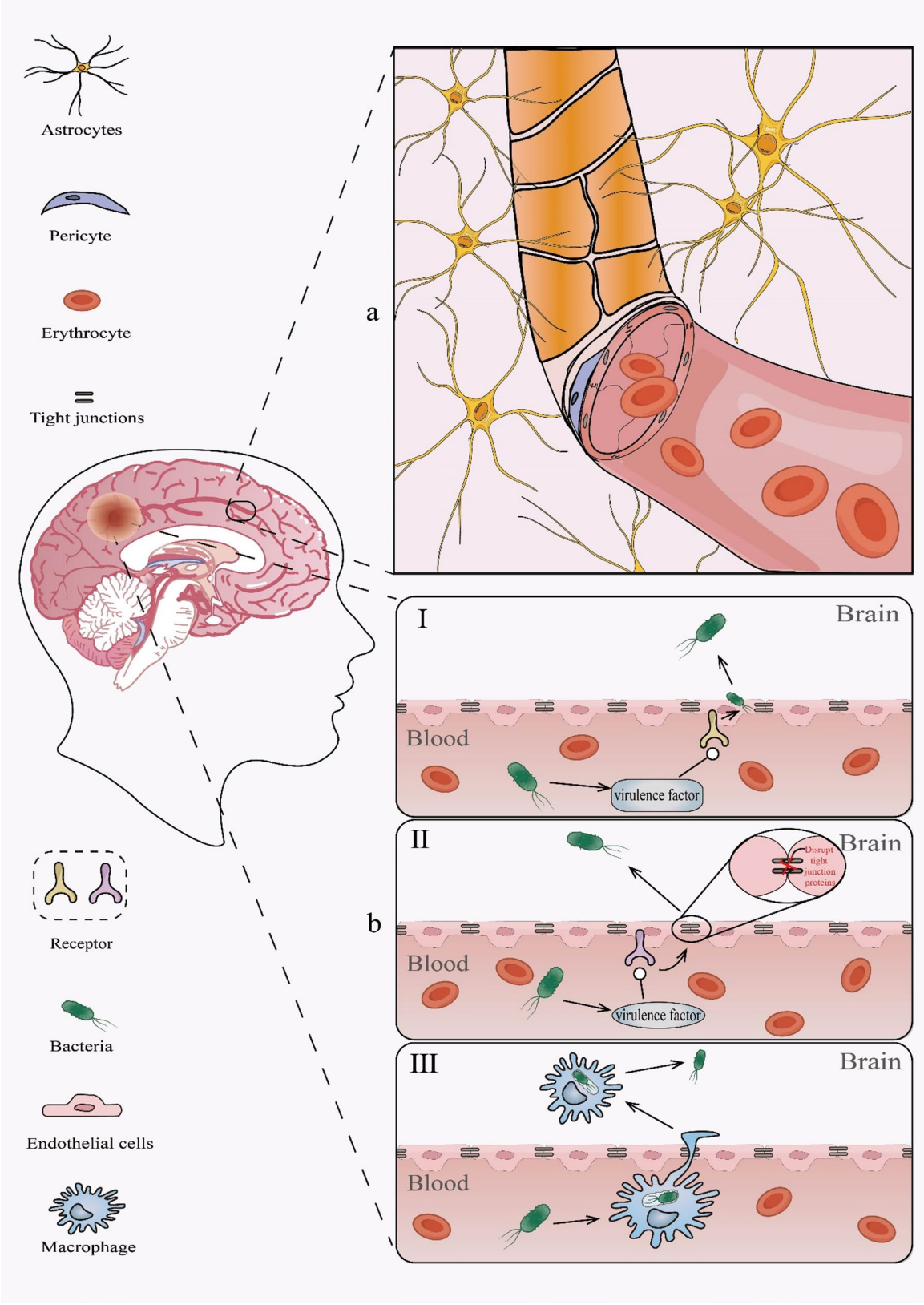

Fig. 1 The structure of the blood-brain barrier and the classic way to penetrate the blood-brain barrier. (**a**) Schematic diagram of blood-brain barrier structure. The blood-brain barrier consists of endothelial cells, pericytes, astrocytes, and tight junction proteins. Endothelial cells are connected by tight junction proteins to form a blood vessel wall, which is covered by a small part of the pericytes, while astrocytes wrap the blood vessels at the outermost layer. (**b**) The classic way for bacteria to cross the blood-brain barrier. (**I**) Transcellular pathway. (**II**) Paracellular pathway. (**III**) Trojan-horse mechanism

The molecular mechanism of the blood-brain barrier

There are two different multiprotein complexes located in the CNS, adherens junctions (AJs) and TJs, which are structurally and functionally closely linked, and together they form the physical barrier of the BBB, thereby sealing the gap between BECs [24]. The TJs are located at the site of fusion and articulate adjacent BECs or the outer surface of the plasma membrane of the same cell, whereas the adhesive link consists of the calreticulin-conjugated protein complex and its associated proteins [13]. TJs and AJs exhibit different but complementary functional properties in the cellular barrier system, with TJs primarily regulating the diffusion of solutes and ions and restricting the free movement of lipids and proteins from the cell surfaces of the parietal and basolateral sides [24, 25], while AJs initiate contact between cells, promote their maturation, maintenance, and plasticity, and regulate turgor [24]. TJs consist of complexes of proteins (Occludin and Claudins) and junctional adhesion molecules (JAMs) that span cellular interstitial spaces [26] and Occludin and Claudins can connect to cytoplasmic scaffolds, zonula occlude proteins (ZO-1, ZO-2, ZO-3) and cingulin, which play an important role in the roles that TJs play [26, 27]. Among them, the Claudin family of membrane proteins is a key component concerning their structure and function [28, 29], in particular, Claudin-1 and Claudin-5 are the main components in the formation of the BBB in the brain [30], and Occludin, as a regulatory protein, is highly expressed in BECs and regulates paracellular permeability [31]. JAMs are members of the immunoglobulin superfamily that are located at tight junctions between endothelial or epithelial cells and regulate leukocyte exudation and paracellular permeability [32, 33]. In AJs, cadherin is the main component of connecting membrane proteins, which can span the intercellular gap and connect the actin cytoskeleton through intermediate proteins and catenin to form adhesive contacts between cells [26]. Studies have shown that TJs interact with AJs that connect all ECs, especially ZO-1 and catenin, and affect the formation of TJs [34].

Mechanisms of pathogens breaching the blood-brain barrier

When bacteria cause meningitis disease, they first need to cross the BBB, and so far, three classic pathways for bacteria to cross the BBB have been proposed [35] (Fig. 1), including the transcellular pathway, the paracellular pathway, and the Trojan horse pathway. The transcellular pathway refers to the mechanism in which the pathogen penetrates the barrier through receptors without destroying the destruction of TJs between cells. The paracellular mechanism refers to the fact that the pathogen penetrates the BBB, often accompanied by TJs interruption, resulting in increased BBB permeability. The Trojan horse mechanism is that the pathogen uses infected blood cells or hijacks infected phagocytes, which can migrate from the periphery to the CNS. Pathogens can use one or more of these pathways simultaneously to break through the BBB and invade the brain.

Gram-positive bacteria

Streptococcus pneumoniae

S. pneumoniae is a gram-positive extracellular coccus and it colonizes the upper respiratory tract, nasal cavity, and sinuses and can cause aggressive diseases such as pneumonia, sepsis, and acute meningitis [36, 37], in particular, infants and the elderly are both susceptible groups. *S. pneumoniae*-related diseases are currently an important public health issue around the world; among them, *S. pneumoniae* meningitis has the characteristics of high incidence and high mortality rate and has attracted much attention. Clarifying the mechanism of *S. pneumoniae* meningitis is of great significance for selecting treatment pathways and reducing the neurological sequelae of *S. pneumoniae* meningitis.

S. pneumoniae surface proteins play an important role in promoting adhesion to host cell receptors. The choline-binding protein CbpA (also known as PspC) binds to the laminin receptor (LR) and promotes *S. pneumoniae* adhesion to human brain microvascular endothelial cells (hBMECs) [38]. Surface neuraminidase A (NanA) can interact with LR and platelet endothelial adhesion molecule-1 (PECAM-1), thereby promoting the attachment of *S. pneumoniae* to the BBB. At the same time, the main adhesin (RrgA) of *S. pneumoniae* pilus-1 can bind to the polymeric immunoglobulin receptor (pIgR) and PECAM-1, and can also promote the attachment of *S. pneumoniae* to the BBB [39, 40]. In addition, the glycolytic enzyme on the surface of *S. pneumoniae*, enolase (Eno), enhances *S. pneumoniae*'s adhesion to hBMECs by binding to plasminogen (PLG) bound to the surface of hBMECs [41] (Fig. 2 (I), Table 1).

S. pneumoniae surface proteins are necessary for binding to host cells and for cross-cellular reactions. In addition to receptor-mediated intracellular uptake, *S. pneumoniae* can also disrupt the integrity of the BBB by having certain effects on cells, such as stimulating changes in some signaling pathways in cells or causing apoptosis. *S. pneumoniae* 's alpha-glycerol phosphate oxidase (GlpO) produces hydrogen peroxide through the metabolism of alpha-glycerol phosphate present in the brain, mediating toxicity to hBMECs, thereby disrupting the integrity of the BBB [42]. Recent studies have shown that *S. pneumoniae* cytolysin (Ply) can promote the high expression of CERB (cAMPresponse element-binding protein) binding protein (CBP) in human cerebral microvascular endothelial cell line D3 (hCMEC/D3) cells in vivo and in vitro. CBP promotes the release of

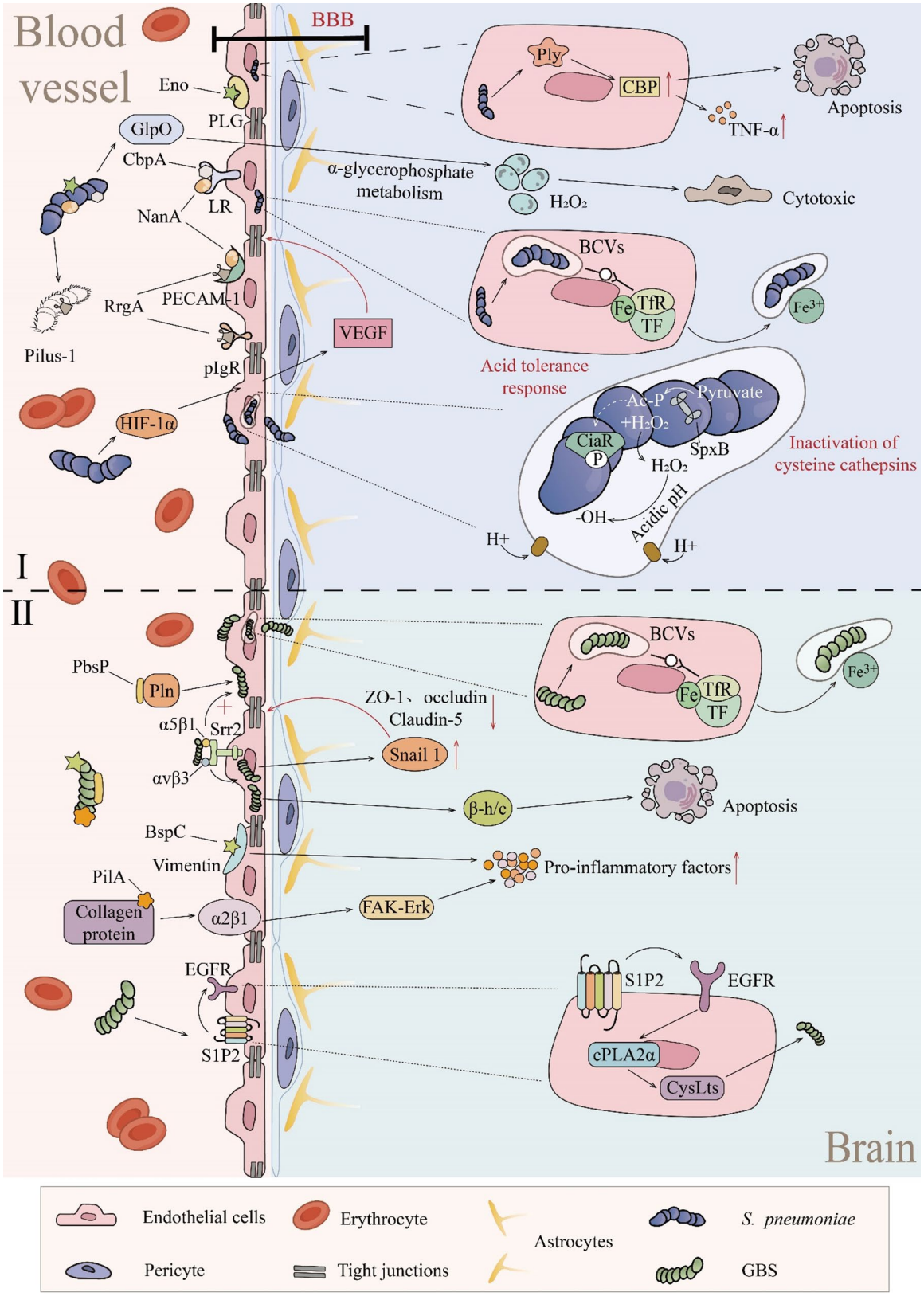

Fig. 2 (See legend on next page.)

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Fig. 2 The main mechanism for *S. pneumoniae* and GBS to break through the BBB. (**I**) *S. pneumonia*. *S. pneumonia* virulence factors bind to receptor proteins to promote adhesion of *S. pneumonia* to BECs and degrade the extracellular matrix by affecting BBB permeability through signalling pathways. *S. pneumonia* infection releases pro-inflammatory cytokines to cause apoptosis, and can also utilise host α-glycerophosphate to produce hydrogen peroxide for toxic effects on BECs, and *S. pneumonia* is able to evade intracellular degradation with the help of pyruvate oxidase. In particular, *S. pneumonia* can penetrate the BBB using the transcytosis of TfR. (**II**) GBS. GBS virulence factors bind to host receptors to promote GBS adhesion and invasion and GBS invasion disrupts tight junction proteins causing cellular autophagy and pro-inflammatory factor release. Specifically, GBS can also penetrate the BBB via the S1P2-EGFR-cPLA2 α-CysLts signalling network, and similarly GBS can cross the BBB using transcytosis by TfR

tumor necrosis factor-α (TNF-α), further promoting cell apoptosis, which in turn increases BBB permeability [43] (Fig. 2 (I), Table 1).

In addition to causing cells to react, *S. pneumoniae* can also use some chemicals in cells to help it escape intracellular degradation and use some of the cells "transcellular mechanisms" to achieve cross-BBB transport. Pyruvate oxidase (SpxB), a sugar metabolic enzyme of *S. pneumoniae*, can produce acetyl phosphate (AcP) and hydrogen peroxide through its enzymatic activity. *S. pneumoniae* maintains vitality at the fatal acidic pH of BECs vacuoles by using acetyl phosphate to promote the activation of acid-tolerant stress responses, and hydrogen peroxide can oxidize and degrade lysosomal cysteine cathepsin, thereby impairing lysosomes' proteolytic ability. With the help of pyruvate oxidase, *S. pneumoniae* can escape intracellular degradation and successfully pass through hBMECs for transcytosis [44]. Transferrin receptor (TfR) transport is one of the few transport pathways in hBMECs [45]. TfR can be highly expressed in the BBB, bind to the iron-binding protein transferrin (TF) in the blood, and then achieve iron transport across cells through reticin-mediated endocytosis and vesicle internalization. Therefore, after invading hBMECs, *S. pneumoniae* stays in membrane-bound vesicles, and bacteria-containing vesicles (BCVs) fuse with TfR vesicles, and penetrate the BBB through transcytosis of the TfR [46](Fig. 2 (I), Table 1).

In addition, *S. pneumoniae* can also alter the permeability of the BBB through paracellular pathways. Studies have shown that bacterial infections generally activate the hypoxia-inducible factor HIF-1α, and the activation of HIF-1α is a common phenomenon in secreting vascular endothelial growth factor (VEGF). VEGF can lead to paracellular permeability and is itself responsible for the collapse of the BBB. Therefore, the hypoxia-inducible factor/vascular endothelial growth factor (HIF-1α/VEGF) signaling pathway plays a key role in changing the BBB permeability in *S. pneumoniae* meningitis, which suggests that *S. pneumoniae* can use paracellular pathways to migrate across the BBB [47]. *S. pneumoniae* can also interact with microglia to mediate BBB damage. As a new member of the B7 superfamily (belonging to the immunoglobulin superfamily, most of which are transmembrane proteins, which can transmit synergistic stimulating signals in the body's immunity), B7-H3 (also known as B7RP-2) can regulate T cell-mediated immune responses, and matrix metalloproteinase-9 (MMP-9, a human proteolytic enzyme) can damage the BBB by degrading extracellular matrix components. B7-H3 enhances the secretion of MMP-9 by *S. pneumoniae*-stimulated microglia, thereby damaging the BBB [48] (Fig. 2 (I), Table 1).

In a recent study, through proteomics-bioinformatics analysis, candidate proteins that regulate this process when *S. pneumoniae* adheres to hBMECs may also be: adhesion lipoprotein, *S. pneumoniae* histidine triad protein A (PhtA), Endo-β-N acetylglucosaminidase and two hypothetical proteins (Spr0777 and Spr1730) [49]. However, the receptors of these proteins on BECs are unclear and further exploration is needed.

Group B Streptococcus

GBS is a gram-positive extracellular bacterium, and the most susceptible groups to GBS are fetuses and newborns, which can cause sepsis, meningitis, pneumonia, and other diseases, and is the largest cause of neonatal meningitis [50]. Neonatal GBS infections are usually transmitted from mother to child during childbirth, and 1% of them will develop into invasive infections [51, 52]. The bacteria pass through the fetal respiratory and gastrointestinal mucosa, reproduce in the blood, and finally enter the CNS. It is crucial to deeply understand the pathogenesis of GBS-induced meningitis and find treatment targets to reduce GBS infection.

After GBS survives in the circulatory system, it can interact with BECs, causing invasion of the BBB, which in turn triggers meningitis, and the first indispensable step for GBS to adhere to BECs and break through the BBB is the interaction between bacterial surface proteins and BECs receptors. Lipoteichoic acid (LTA) mediates the adhesion of GBS to hBMECs, while other bacterial adhesins can interact with basement membrane components, such as PilA (the adhesin located at intervals along the pilus backbone), serine-rich repeat protein (Srr), streptococcal fibronectin-binding protein (Sfb) and alpha-C protein (ACP), which bind to collagen, plasminogen, fibronectin, and glycosaminoglycans, respectively [53]. Among them, PilA binds to collagen to bridge the interaction with the α2β1 integrin, promotes bacterial adhesion to hBMECs, and activates the release of pro-inflammatory chemokines through the focal adhesion kinase - extracellular signal-regulated kinases (FAK-Erk) pathway [54]. Srr2 (a unique high-molecular-mass

repeating protein, a type of Srr), a major CC17-GBS-specific adhesin, spreads GBS and promotes GBS invasion by hijacking ligands from the host's coagulation system [55]. Recent research shows that the host transmembrane receptors α5β1 and αvβ3 integrins are ligands for Srr2, and both of these integrins contribute to the adhesion and internalization of CC17-GBS [56]. But how these proteins play a role in promoting crossing the BBB is unclear. Recently, the cell-wall anchoring adhesin (plasminogen-binding surface protein (PbsP)) necessary for CC17-GBS to invade the brain has been discovered. It can bind to host plasminogen [57], but the specific mode of action of PbsP and the reaction pathways it participates in still need further study. The GBS cell wall protein, or the GBS secretion protein BspC (an antigen I/II family adhesin), may interact with Vimentin, an intermediate filament protein that is highly expressed in ECs, to activate the pro-inflammatory response to promote adhesion between GBS and HCMEC/D3 cells [58](Fig. 2 (II), Table 1).

After GBS adheres to and invades BECs, GBS can also destroy TJs between cells, which in turn causes meningitis infection. For example, when GBS infects hBMECs, it can induce the expression of the host transcription inhibitor Snail 1, block the expression of the TJ genes ZO-1, Claudin-5, and Occludin, and promote penetration of the BBB [59]. Interestingly, in addition to destroying intercellular TJ proteins, GBS can also destroy the BBB by causing autophagy. GBS expresses a pore-forming β-hemolysin/cytolysin (β-h/c), which can cause autophagy, cause hBMECs to dissolve, and help destroy the BBB [60]. These suggest that bacteria may destroy the integrity of the BBB through paracellular pathways. Of course, cellular damage caused by secreted cytotoxins and induced host inflammatory responses may also induce destruction of the BBB. Host cell signaling networks also play an important role in GBS crossing the BBB. Recent studies have shown that GBS can utilize a clear (sphingosine 1-phosphate)-epidermal growth factor receptor-cytoplasmic phospholipase 2α-cysteinyl leukotrienes (S1P2-EGFR-cPLA2α-CysLts) host cell signaling network to penetrate the BBB [61]. Similarly, GBS can also use the transcytosis of TfR to penetrate BCVs through cells and cross the BBB, like *S.pneumoniae* and *meningitis-associated Escherichia coli* [46](Fig. 2 (II), Table 1).

It has been proposed that the membrane-bound enzyme MprF of GBS can synthesize a new cationic glycolipid lysyl-glucosyl-diacylglycerol (Lys-Glc-DAG), which plays a role in invading hBMECs. It is speculated that Lys-Glc-DAG may be an important lipid in the pathogenesis of meningitis and may be involved in the formation of membrane vesicles (MVs) of GBS. Previous studies have shown that MVs have a role in promoting inflammatory responses [62]. However, these need to be further explored in future research.

Streptococcus suis

S. suis is a gram-positive bacterium that as an emerging zoonotic pathogen, it can cause arthritis, endocarditis, pneumonia, and in severe cases, it can also cause septicaemia and meningitis, and even death, in both humans and pigs [63, 64]. Currently, there are 29 serotypes of *S. suis*, of which *S. suis* type 2 (*S. suis* 2) is the most widespread and most pathogenic [65], and China has had two large-scale epidemics of human infection with *S. suis* in Jiangsu in 1998 and Sichuan in 2005 [66, 67]. Studying the mechanism of *S. suis* breaking through the BBB and causing meningitis can provide new ideas for the treatment of *S. suis* meningitis.

S. suis has multiple virulence factors, which play an important role in the process of *S. suis* breaking through the BBB. First, *S. suis* must adhere to BECs. SsPepO (a secretary immunogenic protein) increases BBB permeability through interaction with fibronectin (FN) and integrin, and can significantly increase the adhesion of *S. suis* to hBMECs in vitro [68]. In addition, the glycoprotein SssP1, a pili component of *S. suis*, can interact with the BBB through vimentin, promoting bacterial adhesion to hBMECs, but is not involved in the rearrangement of the actin cytoskeleton and the destruction of intercellular TJs, so its mode of action may be an unknown way to indirectly penetrate the BBB or activate the inflammatory response [69]. Interestingly, the *S. suis* factor H-binding protein-glycolipid receptor (FHb-Gb3) plays a role in adhesion and crossing the BBB model through the Rho/Rho-associated protein kinase (Rho/ROCK) signaling pathway [70, 71]. After the adhesion and contact of *S. suis* and BECs, it can cause cell translocation through some reactions. Studies have shown that the adenosine of the *S. suis* surface enzyme (Ssads) increases the permeability of the BBB by activating the adenosine receptor protein (ARs) signaling cascade on HCMEC/D3 cells and the translocation of BECs [72, 73](Fig. 3; Table 1).

In addition, permeability can be changed by disrupting the integrity of the BBB. Eno can promote the release of IL-8 from porcine brain microvascular endothelial cells (PBMECs), change the paracellular barrier and transcellular barrier, destroy the integrity of the BBB, and significantly enhance the permeability of the BBB [74]. However, how IL-8 enhances BBB permeability still needs further research. Eno, as an essential enzyme for glycolysis, can bind to human plasminogen (Plg) and plasmin (Pln). Plg is known to be converted to Pln, a type that cleaves host proteins and monocyte chemotactic protein 1 (MCP1) in the ECM to destroy tightly connected proteases and promote bacteria to cross the BBB [75]. Moreover, lysozyme-releasing protein (MRP) can

Table 1 Study on the mechanism of pathogenic bacteria destroying BBB and invading BBB

Pathogen name	The mechanism of pathogens breaking through BBB	Downstream effects	Reference
S. pneumoniae	CbpA, NanA binding to LR; NanA, RrgA interacting with PECAM-1: RrgA binding to pIgR; Eno binding to PLG	Promotes adhesion of *S. pneumoniae* to the BBB	[38–41]
	Ply combined with GlpO	Produces hydrogen peroxide, which is cytotoxic and breaks BBB integrity	[42]
	Ply promotes high CBP expression in BECs	CBP promotes the release of TNF-α, promotes apoptosis, and increases BBB permeability	[43]
	AcP and hydrogen peroxide produced by SpxB	Avoid intracellular degradation	[44]
	Fusion of BCVs with TfR vesicles	Penetrating the BBB using transcytosis of TfR	[46]
	HIF-1α/VEGF signaling pathway	Increased paracellular permeability	[47]
	B7-H3 upregulates MMP-9 activity	Stimulation of microglia secretion of MMP-9 degrades the extracellular matrix-damaged BBB	[48]
GBS	LTA; PilA binding collagen interacting with α2β1; Srr2 binding fibrinogen; Sfb binding fibronectin; ACP binding glycosaminoglycan	Promotes GBS adhesion to BECs and GBS invasion	[53–55]
	PbsP binds fibrinogen	Promotes GBS invasion	[57]
	BspC interacts with Vimentin	Activates pro-inflammatory responses and promotes GBS adhesion to BECs	[58]
	Induced expression of Snail 1	Blocks expression of ZO-1, claudin-5, and occludin, increases BBB permeability	[59]
	Expression of β-h/c	Causes cellular autophagy, lyses hBMEC and destroys BBB	[60]
	S1P2-EGFR-cPLA2α-CysLts signaling network	Penetrates the BBB	[61]
	Fusion of BCVs with TfR vesicles	Penetrates the BBB using transcytosis of TfR	[46]
S. suis	SsPepO interacts with FN and Integrin; SssP1 interacts with Vimentin; FHb-Gb3 activates the Rho/ROCK signaling pathway	Promotes bacterial adhesion and increases BBB permeability	[68–71]
	Adenosine activation of ARs by Ssads	Promotes brain endothelial cell migration and increases BBB permeability	[72, 73]
	Eno promotes the release of IL-8	Disrupts BBB integrity	[74]
	Eno binds Plg and Pln	Promotes bacterial crossing of the BBB	[75]
	MRP	Promotes adhesion to penetrate hBMEC, inhibits AJs, increases BBB permeability	[76]
	In the hemolytic products of SLY, MMP-9 mediates IL-33	Disrupts claudin-5, releases IL-6 and IL-8, increases BBB permeability	[78]
	Induces STK/STP activity and affects HECTD1 expression	Degrades claudin-5	[79]
	VraSR	Downregulates TJ expression and increases BBB permeability	[80]
	Activates NLRP3, secretes IL-1β, IL-6, TNF-α, CCL-2, CXCL-2, cleaves GSDMD	Down-regulates the expression of TJ	[81]
	Eno binds RPSA, promotes p38, ERK and eIF4E phosphorylation, increases expression of HSPD1	Induces host cell apoptosis, triggering BBB damage and increasing permeability	[82, 83]
	SLY stimulates TNF-α release from TLR4, overexpresses PLA2G3	Induces hBMEC apoptosis, remodeling the actin backbone and increasing BBB permeability	[85, 86]
N. meningitidis	TFP binds CD147; TFP activates β2AR to form cortical plaques; Opa binds CEACAM-1;	Promotes adhesion of *N. meningitidis* to endothelial cells	[92, 94, 97]
	Opc activates Src	Rearrange action to promote *N. meningitidis* uptake	[98]
	Opc interacts with α-Actinin	Promotes *N. meningitidis* passage through the endothelial barrier	[99]
	MMP-8 cleaves occludin	Attenuates barrier function	[100]
	NalP cleaves MHBA	Induces internalization of VE-cadherin and alters permeability	[101]

Table 1 (continued)

Pathogen name	The mechanism of pathogens breaking through BBB	Downstream effects	Reference
Meningitis-associated E. coli	SLURP1 enhances the activity of α7nAChR	Promoting the invasion of BBB by *E. coli* K1	[106]
	IbeA binding to Caspr1	Activation of adhesion patch kinase signaling promotes internalization of *E. coli* K1 into BECs	[107]
	Activation of PPARβ/δ signaling pathway induces ANGPTL4 expression	Activation of ARHGAP5/RhoA/MYL5 signalling cascade disrupts BBB structure	[108]
	Activation of SphK2-S1P-S1P2-EGFR cascade, activation of c-Src	Regulation of the actin cytoskeleton promotes *E. coli* invasion of BECs	[109]
	EGFR and ErbB3 dimerization, recruitment, and catabolism of ACTN4	Breakdown of the actin cytoskeleton promotes bacterial invasion of endothelial cells	[110]
	Hcp1 is specifically recognized by brain microvascular endothelial cells	Causes cytoskeletal rearrangement, apoptosis, activation of caspase 8 and cytokine release, initiating the body's inflammatory response	[111]
	Activation of FAK/PI3K signaling pathway in hBMEC by ilvB	Induction of actin cytoskeleton rearrangement promotes bacterial invasion and penetration of BBB	[112]
	OmpA binds Ecgp, activates PKC α signaling, and interacts with VEC	Dissociation of β-conjugated proteins and VEC, leading to increased BBB permeability	[113]
	α7nAChR/CISH/JAK2/STAT5 axis	Influence on the expression of TJ proteins	[114]
	Egr-1 activates RhoA, rac1, CD42, and induces expression of VEGFA, ANGPTL4, PDGFB	Altered cytoskeleton, degraded TJ, destroyed BBB	[115]
	Overexpression of LncRSPH9-4 increases MMP-3 expression via miR-17-5p	Regulates TJ and disrupts BBB	[116]
	Upregulation of circ_2858 expression promotes VEGFA expression via miR-93-5p	Downregulates ZO-1, occludin and Claudin5	[117]
	Induction of IL-17 A inhibits the PRTN3/PAR-2 axis	Degrades TJs and AJs increase BBB permeability	[118]
	Up-regulation of PDGE-B in meningitis *E. coli* infected with hBMEC	Decreases TJ expression and enhances BBB permeability	[119]
	IL-22 activates STAT3 and induces secretion of VEGFA	Disrupts ZO-1, occludin, Claudin-5, causing BBB dysfunction	[120]
	Fusion of BCVs with TfR vesicles	Penetrates the BBB using transcytosis of TfR	[46]
	HlyA attenuates TGFβ1 receptor TGFBRII and hedgehog signalling transcription factor Gli 1/2 in BMEC	Interference with functional interactions between astrocytes and BMEC, causing BBB dysfunction	[121]
	Astrocyte-derived WNT5B activates the JNK/c-JUN pathway in hBMECs via ROR1	Inhibits ZO-1 expression and impairs BBB integrity	[122]
Staphylococcus aureus	Infection of endothelial cells	Reduces the expression of ZO-1, claudin-5 and enhances BBB permeability;	[123]
	Promotion of IL-1α, IL-1β, IL-6, TNF-α, MCP-1 and MIP1α expression	Disrupts the BBB	[123]
	LTA	Mediates adhesion to hBMEC and penetration of the BBB	[124]
	Induces release of pro-inflammatory cytokines, activation of oxidative stress, and NF- κB	Reduces TJ expression and disrupts BBB integrity	[123]
	SpA	Enhanced BBB permeability	[123]
Bacillus anthraci	With InhA and BsIA	Breaks down ZO-1 and disrupts BBB integrity	[125]
	BsIA	Promotes adhesion to BBB	[126]
	Lethal toxins	This leads to endothelial cell dysfunction	[127]
Streptococcus equi subsp. Zooepidemicus	Release of SzM-containing extracellular vesicles to enter hBMEC with the aid of vesicle endocytosis	Causes autophagic cell death and disrupts BBB integrity	[128]
	BifA leads to moesin phosphorylation, activating RhoA	Disruption of the endothelial barrier allows penetration of the BBB	[129]

Table 1 (continued)

Pathogen name	The mechanism of pathogens breaking through BBB	Downstream effects	Reference
Haemophilus influenzae	Omp2 combined with LR	Promoting *Haemophilus influenzae* penetration of the BBB	[38]
	LPS with the help of OMV	Crosses the BBB by a "Trojan horse" pathway	[131]
	Hia releases adenosine when infected with hBMEC, binds to adenosine A2B receptor	Releases VEGF, which destroys the BBB	[132]
Borrelia burgdorferi	The Rrp2-RpoN-RpoS pathway controls OspC	Facilitating BBB migration	[133]

also promote the adhesion and penetration of *S. suis* to hBMECs, inhibit the BBB's AJs protein p120-content, and increase the permeability of the BBB [76]. SLY (Suilysin, a pore-forming cholesterol-dependent cytolysin secreted) produced by *S. suis* can promote the adhesion of *S. suis* and the invasion of host cells [77]. Among the hemolysis products of SLY, IL-33 can be mediated by MMP-9, destroying the expression of Claudin-5 in HCMEC/D3 cells, and further promoting the release of IL-6 and IL-8 through the coordination of p38-mitogen-activated protein kinase signaling, ultimately increasing the permeability of the BBB [78]. Studies have also pointed out that *S. suis* relies on the expression of the *stk* gene, and its interaction can induce the activity of serine/threonine kinase (STK/STP), which in turn affects the expression of the E3 ubiquitin ligase HECTD1, increases the degradation of Claudin-5, and crosses the BBB through the paracellular pathway [79]. However, a recently proposed theory is that the *S. suis* vancomycin resistance-related sensor/regulator dual-component signal transduction system (VraSR) can downregulate TJs expression, increase BBB permeability, and participate in the inflammatory storm induced by *S. suis* [80]. *S. suis* infection can also activate NLRP3 inflammatory bodies in hBMECs, leading to the secretion of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) and chemokines (CCL-2 and CXCL-2) and the cleavage of Gasdermin D (GSDMD, also called GSDMDC1, DFNA5L, or FKSG10). At the same time, *S. suis* infection significantly downregulates the expression of TJs protein [81](Fig. 3; Table 1).

The interaction of *S. suis* with BECs can also disrupt the integrity of the BBB by inducing apoptosis. Eno can bind to the 40 S ribosomal protein SA (RPSA) on the surface of PBMECs, gradually promote the phosphorylation of p38, the extracellular signal-regulated kinases (ERK) and eukaryotic cell initiation factor 4E (elF4E), increase the expression of heat shock protein family D member 1 (HSPD1), promote the translocation of HSPD1 from mitochondria to cytoplasm, cause cell morphology changes and induce host cell apoptosis, trigger BBB damage and increase permeability [82, 83]. Recent studies have shown that the deletion of O-acetyl homoserine hydrolase (OAHS) leads to a decrease in Eno expression, which in turn inhibits the process of inducing apoptosis and reduces damage to the BBB. However, how OAHS regulates Eno expression needs further research [84]. SLY can also stimulate HCMEC/D3 cells to release TNF-α in a Toll-like receptor 4 (TLR4)-dependent manner, thereby overexpressing secreted group III secretory phospholipase A2 (PLA2G3), inducing apoptosis of HCMEC/D3 cells and remodeling of the actin skeleton, increasing the paracellular permeability of the BBB [85, 86](Fig. 3; Table 1).

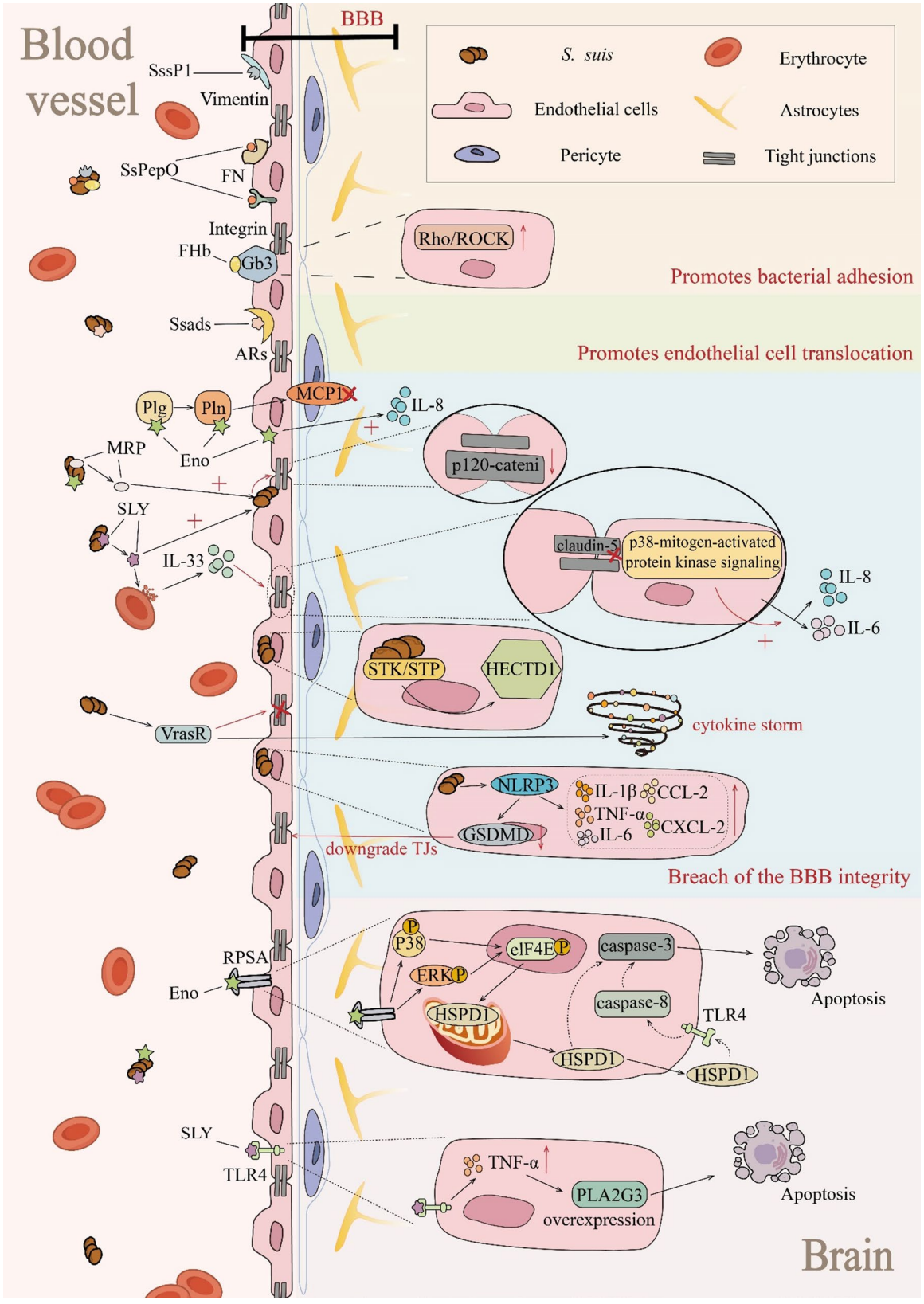

Fig. 3 The main mechanism for *S. suis* to break through the BBB. The combination of virulence factors of *S. suis* and receptor proteins promotes adherence of *S. suis* to invade BECs and also promotes BECs migration, and *S. suis* invasion can disrupt the integrity of the BBB by disrupting TJs, causing inflammatory storms, etc. Similarly, *S. suis* can cause a range of responses leading to apoptosis

In addition, the results of the action of the *S. suis* 2 genomic phage library on the BBB model were analyzed to screen out other virulence genes that may be related to the crossing of the BBB by *S. suis* 2 [87]. Bacterial collagenase can degrade collagen in the extracellular matrix and host connective tissue, and it is considered that it may destroy the TJs of the BBB; O-acetyl homoserine hydrolase can catalyze O-acetyl homoserine in the body into homocysteine. High concentrations of homocysteine can damage BECs, and it is considered that it may promote *S. suis* 2 to penetrate the BBB; The promotion of the formation of the BBB by astrocyte-endothelium is based on the Hedgehog pathway. The node protein of this pathway is the desert hedgehog(DHH) family protein [88]. Therefore, the DHH family protein of *S. suis* 2 may inhibit the formation of the BBB by blocking the Hedgehog pathway. However, what role these virulence factors play on the BBB during the pathogenesis of disease needs to be further explored. This information only provides some inspiration for later studies on the penetration of *S. suis* 2 through the BBB.

Gram-negative bacteria

Neisseria meningitidis

N. meningitidis is a gram-negative diplococcus that causes severe invasive infections [89], and the only host of *N. meningitidis* is humans, which can colonize outside the nasopharyngeal cells, and 2-10% of infected people carry only bacteria without obvious symptoms. *N. meningitidis* can cause acute meningitis and sepsis after infecting people, with high morbidity and mortality rates [89, 90]. Clarifying how *N. meningitidis* manipulates host signaling pathways during its invasion of the CNS will not only better understand the pathogenesis of *N. meningitidis* meningitis but will also help discover therapeutic approaches to control and manage *N. meningitidis* infection.

N. meningitidis attachment to HCMEC/D3 cells relies on type IV pili (TFP), which can mediate bacterial aggregation and initiate certain signaling events in host cells [91]. *N. meningitidis* can achieve TFP pili-dependent BECs adhesion through CD147, a member of the immunoglobulin superfamily, which is highly expressed on the surface of brain capillaries [92]. Binding *N. meningitidis* to HCMEC/D3 cells can be prevented by interfering with the interaction of TFP and CD147. However, this is only based on the identification of *N. meningitidis* 2C4.3 strain with high adhesion and its pili protein. As for whether CD147 is a receptor for TFP targeting BECs, further identification of clinical isolates is needed [92]. Moreover, TFP-pilus-mediated signal transduction can promote the translocation of TJs molecules (such as VE-cadherin, ZO-1, and Claudin-5) between cells to bacterial adhesion sites, changing endothelial permeability [93]. In addition, when *N. meningitidis* attaches to HCMEC/D3 cells, cortical plaques are formed due to TFP activation of the G protein-coupled receptor β2AR, and this process also activates the β2-adrenergic receptor/β-arresting pathway, thereby promoting bacterial adhesion [94]. It was once believed that the membrane cofactor protein CD46 is the host receptor of *N. meningitidis* TFP, but CD46 does not directly interact with any pili component, and the specific down-regulation of CD46 expression cannot change the *N. meningitidis* binding efficiency, so this statement was overturned [95](Fig. 4 (I), Table 1).

Interestingly, in hBMECs using a special treatment to express the human carcinoembryonic antigen-associated cell adhesion molecule-1 (CEACAM-1) protein, the outer membrane protein Opa of *N. meningitidis* was found to be able to bind to carcinoembryonic antigen-associated cell adhesion molecule-1 (CEACAM-1), where CEACAM-1 can mediate the involvement of Opa proteins in bacterial adherence and entry into host cells [96]. The outer membrane protein Opc can be expressed by several virulent *N. meningitidis*, but interestingly, it was missing in endemic isolates, suggesting that Opc may enhance bacterial binding to BECs [97]. In addition, in hBMECs, activation of the non-receptor tyrosine kinase c (Src kinase) relies on Opc, which rearranges actin and promotes *N. meningitidis* uptake [98]. Once *N. meningitidis* enters hBMECs, Opc can interact with the cytoskeletal protein α-Actinin (a regulator of signaling pathways and cytoskeletal function), thereby facilitating passage across the endothelial barrier [99](Fig. 4 (I), Table 1).

During the process of *N. meningitidis*-induced meningitis, *N. meningitidis* can also regulate the expression of TJs in BECs. Infection of BECs by *N. meningitidis* will lead to degradation of the Occludin protein. For example, in *N.meningitidis*-infected cells, matrix metalloproteinase-8 (MMP-8) mediates the cleavage of Occludin, which leads to the weakening of the barrier function of hBMECs [100]. Similarly, *N. meningitidis* heparin-binding antigen (NHBA) can be cleaved by NalP protease, inducing internalization of the adhesion connexin protein VE-cadherin, and changing endothelial permeability [101](Fig. 4 (I), Table 1).

A recent study found through bioinformatics analysis that adhesin MafA (which one of the multiple adhesin family), major outer membrane protein P.IB, possible adhesin/invasion proteins, possible lipoproteins, and membrane lipoproteins all showed interactions with hBMECs [102], but the specific mechanism has not yet been clarified and still needs to be explored. Due to the human specificity of *N. meningitidis*, there are not many studies to explore the molecular mechanisms of *N. meningitidis* meningitis. In future research, clarifying the pathway of action by *N. meningitidis* in causing meningitis remains a difficult task.

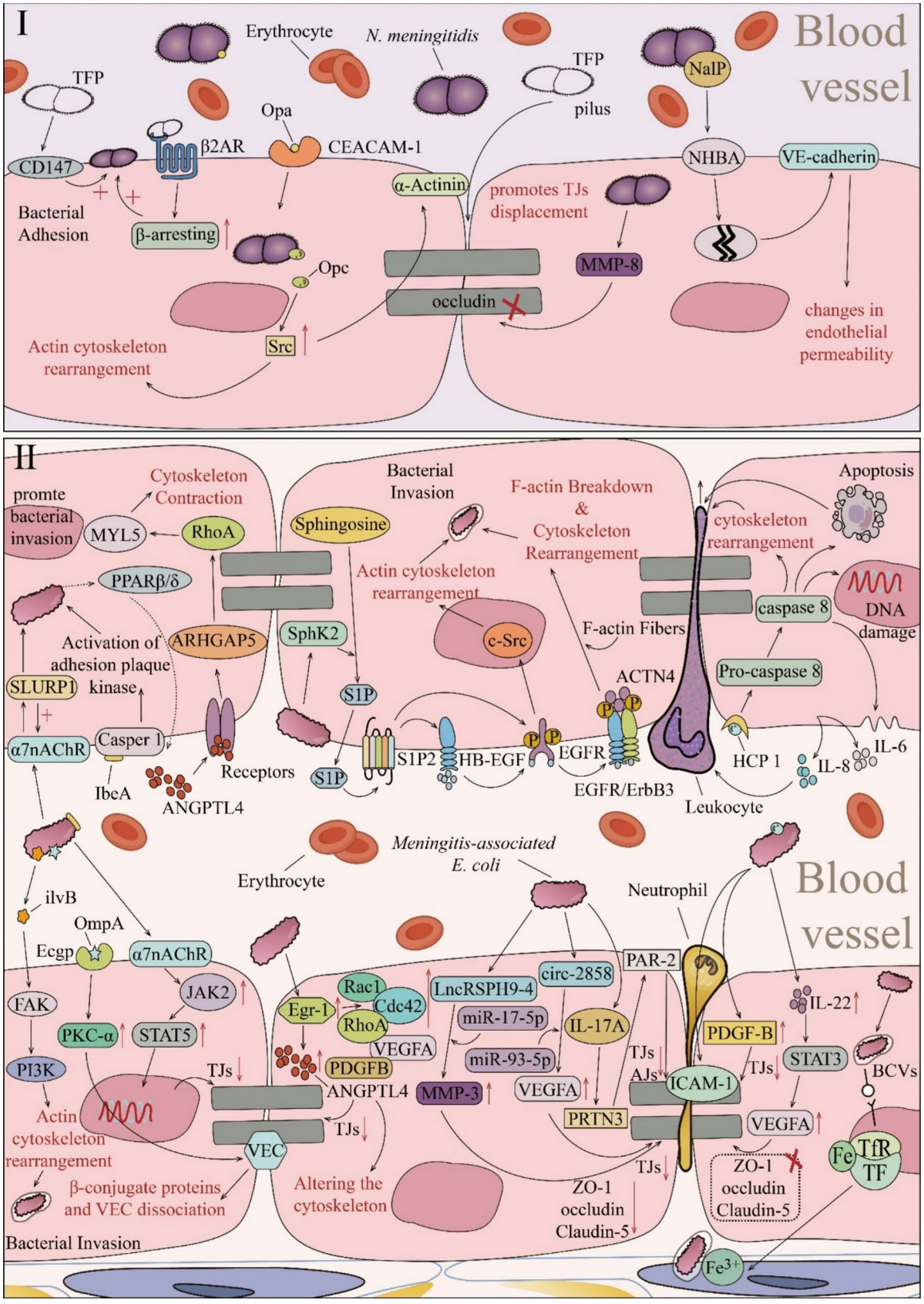

Fig. 4 (See legend on next page.)

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Fig. 4 The main mechanism of *N. meningitidis* and *meningitis-associated E. coli* breaking through the blood-brain barrier. (**I**) *N. meningitidis*. Binding of virulence factors of *N. meningitidis* to receptors promotes bacterial adhesive invasion, and *N. meningitidis* infection disrupts TJs, induces rearrangement of the actin cytoskeleton, and alters the permeability of BECs. (**II**)*Meningitis-associated E. coli.* Binding of E. coli virulence factors to the receptor promotes bacterial adhesion to invade BECs, and following invasion *meningitis-associated E. coli* activates a series of signalling cascades to regulate host cell actin cytoskeletal rearrangements, causing apoptosis, releasing inflammatory factors, and affecting the expression of TJs. Specifically, *meningitis-associated E. coli* can also penetrate the BBB using TfR transcytosis

Meningitis-associated Escherichia coli

E.coli is a common extracellular parthenogenetic anaerobic gram-negative bacterium that is an important constituent of the normal gut microbiota of humans and other mammals. It does not always pose a pathogenic risk to carriers, but there are a few strains of *E.coli* with virulence factors that can cause serious infections in their hosts [103]. Due to the different locations of the disease, *E. coli* is divided into enteric pathogenic *E. coli* and extraenteric pathogenic *E. coli*. One of the extraenteric pathogenic *E. coli*, *meningitis-associated E. coli*, can cause the host to develop clinical symptoms such as meningitis and sepsis [104], and it is also the second leading cause of neonatal meningitis [105]. In recent years, research on the pathogenesis of *meningitis-associated E. coli* has gradually deepened.

E. coli K1 infection releases the endogenous alpha 7 nicotinic acetylcholine receptor (α7nAChR) ligand, the secreted Ly6/Plaur domain containing protein 1 (SLURP1), and SLURP1 can enhance the activity of α7nAChR to promote *E. coli* K1's invasion of the BBB [106]. In addition, the single channel transmembrane protein Caspr1 (contactin-associated protein 1, also known as paranodin) in hBMECs is a receptor for the virulence factor IbeA of *E. coli*. The extracellular domain of IbeA and Caspr1 interact to activate focal adhesion kinase signals, leading to internalization of *E. coli* into hBMECs [107]. Internalization into cells can cause activation of a series of pathways in cells, which in turn destroys the integrity of the BBB. For example, *meningitis-associated E. coli* activates the peroxisome proliferator-activated receptor β/δ(PPAR β/δ) signaling pathway and induces expression of angiopoietin like protein 4 (ANGPTL4), which disrupts the BBB by activating the ARHGAP5/RhoA/MYL5 signaling cascade in hBMECs [108](Fig. 4 (II), Table 1).

After *E. coli* enters the cell, it can cause the cytoskeleton rearrangement through a series of molecular mechanisms, thereby changing the structure of the BBB and facilitating the bacteria to cross the BBB. When *E. coli* invades hBMECs, it activates sphingosine kinases 2 (Sphk2), which catalyzes sphingosine to synthesize sphingosine 1-phosphate (S1P), which is then secreted to the outside and binds to the sphingosine 1-phosphate receptor 2 ($S1P_2$) receptor, thereby participating in the activation of epidermal growth factor receptor (EGFR) and the up-regulation and release of its related ligand heparin-binding EGF-like ligand (HB-EGF). The released HB-EGF can bind to the extracellular ligand binding domain of EGFR, leading to tyrosine phosphorylation of the cytoplasmic kinase domain of EGFR. The SphK2-S1P-$S1P_2$-EGFR cascade induces the activation of c-Src tyrosine kinase, which serves as an intracellular mediator that regulates host cell actin cytoskeletal rearrangements, leading to *E.coli* invasion of hBMECs [109]. Further elucidating this network will help us understand the pathogenesis of *E. coli* meningitis. Recent studies have shown that activated EGFR dimerizes with its heterogenous partner ErbB3 (human epidermal growth factor receptor 3), which in turn competitively recruits and decomposes α-actinin-4 (ACTN4) from intracellular actin fibers, leading to the decomposition and reorganization of the actin cytoskeleton, and ultimately promoting the bacterial invasion of hBMECs [110]. In addition, the type VI secretion system (T6SS) is involved in the pathogenicity of gram-negative bacteria, and Hemolysin-coregulated protein1 (Hcp1) is a component protein of T6SS. After bacteria secrete it into the body, it will be recognized by specific receptors of hBMECs, which in turn causes cytoskeletal rearrangement, apoptosis, activation of caspase 8, and release of cytokines, thereby initiating the body's inflammatory response, including the migration of white blood cells across hBMECs [111]. Recent research reveals that when *E. coli* enters iron-deficient blood, ferric uptake regulator (Fur) is inactivated, releasing the restriction of csiR (a GntR family regulator), thereby inducing the expression of downstream effector *ilvB*. The *ilvB* promotes bacterial invasion and penetration of the BBB by activating the focal adhesion kinase/phosphatidylinositol 3-kinase (FAK/PI3K) signaling pathway in hBMECs and inducing actin cytoskeleton rearrangement [112](Fig. 4 (II), Table 1).

In addition to causing cytoskeletal rearrangements, *E. coli* infection can also disrupt the integrity of the BBB by destroying TJs. During the adhesion process of *meningitis-associated E. coli* and hBMECs, the outer membrane protein OmpA expressed by it binds to endothelial cell glycoprotein (Ecgp), activates protein kinase C (PKC)-α, and interacts with vascular endothelial cadherin (VEC) at the TJ, leading to the dissociation of β-catenin and VEC, resulting in increased permeability of hBMECs [113]. In particular, α7nAChR activates the Janus kinase2-signal transducer and activator of transcription5 (JAK2-STAT5) signaling pathway during the BBB disruption stage of *E.*

coli K1, affecting the expression of TJs. Cytokine-inducible SH2 domain protein (CISH) inhibits the activation of JAK2-STAT5, interestingly, the expression of CISH can be regulated in BECs by α7nAChR [114]. Therefore, the α7nAChR/CISH/JAK2/STAT5 axis plays an important role in the pathogenesis of *E. coli* 's destruction of the BBB. When *meningitis-associated E. coli* infects hBMECs, it also activates early growth factor 1 (Egr-1), a key regulator that maintains BBB integrity. Egr-1 can promote the activation of Ras homolog gene family member A (RhoA), Ras-related C3 botulinum toxin substrate 1 (Rac1), and Cell division cycle protein 42 (Cdc42), induce the expression of vascular endothelial growth factor A (VEGFA), angiopoietin-like protein 4 (ANGPTL4) and platelet-derived growth factor B subunit (PDGFB), thereby changing the cytoskeleton, degrading TJs, and destroying BBB [115]. Studies have shown that when *meningitis-associated E. coli* infects hBMECs, overexpression of the long non-coding RNA LncRSPH9-4 regulates the permeability of hBMECs by acting as a competitive sponge for miR-17-5p, and increases the expression of matrix metalloproteinase-3 (MMP-3) regulates TJ, thereby destroying the BBB [116]. Recently, it was found that when *E. coli* invades hBMECs, the expression of circ_2858 in circular RNA (CircRNA) is upregulated, and by competitively binding to miR-93-5p, it promotes the expression of VEGFA, and ultimately down-regulates ZO-1, Occludin, and Claudin-5, causing BBB dysfunction [117]. In addition, *E. coli* can also induce a pro-inflammatory cytokine, interleukin-17 (IL-17A), inhibit the protease 3 (PRTN3)/protease-activated receptor 2 (PAR-2) axis, degrade hBMECs TJs and AJs, and increase BBB permeability [118]. In recent years, two important host factors have been found through RNA sequencing: platelet-derived growth factor-B (PDGF-B) and intercellular adhesion molecule-1 (ICAM-1). *E. coli* infection can reduce the expression of TJs through the increase of PDGF-B and directly increase the permeability of the BBB. The upregulation of ICAM-1 induced by infection can help recruit neutrophils or monocytes and initiate the CNS inflammatory response [119]. *Meningitis-associated E. coli* can also induce the expression of IL-22 during infection of hBMECs, and IL-22 can activate STAT3 signal and induce VEGFA secretion, which in turn destroys ZO-1, Occludin, and Claudin-5, causing BBB dysfunction [120](Fig. 4 (II), Table 1).

Similarly, neonatal *meningitis-associated E. coli* can also use the vesicle fusion mechanism of the host cell to reduce intracellular killing and pass through the BBB through the transcytosis of TfR [46]. In addition to its interaction with BECs, astrocyte-derived transforming growth factor-β1 (TGFβ1) normally physiologically triggers the TGFβ1-TGFBRII-Smad2/3-Gli1/2-ZO-1 axis in hBMECs to maintain normal BBB function. After infection with *E. coli*, α-hemolysin (HlyA) effectively interferes with this functional interaction between astrocytes and hBMECs by weakening the TGFβ1 receptor TGFBRII and the hedgehog signaling transcription factor Gli1/2 in hBMECs, resulting in BBB dysfunction [121]. Astrocyte-derived WNT5B also activates the non-classical wingless-related integration site (Wnt) signaling pathway JNK/c-JUN in hBMECs through its receptor tyrosine kinase-like orphan receptor 1 (ROR1), resulting in inhibition of ZO-1 expression and impairment of TJ integrity in hBMECs [122].

Other important meningitis-causing bacteria

In addition to the bacteria mentioned above, other pathogenic bacteria can also break through the BBB.

Staphylococcus aureus (*S.aureus*) can reduce the expression of Claudin-5 and ZO-1 to enhance the permeability of the BBB. It can also promote the up-regulation of IL-1α, IL-1β, IL-6, TNF-α, MCP-1, and macrophage inflammatory protein-1α (MIP-1α) in hBMECs, thereby destroying the BBB [123]. Membran-anchored lipoteichoic acid (LTA) can mediate *S.aureus* adhesion to hBMECs and penetration through the BBB [124]. New research shows that *S.aureus* infection with hBMECs can induce the release of pro-inflammatory cytokines, activate oxidative stress and NF-κB, reduce the expression of TJs, thereby destroying the integrity of the BBB, and adhesin protein A (SpA) can also enhance the permeability of the BBB [123](Table 1).

Bacillus anthracis (*B.anthracis*) can decompose ZO-1 through its pathogenic factors enoyl acyl carrier protein reductase (InhA) and burst-suppression-isoflurane-anaesthesia (BsIA), thereby invading hBMECs, destroying the integrity of the BBB [125], and BsIA can also promote its adhesion to hBMECs [126]. In addition, the lethal toxin of *B.anthracis* can also cause dysfunction of the endothelial barrier, suggesting that its lethal toxin also plays a certain role in breaking through the BBB [127](Table 1).

Streptococcus equi subsp. Zooepideicus (*S.equi subsp. Zooepidimicus*, SEZ) can release extracellular vesicles containing SEZ M protein (SzM). Due to the endocytosis of the vesicles, SzM enters hBMECs and causes cytotoxicity, causing autophagic death and destroying the integrity of the BBB [128]. British intestinal failure alliance (BifA), a protein that contains the Fic domain, promotes the transport of SEZ across hBMECs, which causes moesin phosphorylation and activates downstream RhoA, thereby breaking the endothelial cell barrier and allowing penetration of the BBB [129](Table 1).

Haemophilus influenzae (*H.influenzae*) is divided into capsular and non-capsular types, of which the most pathogenic is *H.influenzae* type b (Hib). Hib can enter the CNS by binding to LR and platelet-activating factor

receptor (PAFR), causing meningitis [130]. And its outer membrane protein P2 (OmpP2) can target LR to interact with BECs [38]. Interestingly, Hib's lipopolysaccharide (LPS) exists in the outer membrane vesicles (OMV), which can be used to cross the BBB in a "Trojan horse"-like manner to achieve the purpose of delivering LPS [131]. *H.influenzae* type A (Hia) releases high concentrations of adenosine when infecting hBMECs, which then binds to the adenosine A_{2B} receptor (one of the adenosine receptors) on hBMECs, triggers the release of VEGF and destroys the BBB [132](Table 1).

Borrelia burgdorferi is regulated by the Rrp2-RpoN-RpoS pathway when crossing the BBB, and this pathway also controls the surface lipoprotein outer surface protein (OspC), which promotes BBB migration [133](Table 1).

Outlook

Based on recent research, it is not difficult to find that bacterial pathogens have different mechanisms for destroying the BBB and bacteria-host interactions, promoting the occurrence of meningitis. Currently, research is underway to clarify the mechanism of bacteria crossing the BBB, causing meningitis, and some progress has been made. It is worth noting that bacteria can interact directly with barrier components to cross it, suggesting that these pathogens can open transcellular or paracellular pathways to disrupt the stability of the BBB.

Before destroying the BBB, the bacteria usually need to adhere to the BECs, a step that is usually achieved by the interaction of certain virulence factors of the bacteria with receptor proteins on the BECs. Different virulence factors of different bacteria usually bind to different receptors, e.g., RrgA of *S. pneumoniae* binds to pIgR [40], PilA of GBS binds to collagen [53], Ssads of *S. suis* binds to ARs [73], Opa of *N. meningitidis* binds to CEACAM 1 [96], and IbeA of *meningitis-associated E. coli* binds to Caspr1 [107]. Different virulence factors of the same bacterium may also bind the same receptor protein, e.g., both CbpA and NanA of *S. pneumoniae* bind to LR [38, 39], while both NanA and RrgA interact with PECAM-1 [39, 40]. In addition, the same virulence factor from the same bacterium can bind to different proteins, e.g., NanA from *S. pneumoniae* binds both LR and PECAM-1, while RrgA binds both PECAM-1 and pIgR [38–40]. Interestingly, virulence factors of different bacteria may also bind the same receptor protein, for example, the virulence factor of *S. pneumoniae* binds to LR, and similarly, Omp2 of *H.influenzae* interacts with LR [38]. Both BspC of GBS and SssP1 of *S.suis* can bind to Vimentin [58, 69]. In turn, similar virulence factors from different bacteria bind different receptor proteins, e.g., Eno from *S.pneumoniae* binds PLG, whereas Eno from *S.suis* binds RPSA [41, 82].

After adherence, the bacteria then interact with the BECs to destroy the BBB and promote better invasion or passage of the bacteria through the BECs. Most commonly, bacteria further undermine the integrity of the BBB by destroying tight junction proteins between BECs, such as ZO-1, Occludin, and Claudin-5, which is seen in GBS, *S.suis*, *N. meningitidis*, *meningitis-associated E. coli*, *S.aureus*, and *B.anthracis* [59, 78, 100, 117, 123]. Bacteria are also able to break the BBB structure by causing apoptosis or autophagy, e.g. *S.pneumoniae*, *S.suis*, and some virulence factors of *meningitis-associated E. coli* cause apoptosis [43, 83, 111], whereas GBS infection of BECs may cause autophagy [60], and similarly in SEZ of the animal plague, the SzM contained in the extracellular vesicles can cause autophagic death of the cells [128]. Of note here is that in *meningitis-associated E. coli*, the component protein of its T6SS, Hcp1, is recognised by the specific receptor for hBMECs, thereby triggering a series of reactions that ultimately result in the destruction of the BBB [111]. Eight secretory systems are known (T1SS, T2SS, T3SS, T4SS, T5SS, T6SS, T7SS, and T9SS), whereas T4SS and T7SS are found in both gram-positive and gram-negative bacteria [134], and then the research related to these two becomes quite important. Analogously to the component proteins of T6SS, it was considered whether the component proteins of T4SS as well as T7SS also play a role in bacterial disruption of the BBB. Interestingly, bacteria can exploit several roles in the host cell for the purpose of self-transfer, e.g., *S.pneumoniae*, GBS, and *meningitis-associated E. coli* can all use the transcytosis of TfR to infiltrate BCVs across the cell and thus across the BBB [46].

Bacteria often cause the release of a few pro-inflammatory cytokines, such as IL-6, IL-8, IL-1β, and TNF-α, following infection of BECs. Pro-inflammatory factors may have some effect on the TJs of the BBB, e.g., IL-33, a lysis product of *S.suis* SLY, disrupts the expression and distribution of Claudin-5 in HCMEC/D3 cells [78], and *S.aureus* induces the release of pro-inflammatory cytokines and reduces the expression of TJs [123]. This is also demonstrated in *meningitis-associated E. coli*, which induces IL-17 A to inhibit the PRTN3/PAR-2 axis thereby degrading TJs and AJs, and it also induces IL-22 to activate STAT3, which induces the secretion of VEGFA, thereby disrupting ZO-1, Occludin, and Claudin-5 [118, 120]. Among them, the pro-inflammatory factor TNF-α may play a role in promoting apoptosis [43], thereby increasing BBB permeability, e.g., Ply in *S.pneumoniae* promotes high expression of CBP, which in turn promotes the release of TNF-α and apoptosis, and similarly in *S.suis*, SLY stimulates the release of TNF-α from hBMECs in a TLR4-dependent manner, which results in the overexpression of PLA2G3, the induces apoptosis in hBMECs [85]. Although a large number of studies have been conducted, the specific mechanisms of BBB

disruption under infectious or inflammatory conditions remain to be further explored.

Due to the special physiological structure and function of the BBB, drugs are also generally unable to be delivered to the CNS through the barrier, so some new ideas for drug delivery were considered by exploring the mechanism of bacterial trans-BBB. Through previous research, three major directions can be provided for the development of targeted treatment strategies: blocking strategies to target bacterial adhesion, biomimetic delivery systems, and anti-inflammation and barrier protection.

Firstly, concerning blocking strategies targeting bacterial adherence, although bacterial binding to the receptor may have occurred during treatment, such an approach may reduce the extent of subsequent bacterial binding to the receptor to some extent. Studies pointed out that a heavy chain domain (VHH) was successfully developed using an improved phage display technology. The production of VHH can block the interaction between *Neisseria* adhesin A (NadA) and its receptor, thereby reducing *N. meningitidis* on hBMECs, as well as reducing the translocation of *N. meningitidis* across the BBB [135]. This can also be considered as a new treatment for meningitis.

Secondly, about bionic delivery systems, bacteria themselves or their components are used, modified to retain their structural features and make them non-toxic, and further bound to receptors or through specific pathways to deliver drugs into the BBB. In vitro, the methotrexate (MTX) was loaded into hollow manganese dioxide (MnO2) nanoparticles to further surface modify the Opca protein of *N.meningitidis*. It was found that the biomimetic nanoparticle system (MTX@MnO_2-Opca) could penetrate the BBB [136]. This raises the question of whether therapeutic drugs can be added to this system to cross the BBB and reach the brain. Interestingly, dead *E. coli* K1 (EC-K1) does not have potential bacterial toxicity but can penetrate the BBB. Based on this, a relatively safe "dead EC-K1" drug delivery system was developed, that is, a therapeutic drug modified by maltodextrin (MD) loaded on EC-K1 and then inactivated by ultraviolet light. This system is called "Inactive Trojan horse EC-K1" [137]. In addition, inspired by *E. coli* to penetrate the BBB by combining outer membrane proteins with the endoplasmic reticulum resident protein GRP94 (also called gp96), a non-toxic DH5α outer membrane protein-coated nanocapsules (Omp@NCs) was developed, which can also recognize GRP94 to cross the BBB [138]. This suggests that we can use this capsule to wrap the drug and transport it to the brain for therapeutic effects. In addition to this, drugs can be delivered by exploiting the properties of immune cells, for example, new research suggests using the ability of neutrophils to penetrate the BBB to create a "CellUs" system that can encapsulate drugs across the BBB to treat brain infections [139].

Finally, there is anti-inflammation and barrier protection. In bacterial infections, antibiotic treatment, although necessary, leads to the rapid release of components of the bacterial cell envelope, further exacerbating the inflammatory response, which can be appropriately mitigated by the combined use of anti-inflammatory drugs such as dexamethasone [140]. In *S.pneumoniae* meningitis, remission can be achieved with steroid therapy, but the role of adjunctive steroid therapy in adult bacterial meningitis is controversial [141]. What's interesting is that, in *S. pneumoniae*, the endogenous protein AC2-26 shows a significant anti-inflammatory effect, and its protective effect is mediated through the formyl peptide receptor 2 (FPR2), which suggests an option for treating bacterial meningitis [142]. In addition, in the study of the mechanism of α7nAChR participating in the destruction of the BBB, it was found that the antagonists of α7nAChR (methylaconitine MLA and memamine hydrochloride MEM) protect infected hBMECs [114], which suggests that we can start from important substances in the pathogenesis and select their antagonists to inhibit their destruction of the BBB, thereby achieving the purpose of treatment.

Although we have made significant progress in understanding the pathogenesis of bacterial meningitis, there are still many questions to be answered. First, why are some bacteria able to penetrate the BBB and cause meningitis but not all bacteria? Secondly, among the pathways taken by bacteria to penetrate the BBB, are there any other pathways in addition to the three classic pathways? In addition, several common bacteria adopt the same strategy in breaking through the blood-brain barrier. Finally, there are certain doubts as to whether the data from in vitro experiments are fully adapted to in vivo. After all, in vitro models cannot fully simulate the real situation of the BBB in vivo. Therefore, in future research, the focus will still be on elucidating the pathogenic mechanism of bacterial meningitis and the interaction between bacteria and host when crossing the BBB, to provide new insights into meningitis treatment strategies.

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Author contributions
Y.W., B.L. and Y.Q. conceived and designed the manuscript.Y.Q., Y.W., S.G. and S.S. wrote and revised the first draft of the manuscript.Y.Q. and S.Y. was responsible for the drawing part.Y.W. and B.L. revised the manuscript.Y.W. provided the funding.All authors gave final approval for the publication of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

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Not applicable.

Competing interests
The authors declare no competing interests.

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