细菌易位穿透血脑屏障的分子机制

李怡璇 薛莹 朱洪伟* 张兴晓*

(鲁东大学生命科学学院, 烟台市动物病原微生物与免疫学重点实验室, 烟台 264025)

摘要 血脑屏障(blood brain barrier, BBB)主要由脑微血管内皮细胞构成, 是维持中枢神经系统稳态的重要膜性生物屏障。细菌可通过受体介导的识别和黏附机制入侵微血管内皮细胞或吞噬细胞, 随后通过信号转导和炎症反应机制调控胞吞、胞吐和细胞迁移过程, 介导细菌的跨细胞、细胞旁和特洛伊木马3种通过途径。该文在综述典型脑膜炎致病菌对BBB结构完整性和通透性调节机制基础上, 讨论了沙门氏菌跨BBB感染致病的可能机制, 以期为该肠道菌的神经致病性机制研究提供参考。

关键词 血脑屏障; 细菌易位; 紧密连接; 沙门氏菌

Mechanism of Bacterial Traversal across the Blood Brain Barrier

LI Yixuan, XUE Ying, ZHU Hongwei*, ZHANG Xingxiao*

(*Yantai Key Laboratory of Animal Pathogenic Microbiology and Immunology, School of Life Sciences, Ludong University, Yantai 264025, China*)

Abstract The BBB (blood brain barrier), composed mainly of specialized brain microvascular endothelial cells, is an important membrane barrier that maintains biochemical homeostasis in the CNS (central nervous system). Bacteria use a variety of different virulence factors that enable them to attach to and invade microvascular endothelial cells or phagocytes through receptor-mediated recognition and adhesion mechanism. Endocytosis, exocytosis, and migration can be manipulated by these bacteria through host cell signaling and inflammatory response mechanisms, which will facilitate traversal of BBB via transcellular passage, paracellular passage and "Trojan horse" mechanism. Based on the crossing mechanism of BBB applied by typical meningitis bacteria, hypothesis of BBB traversal by *Salmonella* oral infection is proposed which may serve as hints for neuropathogenic mechanism of this enterobacteria.

Keywords blood brain barrier; bacterial translocation; tight junction; *Salmonella*

血脑屏障(blood brain barrier, BBB)是具有主动调节功能的膜性结构, 是机体固有免疫的内部屏障之一。细菌在特定情况下可入侵中枢神经系统(central nervous system, CNS), 导致细菌性脑膜炎, 具有较高的临床发病率和死亡率。突破外周循环系统与CNS之间的BBB是病原菌建立CNS感染的关键, 也是该领域关注的重要科学问题。近年来, 细菌易位突破BBB屏障的分子机制研究取得了重要进展。本文总结了BBB的结构组成与调控机制, 并梳理了典型细菌易位穿透BBB的途径和分子机制, 在此基础上, 对沙门氏菌的BBB入侵机制进行了探讨, 以期为该菌和其他肠道细菌的神经致病性

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*通讯作者。Tel: 0535-6654527, E-mail: hwzhu@ldu.edu.cn; zhangxingxiao@ldu.edu.cn

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*Corresponding authors. Tel: +86-535-6654527, E-mail: hwzhu@ldu.edu.cn; zhangxingxiao@ldu.edu.cn

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机制研究提供参考。

1 血脑屏障结构组成与生理功能

BBB由脑微血管内皮细胞(brain microvascular endothelial cells, BMECs)、星状细胞、周皮细胞、小胶质细胞、基底膜、紧密连接(tight junction, TJ)和黏附连接(adherens junction, AJ)分子等构成。

1.1 脑微血管内皮细胞

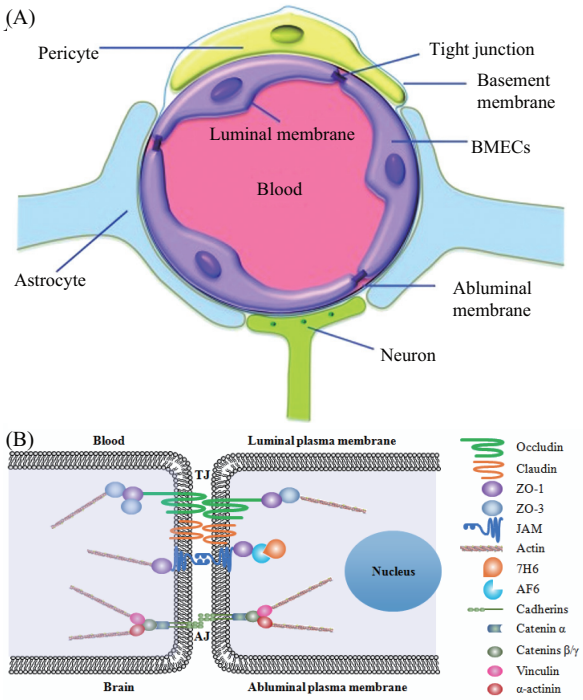
BMECs是BBB的结构和功能基础。BMECs的顶端与血液接触, 基底面与脑细胞连接, 可阻止病原和其他大分子物质进入脑室, 又参与维持脑间质液电解质平衡, 保护神经元免受损伤。BMECs表面表达大量胞间TJ分子, 形成致密单层, 具有较高的跨内皮电阻, 阻碍细胞旁物质内流。此外, BMECs的表面仍表达或诱导表达细胞间黏附分子, 调节白细胞游走、内渗进入CNS, 发挥吞噬功能(图1)。

1.2 TJ分子

TJ、AJ和间隙连接(gap junction, GJ)构成脑微脉管系统的连接复合体。在BBB中, TJ位于基底外侧膜的顶端, 连接相邻的内皮细胞, 构成高电阻细胞旁屏障, 参与建立内皮细胞极性[1]。TJ主要由4种膜蛋白组成, 分别是Occludin、Claudin、连接黏附分子(junctional adhesion molecule, JAM)和内皮细胞选择性黏附分子(endothelial cell-selective adhesion molecule, ESAM)。它们通过细胞质内的闭锁连接蛋白(zonula occludin, ZO)与肌动蛋白细胞骨架相连。其中, Occludin构成TJ的结构基础, 参与TJ相关基因的调控表达[2], 维持脑组织BBB的低通透性[3]。Claudin主要起栅栏和屏障功能, 决定TJ的选择性及强度。ZO-1与Occludin的C-端结合, 将Occludin与细胞骨架连接在一起, 并能识别TJ位置, 传递信号分子[4]。破坏ZO-1与TJ的其他成员的连接, 可改变TJ的结构与功能(图1)[5-6]。

1.3 BBB通透性调控分子

多种生长调控类因子可调节BBB通透性, 在脑损伤、感染性脑膜炎和神经系统炎症等病理变化过程中发挥作用[7-16]。其中, 血管内皮生长因子(vascular endothelial growth factor, VEGF)、基质金属蛋白酶(matrix metalloproteinase, MMP)、一氧化氮(nitric oxide, NO)和内皮素(endothelin, ET)具有增强BBB通透性作用。血管生成素-1(angiopoietin-1, ANG-1)、音猬因子(Sonic hedgehog, SHH)和胰岛素样生长因子-1(insulin like growth factor-1, IGF-1)则具有维持BBB完整性的作用(表1)。



A: BBB的结构组成; B: BMECs间的TJ与AJ分子。

A: structural constitution of BBB; B: TJ and AJ molecules between BMECs.

图1 BBB的结构组成(根据参考文献[5-6]修改)

Fig.1 Structure constitution of BBB (modified from references [5-6])

表1 BBB通透性调控分子及其作用机制

Table 1 Regulatory molecules of BBB permeability and its mechanism

调控分子 Regulator	分子类型 Type of molecule	作用机制 Mechanism	参考文献 References
VEGF	Cysteine knot growth factor superfamily	Induce proliferation, migration and enhance microvascular leakage, regulate angiogenesis, VEGF-induced BBB permeability is associated with increasing matrix metalloproteinase activity	[7]
MMP	Zinc dependent endopeptidase	Degradation of extracellular matrix such as TJ, adhesin, collagen and fibronectin expressed in endothelial cells	[8]
NO	Nitrogen oxide	Endovascular dilators, induce endothelial cell apoptosis	[9-10]
ET	Vasoconstrictive peptide	Promote monocytes through BBB, induce the production of inflammatory mediators	[11]
ANG-1	Secretory glycoprotein	Bind to the tyrosine kinase Tie-2 receptor on endothelial cells and mediate the repair of TJ molecule	[12]
SHH	Hedgehog family glycoprotein	Astrocytes secrete SHH and bind to endothelial cell receptors to promote the formation and integrity of BBB, reduce the expression of proinflammatory factors and leukocyte migration, promote the immune quiescence of BBB	[13]
IGF-1	Insulin family protein	Bind with IGF-1R receptor promotes the proliferation, survival and differentiation of BBB-related cells	[14-15]
APOE	Apolipoprotein family	Regulation of lipid transport and injury repair in brain	[16]

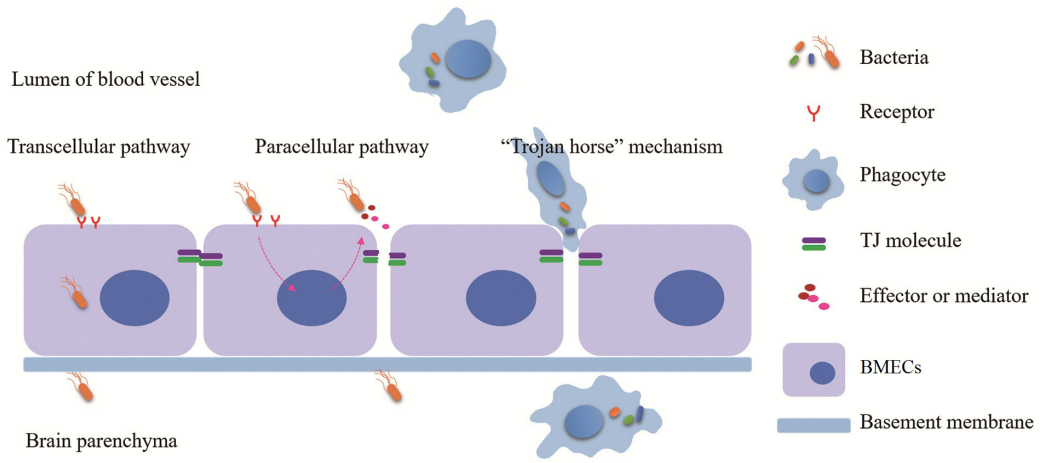


图2 病原菌穿透BBB途径

Fig.2 Mechanisms of bacterial traversal of the BBB

2 病原菌穿透BBB的机制

穿透BBB对于建立CNS感染至关重要, 其相关机制也备受关注。目前, 研究发现的机制包括以下几种(图2)。

2.1 跨细胞途径

病原菌跨细胞途径(transcellular pathway), 即胞吞胞吐途径, 病原菌与内皮细胞近腔侧膜表面受体结合, 介导对细菌的内吞作用, 再通过细胞远腔侧的胞吐作用, 实现跨细胞入侵, 该途径在不破坏TJ的前提下跨细胞穿透BBB。细菌对BMECs的表面结合、跨膜入侵表型决定了该菌的CNS侵袭能力。已证明, 大肠杆菌K1菌株(*Escherichia coli* K1)[17-18]、B族链球菌(Group B *Streptococcus*, GBS)[19]、李斯特菌(*Listeria monocytogenes*)[18]、结核分枝杆菌(*Mycobacterium tuberculosis*)[20]、脑膜炎奈瑟氏菌(*Neisseria meningitidis*)[21-22]和肺炎链球菌(*Streptococcus pneumoniae*)[23-24]等均可通过跨过细胞途径穿透BBB。

2.2 细胞旁途径

细胞旁途径多因内皮细胞间TJ分子遭到破坏, BBB通透性增强, 病原菌通过细胞间隙进入CNS[21]。研究证实, *L. monocytogenes*[18]、*M. tuberculosis*、*N. meningitidis*、梅毒螺旋体(*Treponema pallidum*)等细

菌可通过细胞旁途径迁移穿透BBB[25]。TJ完整性遭破坏的原因通常有以下两个方面: 第一, 细菌分泌的效应因子破坏了TJ分子, 导致BBB渗透性增强; 第二, 细菌的病原相关分子模式(pathogen-associated molecular pattern, PAMP)刺激免疫细胞分泌细胞因子(cytokine)和趋化因子(chemokines)等炎性介质, 引起白细胞浸润, 血管和周围组织损伤, BBB完整性遭破坏。通常情况下, 多数病原菌即可利用跨细胞途径, 又可通过细胞旁途径进入CNS[26]。

2.3 “特洛伊木马”机制

巨噬细胞、单核细胞、多形核中性粒细胞(polymorphonuclear neutrophils, PMN)等吞噬细胞内的细菌, 借助细胞迁移进入BBB的方式被称为“特洛伊木马”机制。BBB通透性增强是允许吞噬细胞通过的前提。已证实, 人体免疫缺陷病毒(human immunodeficiency virus, HIV)可增强外周单核细胞穿透BBB的能力, 致使BBB通透性增强。在HIV阳性的患者中, 脑膜炎发生的比例高于HIV阴性的患者[27]。此外, TJ完整性与否主要影响细胞旁路通道, 很显然, 旁路的破坏对巨噬细胞的迁移是有促进作用的, 如*M. tuberculosis*以及*L. monocytogenes*。Rho家族GTP酶RhoA可通过mDia和ROCK信号级联机制调节细胞骨架蛋白的活化, 调控免疫细胞穿透BBB。最近研究发现, PKC信号通路也参加了BBB通透性的调节, 是介导“特洛伊木马”机制的重要信号通路之一[28]。值得注意的是, 多数病原菌并非只依赖一种机制穿透BBB, 如*L. monocytogenes*既可通过跨细胞途径, 又可通过RhoA介导的“特洛伊木马”机制进入CNS, 导致脑膜炎[29]。

3 典型病原菌穿透BBB的入侵机制

3.1 大肠杆菌K1菌株

E. coli K1是婴儿细菌性脑膜炎的主要原因之一。K1荚膜多糖和*O*-脂多糖是脑膜炎致病的关键因子。该类菌株可在血液中大量增殖, 通过OmpA、I型菌毛等黏附在BMECs表面[30]。随后, *E. coli* K1的细胞毒性坏死因子1(cytotoxic necrotizing factor 1, CNF1)和IbeA参与了入侵过程, 诱导肌动蛋白细胞骨架重排, 触发拉链状包裹机制内化细菌[31]。同时, *E. coli* K1也可通过Ca^{2+}内流激活PKC信号通路, 促进β-连环素(β-catenin)与血管内皮钙黏蛋白(VE-cadherin)解离, 减弱AJ[28,32]。此外, *E. coli* K1特有的IbeA蛋白也可诱导PMN的跨BMECs迁移[33]。最近研究表明, *E. coli* K1可通过劫持BMECs管腔侧Caspr1受体介导其进入内皮细胞。

3.2 链球菌

链球菌的跨细胞途径破坏BBB, 引起急性CNS并发症[34]。其中, 肺炎链球菌(*S. pneumoniae*)通过菌毛的黏附素(rlrA-regulated gene A, RrgA)结合BBB内皮受体、聚免疫球蛋白受体(polymeric immunoglobulin receptor, pIgR)和血小板内皮细胞黏附分子-1(platelet endothelial cell adhesion molecule-1, PECAM-1), 而PECAM-1又作为神经氨酸酶A(neuraminidase A, Nad A)的受体, 参与肺炎链球菌的黏附, 触发转化生长因子-β(transforming growth factor-β, TGF-β)信号级联, 降低屏障完整性, 使得肺炎链球菌穿透BBB, 并破坏BBB[35-36]。而且, 肺炎链球菌可分泌溶血素, 诱导转录辅激活因子Cerb结合蛋白(CERB-binding protein, CBP)的表达, 使细胞释放TNF-α和IL-6, 通过促进细胞凋亡进而提高血脑屏障的通透性[1,35]。

研究表明, B组链球菌与hBMECs直接作用, 穿透BBB并侵染CNS[1]。GBS分泌高毒力GBS黏附素(hypervirulent GBS adhesin, HVGA), 增加对BBB内皮细胞的黏附性, 并分泌溶血素, 破坏BBB屏障功能[37]。另外, GBS还通过诱导型一氧化氮合酶(inducible nitric oxide synthase, iNOS)上调IL-8、ICAM-1和NO的表达水平, 破坏BBB[22,35]。

猪链球菌(*Streptococcus suis*) 2型主要通过细胞旁途径穿透BBB[1,26]。*S. suis*可以黏附并分泌猪溶血素, 刺激BMECs产生IL-6、IL-8、MCP-1等细胞因子, 增加细胞通透性, 诱导BBB的TJ蛋白(ZO-1、Occludin和Cluadin-1)重排, 破坏并扩大细胞间隙, 穿透BBB进入CNS。

3.3 李斯特菌

李斯特菌可通过多种机制进入CNS。(1)细菌表面毒力因子与细胞膜表面蛋白E-cadherin和酪氨酸激酶受体结合, 激活MAPK信号通路, 通过跨细胞、细胞旁途径以及细胞间扩散直接进入BBB[24]。(2)李斯特菌分泌的李斯特菌溶胞素O(listeriolysin O, LLO)可促进其在单核–巨噬细胞内存活; 并且, 李斯特菌通过LLO和细菌磷脂酶PlcA和PLcB使空泡裂解, 胞内菌扩散到胞浆, 进入BBB; 或通过LLO促进内化素C(internalin C, InlC)与IκB激酶复合物(IκB kinase complex, IKKα)亚基互作, 激活NF-κB信号通

路, 降低宿主免疫应答, 进入BBB[35,38]。(3)李斯特菌在颅神经轴突内逆行迁移至大脑[38]。

3.4 脑膜炎奈瑟氏菌

*N. meningitidis*主要在人的鼻咽细胞外定植, 通常无致病性, 但部分菌株可突破黏膜上皮屏障进入血流, 穿透BBB和脑脊液屏障(blood-cerebrospinal fluid barrier, BCSFB), 导致细菌性脑膜炎。菌体表面的荚膜多糖、鞭毛和黏附素等成分有助于逃避免疫杀伤作用。在黏附阶段, 细菌IV型菌毛可与BBB表达的CD147受体结合[35]。鞭毛和Opa蛋白决定黏附的组织具有特异性, 其中, Opa蛋白可结合癌胚抗原相关细胞黏附分子(carcinoembryonic antigen-related cellular adhesion molecule, CEACAM)受体、纤维结合蛋白和/或卵黄蛋白等胞外基质蛋白, 而Opc则可促进Opa与胞外基质蛋白结合, 协助细菌入侵[35,37]。此外, 奈瑟氏菌黏附素A(neisseria adhesin A, NadA)可与人整合素β1亚基、内皮低密度氧化脂蛋白受体1(low-density oxidized lipoprotein receptor 1, LOX1)结合, 在细胞表面形成微菌落, 促进“皮质斑块”形成和细胞骨架重排, 介导细菌内化。*N. meningitidis*通过一系列细胞内信号途径诱导释放MMP-8, 裂解occludin分子, 也可募集Par3/Par6/PKCζ极化复合物, 破坏内皮细胞TJ分子, 增加BBB通透性, 允许细菌从细胞旁途径进入CNS[11,35]。

3.5 肠沙门氏菌

沙门氏菌脑膜炎是典型的肠细菌性脑膜炎, 常引起新生儿或婴儿发病, 发病率虽低, 但死亡率高[39]。鼠伤寒沙门氏菌(*Salmonella enterica* serovar Typhimurium, STm)在颅内定植可引起脑脓肿、脑膜炎和脑脊液多胞症。存活患者复发率高, 且常伴有智力低下、脑瘫、视觉和听觉障碍等神经后遗症[40]。目前, 沙门氏菌脑膜炎的致病机制尚不明确。WICKHAM等[41]通过口服感染建立了STm的小鼠脑膜炎模型, 可被用于沙门氏菌在大脑的感染动力学和自然传播机制的研究。VAN SORGE等[42]通过体外感染模型发现, STm可黏附、侵入并穿透hBMECs, 并可诱导细胞肌动蛋白细胞骨架重排, 说明该菌通过诱导胞吞作用进入细胞。然而与肠上皮细胞内化机制不同的是, 入侵hBMECs的过程却不依赖沙门氏菌致病岛-1(*Salmonella* pathogenicity island-1, SPI-1)编码的3型分泌系统(type 3 secretion system, T3SS)。诱导该过程的效应因子尚待研究发现。此外, STm与BBB互作还可诱导趋化因子IL-8、CXCL-1(chemokine C-X-C motif ligand-1)、CXCL-2(chemokine C-X-C motif ligand-2)与CCL-20(chemokine C-C motif ligand-20)的上调表达, 说明STm感染激活了中性粒细胞和淋巴细胞信号传导和募集。

此外, 本团队通过庆大霉素保护试验和体外BBB感染模型发现, 肠炎寒沙门氏菌(*Salmonella enterica* serovar Enteritidis, SE)可黏附入侵hBMECs, 并可穿透BBB, 说明SE可通过跨细胞和/或细胞旁通路入侵BBB。考虑到沙门氏菌具有较强的吞噬细胞内增殖能力, 并且可刺激BBB上调趋化因子, 募集中性粒细胞和淋巴细胞, 推测SE还可能通过“特洛伊木马”机制穿透BBB(未发表)。此外, 我们的研究表明, 口服感染SE也可导致BALB/c小鼠发生沙门氏菌脑膜炎, 并在大脑内分离到SE和其他易位菌, 说明SE破坏小鼠BBB同时也可能促进了其他细菌的易位(未发表)。

4 问题与展望

目前, 在细菌性脑膜炎的致病机制方面, 跨BBB入侵机制的分子基础研究取得了一定进展, 但病原菌对BBB通透性的调控机制尚不完全清楚, 限制了脑膜炎的预防和临床治疗进展。细菌突破BBB和BCSFB途径的决定因子可以作为新型疗法的分子靶标, 鉴定相关分子机制有利于研发阻断细菌黏附和胞吞作用的拮抗剂, 从根源预防细菌进入CNS。此外, 不同细菌性脑膜炎造成的神经损伤及发病机制有所不同, 在发病初期对病原菌的精准诊断将有助于脑膜炎的治疗。

从病原菌和宿主两方面鉴定BBB渗透性调节因子, 可为CNS靶向给药、靶向药物和疫苗研发提供有价值的参考。新的BBB完整性促进与修复因子、BBB的免疫静息因子的鉴定与开发在CNS感染性疾病的治疗方面应具有重要的临床意义。

随着沙门氏菌肠胃炎和全身感染病例的逐年增加, 沙门氏菌跨BBB感染机制方面也需要引起足够的重视。细菌和宿主细胞的识别机制、参与黏附入侵的效应因子、BBB调控的信号机制等都是要进一步深入研究、明确机制的问题。在小鼠体内模型中, 鉴定CNS入侵的毒力因子、免疫细胞与效应因子及其作用机制也有助于从整体水平阐明沙门氏菌脑膜炎的致病机制。此外, 沙门氏菌感染导致的

肠道菌群结构的改变是否影响脑–肠轴物质交换和BBB通透性调节也是非常值得关注的问题。

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