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Hans汉斯

大肠杆菌K1与血脑屏障细胞致病机制研究进展

包金平*，杨光路#

内蒙古医科大学附属医院儿科，内蒙古 呼和浩特

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摘　要

细菌性脑膜炎是严重危害人类健康的公共健康卫生问题，尤其在儿童甚至是新生儿发病较多，且容易引发神经系统后遗症。大肠杆菌作为细菌性脑膜炎的主要致病病原体，其引起细菌性脑膜炎的发病机制仍未完全明确，病原体与宿主相互作用机制仍有许多学者研究探讨。血脑屏障作为大脑的保护屏障，其通透性改变进而引起血脑屏障结构破坏，大肠杆菌继续定植在脑膜甚至脑实质繁殖引发一系列免疫炎症反应，以此来致病。血脑屏障组成细胞种类较多，并且细胞间也会存在信号分子的交流作用，因此，大肠杆菌细菌性脑膜炎的发病机制极其复杂，理清分子生物水平的作用水平，并提出针对性的预防及治疗手段有非常深远的意义。

关键词

大肠杆菌K1，细菌性脑膜炎，血脑屏障，脑微血管内皮细胞，星形胶质细胞，小胶质细胞，巨噬细胞

Research Progress on the Pathogenic Mechanism of *Escherichia coli* K1 and Blood-Brain Barrier Cells

Jinping Bao*, Guanglu Yang#

Department of Pediatrics, The Affiliated Hospital of Inner Mongolia Medical University, Hohhot Inner Mongolia

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Abstract

Bacterial meningitis is a public health problem that seriously endangers human health, espe-

*第一作者。
#通讯作者。

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cially in children and even neonates, and is prone to cause neurological sequelae. As the main pathogen of bacterial meningitis, the pathogenesis of *Escherichia coli* is still not fully understood, and the pathogen-host interaction mechanism is still being studied by many scholars. As a protective barrier of the brain, the permeability of the blood-brain barrier changes and then causes the destruction of the blood-brain barrier structure, and *Escherichia coli* continues to colonize the meninges and even the brain parenchyma to multiply, triggering a series of immune and inflammatory responses, so as to cause disease. Therefore, the pathogenesis of bacterial meningitis of *E. coli* is extremely complex, and it is of far-reaching significance to clarify the level of action at the molecular biological level and propose targeted prevention and treatment methods.

Keywords

***Escherichia coli* K1, Bacterial Meningitis, Blood-Brain Barrier (BBB), Human Brain Microvascular Endothelial Cells (HBMEC), Astrocyte, Microglia, Macrophage Cell**

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1. 引言

细菌性脑膜炎是细菌引起的脑膜炎症，是全球性的健康卫生问题，发病率约 0.9~80/100,000，幸存者约 20%~60%预后不良，引发慢性神经系统后遗症[1]，该病可引起较重的并发症，如脑水肿、脑室管膜炎、脑出血、脑梗塞等，也会导致较为严重的神经功能缺陷，如视力障碍、行为异常、认知障碍、癫痫等[2]。Ouchenir L.等人的病例研究中，63 例确诊脑膜炎的患者中 37.33%为大肠杆菌[3]，在我国，廖等学者在 44 例确诊细菌性脑膜炎分离出 18 例(40.91%)大肠杆菌感染[4]，回顾新生儿十年病例分析发现，大肠杆菌病原体在细菌性脑膜炎的致病占比有逐年增多趋势[5]，目前已知的大肠杆菌的毒力因子有 OmpA、IbeA、IbeB、yijiP、TraJ、aslA 和 CNF-1 等，大肠杆菌引起细菌性脑膜炎的在血液中形成菌血症后关键一步就是跨过血脑屏障，血脑屏障的各个细胞组成共同参与其中，大肠杆菌的毒力因子也会与血液中的中性粒细胞、巨噬细胞等产生相互作用。

血脑屏障(blood-brain barrier, BBB)由单层内皮细胞组成，周细胞覆盖，星形胶质细胞的末端覆盖基底膜，最外围由基底膜加固[6]。BBB 参与调节血液与大脑之间的信号交流、物质交换，维持中枢神经系统稳态[7]。血脑屏障将大脑与循环血液分开，血脑屏障完整性的破坏是细菌性脑膜炎病理生理学中的标志性事件[8]。血源性细菌可以使用需要病原体内化的跨细胞机制和/或需要紧密连接破坏的细胞旁机制。细菌与脑内皮细胞的粘附是通过细胞旁或跨细胞机制交叉血脑屏障的先决条件[9]。当然，中枢神经系统的保护屏障除了血脑屏障还有脉络丛细胞等，但是有学者的研究表明，大肠杆菌已经侵入血脑屏障时，脉络丛内还尚无大肠杆菌[10]，因此，经血脑屏障的感染途径先于脉络丛，因此，对于大肠杆菌穿过血脑屏障的发病机制有更重要的研究意义。

穿过血脑屏障的过程中需要复杂的宿主－病原体相互作用机制参与[11]。但是关于大肠杆菌引起细菌性脑膜炎的发病机制仍然没有研究完全，并且没有特异性的疫苗预防，并且还存在抗生素耐药的突变株等，本综述旨在于探讨目前的关于大肠杆菌与宿主细胞的相互作用机制以及目前的治疗方法的研究进展以便于更多的了解大肠杆菌的致病机制。

1.1. 脑微血管细胞

脑微血管内皮细胞是血脑屏障重要组成之一，还是血脑屏障物质交换的第一层细胞屏障，其参与大肠杆菌致细菌性脑膜炎的分子机制有较多学者研究，主要分析如下：HB 细胞膜上的 α7nAChR 受体受到大肠杆菌毒力作用后会激活 α7nAChR/JAK2/STAT5 信号通路，诱导了对血脑屏障的破坏，同时通过 α7nAChR 激动剂及抑制剂进一步验证了该受体的作用[12]。另外，大肠杆菌 k1 感染还会促进 SLURP1 的分泌，这是 α7nAChR 的配体，激活信号通路后会引起大肠杆菌侵袭以及中性粒细胞募集，引发更复杂的炎症反应[13]。其中 FimH 毒力因子也可以通过 CD48 和 α7nAChR 复合物来侵袭并募集中性粒细胞，其中涉及 HB 肌动蛋白等细胞骨架结构的破坏相关[14]。同时，大肠杆菌的转录调节因子 YbdO 也会激活大肠杆菌 K1 荚膜的毒力效应来加重对 HB 的侵袭[15]。而且，RpoE 是可直接调控 ompA、cnf1、fimB、ibeA、kpsM 和 kpsF 等致病靶基因，提高了对宿主细胞的适应能力[16]。Rho GTP 酶增加了巨噬细胞对大肠杆菌的吞噬作用，Rho 家族的小 GTP 酶(Rho、Rac1 和 cdc42)可以促进大肠杆菌 K1 入侵，使 HB 的肌动蛋白募集，这与 PAK1 和 PI3K 激活，AKT 磷酸化相关[17] [18]。细胞骨架中间丝的缺失也会使大肠杆菌侵袭减少，中间丝与 α7nAChR 具有相关性，中间丝敲除会引起 α7nAChR 下调，这整体的结果导致了血脑屏障破坏[19]。OmpA 和 Ecgp96 之间的相互作用下调人脑微血管内皮细胞中的过氧化物酶体增殖物激活受体 γ (PPAR-γ)和葡萄糖转运蛋白 1 (GLUT-1)水平，导致屏障完整性破坏和葡萄糖摄取抑制[20]。同时有学者研究烟草烟雾中的尼古丁会减低宿主细胞自噬能力使大肠杆菌侵袭增多，这也与 PI3K/Akt/mTOR 信号通路的激活相关[21]。

1.2. 神经胶质细胞——星形胶质细胞、小胶质细胞

关于星形胶质细胞、小胶质细胞与大肠杆菌 K1 直接侵袭的研究与血管内皮细胞相比较少，但是脑微血管内皮细胞与星形胶质细胞、小胶质细胞之间也存在复杂的信息传递，共同作用导致血脑屏障结构破坏。

大肠杆菌 K1 分泌的 OMVs 刺激小胶质细胞释放促炎因子 TNF-α 激活星形胶质细胞释放趋化因子 CXCL1，进一步促进中性粒细胞表达，中性粒细胞的 CXC 家族趋化因子受体 CXCR1 和 CXCR2，中性粒细胞通过细胞旁和跨细胞途径外渗进入感染部位[22]。脂多糖处理的小胶质细胞组与小胶质细胞联合星形胶质细胞培养组比较，与星形胶质细胞共培养产生的炎症因子更多。小胶质细胞促炎介质诱导反应性星形胶质细胞增生，并且星形胶质细胞也可以通过衍生因子调节小胶质细胞的表型和功能[23]，这两种细胞的相互作用在神经血管单元的结构组成中同样占有重要作用，胶质细胞之间的双向调节作用有助于血管的发育与屏障结构的完整性。CXCR1-CXCR2 轴会引起会引起血脑屏障通透性升高，促进中性粒细胞滞留及跨细胞[24]。小胶质细胞是大脑的免疫哨兵，细菌穿过血脑屏障脂多糖等细菌产物会被小胶质细胞的模式识别受体识别[25]，小胶质细胞释放的因子 NO 会导致神经元损伤，通过 Activin A 激活素可以减少 NO 的释放，减轻神经元的损伤[26]。星形胶质细胞受到小胶质细胞分泌的 Il-1α、TNFα 和 C1q 诱导后会出现功能变化，A1 型星形胶质细胞会产生神经毒性，对部分神经元和少量少突胶质细胞具有杀伤作用，减少 A1 反应性星形胶质细胞的产生有可能会减轻神经系统带的神经毒性作用[27]。同时，有学者找到了一种急性期蛋白 ORM2 参与星形胶质细胞和小胶质细胞之间的新型相互调节介质，ORM2 在反应性星形胶质细胞中高度表达，并且调节小胶质细胞的活化迁移来发挥炎症作用[28]。

1.3. 周细胞

周细胞与内皮细胞、星形胶质细胞等共同分泌衍生的层粘连蛋白等与基底膜等共同形成血脑屏障[29]，如 γ-谷氨酰转肽酶，仅在周细胞分泌，受内皮细胞和星形胶质细胞的调节参与调控渗透性[30]。在

体外血脑屏障模型构建中，周细胞的加入提高了血脑屏障的跨内皮电阻，降低了神经血管单元结构的通透性[31] [32] [33]。周细胞还会分泌中性粒细胞趋化因子和黏附分子等多种分子，可以募集中性粒细胞，并与星形胶质细胞、小胶质细胞等相互作用促进炎症反应[34] [35]，并且周细胞可以介导星形胶质细胞等附着血脑屏障使结构完整[36]。有关周细胞与大肠杆菌 K1 相互作用机制目前研究较少，已报道的在牛原代视网膜周细胞、HBMEC 体外模型中，大肠杆菌 K1 的感染会使周细胞的覆盖减少[37]，但并没有明确大肠杆菌 K1 对周细胞产生黏附、侵袭。也有文献说明，流感嗜血杆菌不会对周细胞直接作用，是首先在大肠杆菌对内皮细胞作用后产生腺苷使周细胞收缩脱失[38]，此外有关寨卡病毒和 HIV-1 病毒直接穿透脉络丛周细胞，并增殖进入脑实质的报道[39] [40]。由此可见，周细胞在大肠杆菌致细菌性脑膜炎的致病机制仍有进一步研究空间。

1.4. 巨噬细胞、中性粒细胞

中性粒细胞、巨噬细胞都属于白细胞，参与机体的免疫及防御作用，在中枢神经系统感染尤其是细菌性脑膜炎的发病机制中，中性粒细胞与巨噬细胞也参与其中，并且与血脑屏障细胞有相互作用参与炎症反应，大肠杆菌的细菌性脑膜炎发病机制中也同样有白细胞的参与。

大肠杆菌的脂蛋白(LPP)会降低 Flic 毒力因子，Flic 减少使中性粒细胞 NADPH 酶活化减低，中性粒细胞不能被激活会使大肠杆菌逃逸，引起更严重的菌血症穿过血脑屏障形成细菌性脑膜炎[41]。大肠杆菌的 cglD 诱导中性粒细胞释放趋化因子 CXCL1、CXCL6 和 CXCL8 以及粘附分子 E-选择素黏附 HB，诱导 NF-κB 通路激活，促进了中性粒细胞对脑微血管内皮细胞的黏附和跨细胞迁移[42]。大肠杆菌 K1 荚膜是一种 PSA 聚集物，与唾液酸结合免疫球蛋白样凝集素(Siglecs)相互作用，在巨噬细胞发挥作用，诱导促炎细胞因子产生，包括 TNF-α、IL-8、MCP-1 和 IL-1β [43]，巨噬细胞和小胶质细胞共同参与信号转导的保护作用，NO 水平增加抑制了 IL-1 的分泌，抑制了本通路对细菌性脑膜炎的保护作用[44]。但是大肠杆菌的 CNF1 毒力因子通过对肌动蛋白丝的抑制来限制细菌内化到巨噬细胞，对侵袭巨噬细胞具有抑制作用[45]。但是大肠杆菌 K1 OmpA (外膜蛋白 A)利用 Fc-γ 受体 I(CD64)结合并进入巨噬细胞，使大肠杆菌在巨噬细胞内存活、繁殖，最终逃逸到血液内，穿过血脑屏障进入中枢神经系统[46] [47]。

2. 治疗新进展

目前诸多学者致力于大肠杆菌细菌性脑膜炎的治疗及预防，大肠杆菌 K1 的减毒菌株删掉了较严重的毒力因子后，保留了跨血脑屏障的能力，并且 Lu J 等学者验证了减毒株的安全性，灭活菌株注射后 72 h 的 bEnd3 细胞血常规、血生化等指标均在正常范围内，有望成为治疗手段之一[48]。同样，无脂多糖大肠杆菌 K1 仿生组装纳米颗粒也是由此启发，利用了外膜蛋白 A 和 gp96 之间的相互作用介导的转胞吞作用跨细胞运输，有望为药物跨血脑屏障运输至大脑内提供一条途径，以重组蛋白 OmpAVac(Vo)PLGA 为主要模式的纳米颗粒也有相关研究[49] [50]，纳米颗粒的抗菌机制可能是阻断了大肠杆菌 K1 中细胞膜的破坏、氧化应激和代谢[51]。也有学者 Gu H 等针对 OmpA 毒力因子探讨 OmpAVac 疫苗的预防大肠杆菌致细菌性脑膜炎的预防性治疗作用[52]。另外针对大肠杆菌 PNAG 毒力因子也设计出了 PNAG 相关的全人源 IgG1 单克隆抗体 F598，已进入 1 期和 2 期人体试验，是预防的关键治疗方法[53]。

另外，有一些药物作用于信号分子相互作用的位点起到了阻断干扰的作用，减少了大肠杆菌穿过血脑屏障。Caspr1 作为 HB 表达的跨膜蛋白，与大肠杆菌 K1 的 IbeA 之间相互作用，该团队学者通过类似 Caspr1 结构的诱导化合物口袋式拦截，干扰其穿过血脑屏障，但是不能起到杀死细菌的作用，但是这一过程明显减轻了中枢神经系统的炎症反应，有助于控制住病情，阻止向更严重的方向进展[54]。鼠李糖乳杆菌上清液(LGG-CM)通过抑制 NF-κB 通路激活、阻断 *E. coli* K1 侵袭和中性粒细胞迁移及维护血脑屏障

完整性来预防 *E. coli* K1 引起的细菌性脑炎[55]。美金刚是宿主细胞 α7nAChR 的阻断剂，可以明显阻断大肠杆菌在 HB 中的存活，同时有利有弊，因为是阻断细胞受体，不能够杀死细胞外的细菌，但是并不会像抗生素一样导致大肠杆菌的耐药性[56]。血管紧张素 II 型受体 1 型(AT1R)与内皮细胞 gp96 相关，gp96 是 HBMEC 中大肠杆菌外膜蛋白 A 的受体，替米沙坦是一种血管紧张素 II 型受体 1 型(AT1R)阻滞剂，有效的阻止了大肠杆菌 K1 侵袭 HB，预防脑膜炎的发作并抑制大脑中性粒细胞浸润和神经胶质细胞迁移[57]。

3. 总结与展望

综上所述，大肠杆菌 K1 细菌性脑膜炎的致病机制十分复杂，需要血液内白细胞如中性粒细胞、巨噬细胞的参与，更需要跨过血脑屏障，尤其是脑微血管内皮细胞，神经胶质细胞的小胶质细胞作为中枢神经系统的免疫哨兵更是参与了重要的免疫应答，引发炎症反应，星形胶质细胞、周细胞也会产生免疫应答，他们共同发挥作用导致血脑屏障通透性增高，使免疫逃逸的大肠杆菌穿过血脑屏障，他们可以通过跨细胞途径如穿过脑微血管内皮细胞，也会通过这些炎症反应破坏细胞间的紧密连接蛋白，使血脑屏障通透性改变，通过细胞旁途径侵袭。同样，目前针对已明确的致病机制都有了相应的阻断剂、疫苗、纳米材料等应用，正如 PNAG 相关的全人源 IgG1 单克隆抗体 F598，已进入 1 期和 2 期人体试验，相信在不久的将来，有关于大肠杆菌细菌性脑膜炎的预防及治疗手段都会有一个质的飞跃。

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