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Hans汉斯

拟杆菌对碳青霉烯类抗菌药物耐药性及耐药机制研究进展

侯美玲，王继春*

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

拟杆菌是引起机会性内源性感染的重要病原体，碳青霉烯类抗菌药物是目前治疗拟杆菌感染的重要抗菌药物之一，近年来，拟杆菌对碳青霉烯类抗菌药物的耐药情况愈加严峻，在不同地区、不同人群间存在显著差异。耐碳青霉烯类拟杆菌可以通过cfiA基因介导碳青霉烯酶的生成、青霉素结合蛋白的构象改变、外膜蛋白和脂多糖的构成改变、外膜孔蛋白数量的减少或缺失及内源性外排系统突变及过度表达等导致碳青霉烯的耐药。了解耐碳青霉烯类拟杆菌的耐药性及耐药机制，对于防控耐药基因的广泛传播、指导临床用药等方面有重要价值。

关键词

拟杆菌，碳青霉烯类抗菌药物，耐药性，耐药机制

Research Progress in Bacteroides Resistance to Carbapenems and Their Resistance Mechanism

Meiling Hou, Jichun Wang*

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

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Abstract

Bacteroides is an important pathogen that causes opportunistic endogenous infections, and carbapenems are one of the important antibacterial drugs for the treatment of bacteroides infection.

*通讯作者 Email: wangjichunemail@126.com

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In recent years, the resistance of bacteroides to carbapenems has become increasingly severe, and there are significant differences between different regions and different populations. Carbapenem-resistant Bacteroides can induce carbapenase resistance through cfiA gene mediated generation of carbapenase, conformational change of penicillin-binding protein, composition change of outer membrane protein and lipopolysaccharide, reduction or loss of outer membrane porin, mutation and overexpression of endogenous efflux system, etc. Understanding the drug resistance and mechanism of carbapenem-resistant Bacteroides is of great value for preventing and controlling the widespread spread of drug resistance genes and guiding clinical drug use.

Keywords

Bacteroides, Carbapenem Antibiotic, Antibiotic Resistance, Resistance Mechanism

1. 引言

人体结肠菌群主要由厌氧菌构成，其中 25%是拟杆菌属细菌(Bacteroides) [1]。拟杆菌属细菌是一类革兰氏染色阴性的专性厌氧菌，无芽孢、无鞭毛、耐胆汁，能形成荚膜。拟杆菌通过阴道分娩垂直传递，新生儿肠腔内多于出生 10 天左右出现拟杆菌[2]，在生命的最早阶段，拟杆菌属细菌即成为肠腔菌群的重要组成部分[3]，通过参与机体营养代谢、生长发育、免疫等过程对宿主产生有利影响[2] [4]。拟杆菌属包括约 60 个种类，人体肠腔内存在多种拟杆菌属细菌，如脆弱拟杆菌、卵圆拟杆菌、普通拟杆菌、单形拟杆菌、多形拟杆菌及粪拟杆菌等，其中以脆弱拟杆菌最为常见[5]。

当机体出现免疫功能紊乱或肠道菌群失调时，肠腔内细菌可发生移位，引起拟杆菌内源性感染，在长期应用广谱抗菌药物、糖皮质激素及免疫抑制剂的人群中尤为常见。发生肠道细菌移位后，基于自身的结构及毒力特征[6]，拟杆菌感染常引发机体各部位脓肿形成，包括腹部、腹部、脑、肝脏、骨盆和肺等[7] [8] [9] [10]。通过改变自身结构，拟杆菌能在一定程度上避免宿主的免疫反应[11] [12]，且因其对多种抗菌药物高度耐药[13]。在临床诊疗中，拟杆菌感染及死亡率极高[14]，有报道称[15] [16]，脆弱拟杆菌的死亡率超过 19%。

碳青霉烯类抗菌药物是除甲硝唑外治疗拟杆菌感染最有效的抗菌药物之一[17] [18]，临床实践中最常应用的碳青霉烯类药物包括亚胺培南、美罗培南、厄他培南和多尼培南，其中，多尼培南对脆弱拟杆菌的抑菌效果与亚胺培南和美罗培南相似，且比厄他培南的抑菌效果高 2~4 倍[19] [20]。近年来国内外报道中，拟杆菌对碳青霉烯类药物的耐药性总体呈上升趋势，且在不同地区、人群中存在显著差异，为拟杆菌感染的临床诊疗带来了严峻挑战。因此，持续监测拟杆菌对碳青霉烯类抗菌药物的耐药情况，对于防控耐药基因的广泛传播、指导临床用药等方面均有重要价值。本文就拟杆菌对碳青霉烯类抗菌药物的耐药性及耐药机制进行了综述。

2. 拟杆菌对碳青霉烯类抗菌药物的耐药性

1986 年，美国报道了拟杆菌属分离株对亚胺培南表现出高水平耐药性，值得注意的是，这些分离株对研究中其他所有 β-内酰胺类抗菌药物均表现出高度耐药性[21]。1990 年，日本岐阜大学研究报道中，拟杆菌对碳青霉烯类抗菌药物的耐药率为 1.38% [22]，美国一项多中心研究报道称[23]，对

1990~1996 年间 4000 多株脆弱杆菌临床分离株进行抗菌药物敏感性试验，结果显示耐药率最低的是碳青霉烯类抗菌药物(亚胺培南和美罗培南)，1995 年只分离出 1 株耐药株，1996 年没有分离到耐药株。2000 年，欧洲对 1284 株拟杆菌进行药敏监测，亚胺培南和美罗培南的耐药率分别为 0.8%和 1.3% [7]。2004 年，Sóki 等人研究的显示[24]，碳青霉烯类耐药拟杆菌分离株在英国和匈牙利分别为 3.8%和 2.8%。2003~2008 年，土耳其对 66 株来自不同部位的脆弱拟杆菌临床分离株进行抗菌药物敏感性试验，其对亚胺培南及美罗培南的耐药率分别为 0.6%和 7.5% [25]。总的来说，大多数国家和地区在上述时期内所报道拟杆菌属细菌对碳青霉烯类药物的耐药率均不超过 10%，部分地区甚至无耐药菌株检出。近十年来，拟杆菌对碳青霉烯的耐药率明显上升，且存在显著地域差异。加拿大一项多中心研究报道[26]，2010~2011 年间 9 家医院共收集 387 例脆弱拟杆菌，其中仅 2 个分离株对亚胺培南耐药，对这些菌株进行药物敏感性监测，其对亚胺培南的敏感性为 97.7%，对厄他培南为 92.0%，多尼培南为 87.3%，总体结果显示这些分离株对碳青霉烯类抗菌药物耐药性均较低。从 1973~1980 年到 2010~2015 年，丹麦一项研究中脆弱拟杆菌对美罗培南耐药率从 0%上升到 2.5% [27]。2014~2019 年，日本对 50 株来自血培养的脆弱拟杆菌临床分离株进行抗菌药物敏感性试验，其对亚胺培南及美罗培南的耐药率高达 54%和 100% [28]。2014~2016 年，匈牙利对 233 株来自不同部位的脆弱拟杆菌药敏试验结果显示，其对美罗培南的耐药率为 15.02% [29]。我国近年来加强了对拟杆菌耐药性的监测，部分报道中耐药率从 0%上升至 29.5% [30] [31]。2017~2019 年，我院王俊瑞等人对 80 株来自不同部位的脆弱拟杆菌药敏试验结果显示，其对亚胺培南及美罗培南的耐药率高达 25.1%和 22.6% [32]。在抗菌治疗过程中，对各类广谱抗菌药物具有高度耐药性的拟杆菌多药耐药(MDR)分离株时有报道[33] [34] [35]，特别是在有抗菌药物应用史的病例中[36]，极大的增加了拟杆菌感染的治疗难度。2017 年，丹麦一项研究对其收集来自粪便标本的 359 株脆弱拟杆菌进行了抗菌药物敏感性测定，结果显示其对美罗培南的耐药率为 5%，既往接触碳青霉烯类药物，与其耐药具有相关性。2019 年，复旦大学附属华山医院抗生素研究所调查了 44 株脆弱拟杆菌耐药情况，其对亚胺培南、美罗培南、厄他培南的耐药率分别高达 18.2%、29.5%、22.7% [30]。不同地域耐药性的显著差异，可能是由于各地抗菌药物的应用方案各有不同，也可能是由于拟杆菌分离株遗传特征存在差异[37]。

此外，在过去的报道中，耐碳青霉烯拟杆菌分离株主要为脆弱拟杆菌，而目前研究发现，检查粪便微生物种其他拟杆菌属菌株也存在很大比例对碳青霉烯类耐药。Sóki 等人研究发现，约 1%的可培养拟杆菌对碳青霉烯类药物具有耐药性[38]。这也提示我们，不应忽视对除脆弱拟杆菌外的其他拟杆菌进行耐药性监测。

3. 脆弱拟杆菌对常用抗菌药物的耐药机制

拟杆菌对碳青霉烯类抗菌药物产生耐药存在不同机制[39]。目前已经确定，生成可水解该类药物的碳青霉烯酶是其最主要的耐药机制，该酶由 cfiA 基因编码[40]。其他可能的耐药机制包括：青霉素结合蛋白的构象改变、外膜蛋白和脂多糖的构成改变、外膜孔蛋白数量的减少或缺失[40]。内源性外排系统突变及过度表达等[34] [41]。

值得注意的是，即使没有抗生素的选择压力，耐药基因的遗传元件仍可保持长期稳定。维持这种稳定性可能的机制是，将抗生素耐药基因与为细菌提供有效定殖的酶进行整合，使其保持在同一整合子中[42]。

YAMAZOE 等人的研究报道中，在 1992 年至 1994 年间分离的脆弱拟杆菌耐药株(亚胺培南的 MIC 为 32 mg/ml)既未检测到 cfiA 基因及其特定插入序列(IS)，也未检测到金属 β-内酰胺酶活性[43]，这也提示我们拟杆菌对碳青霉烯类药物产生耐药性可能存在其他机制。

3.1. cfiA 基因编码碳青霉烯酶的产生

1990 年，RASMUSSEN 等人对脆弱拟杆菌的 B 类 β-内酰胺酶编码基因 ccrA 进行了克隆与测序[44]，发现它存在于多种不同细菌中，与蜡样芽孢杆菌的已知耐药序列具有超过 33%的同源性。ccrA 基因在大肠杆菌内被发现，后更名为 cfiA 基因[45]。cfiA 基因在金属因子 Zn^{2+}的辅助下，编码产生碳青霉烯酶，水解碳青霉烯类药物，从而引起耐药。

拟杆菌所携带的 cfiA 基因表达与否，可能与该基因的上游的特定插入序列(IS)有关。细菌插入序列(IS)是许多细菌染色体的组成部分，属于可移动的双链 DNA 元件，通常只编码参与转位活性的蛋白质。这些插入序列(IS)元件可引起基因组突变和重排，促进基因获取，并通过形成复合转座子来动员 DNA 片段[46]。这些元件的存在或移动可能影响细菌致病性或毒力[47] [48]，以及抗生素的耐药性[49]，并能调节特定基因的表达。目前，IS 942、IS 1186、IS 1187、IS 1188、IS 612、IS 613、IS 614、IS 615、IS 616、IS 4351 与拟杆菌 cfiA 基因的表达相关[50] [51] [52]。

1991 年，RASMUSSEN 发现了一种新的脆弱拟杆菌插入序列 IS 942，并进行了鉴定、克隆和测序[53]。该元件的长度为 1598 个碱基对，它的侧翼是一个 15 碱基对的不完全反向重复序列，并包含一个大开放阅读框，可以编码 430 氨基酸的蛋白质。IS 942 整合在脆弱拟杆菌 ccrA 基因的起始密码子上游 19bp 处，为 ccrA 基因提供转录起始信号。Podglajen (法国，1994 年)等人通过将可能的“耐药因子”转移到碳青霉烯敏感菌株中，探讨 cfiA 沉默基因激活的机制[49]，结果显示，碳青霉烯敏感菌株均突变为高度耐药表型，沉默的 cfiA 基因被激活，其编码的金属 β-内酰胺酶活性在基础水平上增加了 100 倍。沉默的 cfiA 基因被激活，与该基因上游的核糖体结合部位插入序列 IS 1186、IS 1187、IS 1188 相关，这些元件为耐药基因的高效转录提供了启动子，这些启动子要么完全由 IS 元件携带，要么由 IS 和目标序列之间的杂交序列产生[49]。IS 1186 共有 1.3 kb，有两个开放阅读框，编码 41.2 kDa (0RF1)和 22.5 kDa (0RF2)的蛋白质，这些蛋白与 IS 插入序列元件的开放阅读框架或 DNA 重复序列中编码的蛋白质具有同源性。IS 1187 全长 1026 bp，有 21 bp 的反向重复序列，包含一个主要的开放阅读框，可编码 326 氨基酸蛋白质，分子大小为 37.5 kDa，终止密码子位于其右侧的反向重复序列内。IS 1188 全长 1691 bp，有 17 bp 的反向重复序列，包含两个主要的开放阅读框，可编码 448 氨基酸蛋白质，分子大小为 52.5 kDa。IS 1186 插入后转录由 IS 1706 右端的启动子驱动，每个基因组中检测到 3~14 个 IS 1186 拷贝。而 IS 1187 及 IS 1188 的插入都发生在 cfiA 基因起始密码子上游约 90 bp 的位置，非常接近已知或怀疑 cfiA 基因激活启动子的位置[54]。

Sóki 等人分析了来自美国、匈牙利和科威特的耐亚胺培南、cfiA 阳性的脆弱拟杆菌分子特征，有 5 株在其耐药基因上游没有特定序列(IS)插入，但可产生碳青霉烯酶，提示 cfiA 基因可能存在其他活化机制[55]。

不同亚型的 cfiA 基因编码产生不同碳青霉烯酶，其种类及对药物的水解能力各有不同。按照其一级分子结构的分子分类法，碳青霉烯酶可分为 A、B、D 三类，其中以 B 类金属-β 内酰胺酶介导耐药最为常见，该酶由 cfiA 基因编码，以 blaNDM (blaNDM-1~bla NDM-41)、bla IMP (bla IMP-1~bla IMP-91)、bla VIM (blaVIM-1~blaVIM-79)、blaGIM (blaGIM-1~blaGIM-2)和 blaSPM 型为主，需要金属锌作为其活化中心。Ayala 等人对大肠埃希菌 PBP3 基因的同源基因(编码蛋白 PBP2Bfr 的 pbpBBfr)和拟杆菌 ccrA (cfiA)基因进行了测序，探讨分析 PBP2Bfr 和金属内酰胺酶在亚胺培南耐药机制中的作用，结果显示，不同菌株 PBP2Bfr 的氨基酸序列存在差异，与亚胺培南结合亲和力最高的 PBP 为 PBP2Bfr [56]。

此外，与其他细菌一样，拟杆菌属细菌普遍具有多种移动遗传元件，包括质粒、转座子、接合转座子等，它们都与抗菌药物耐药基因的转移密切相关[57]。目前，拟杆菌属细菌的质粒上已发现多种不同类

别抗生素的耐药基因，在临床分离株的 6.4 kb 质粒上发现了 cfiA 基因[58]。此外，由于一个菌株可以积累多个接合转座子，菌株中存在多于一个拷贝的接合转座子会导致反式激活。因此，理论上讲，环境中积累的携带耐药基因的接合转座子越多，这些基因向其他菌种的转移也会随之增加，抗生素的耐药性将不断上升[59]。

3.2. 青霉素结合蛋白的构象改变

在脆弱拟杆菌的耐药菌株中观察到，80 kDa 青霉素结合蛋白(PBP)对亚胺培南的亲和力降低[60]。PBP 2 表达水平降低与鲍曼不动杆菌[61]对碳青霉烯类抗菌药物的敏感性降低有关。PBP 2 对亚胺培南亲和力降低可能是奇异变形杆菌对亚胺培南耐药的原因[62]。在大肠杆菌中，PBP 2 的突变已被证明与亚胺培南易感性降低相关，但与美罗培南无关，因为美罗培南也可以结合 PBP3 在一些脆弱拟杆菌菌株中[63]，PBP2Bfr 亲和力的菌株差异可能与低水平的亚胺培南耐药性有关。一些菌株对亚胺培南耐药性的增加被认为是由于脆弱芽孢杆菌中缺乏 PBP6Bfr [64] [65]。其中，主要是 PBP 1 和/或 PBP 2 的改变，大肠杆菌 PBP 3 基因的直系同源物 pbpBBfr，编码蛋白质 PBP2Bfr 与亚胺培南的结合有关[56] [65]。青霉素结合蛋白(PBPs)的改变已被研究为某些细菌对碳青霉烯耐药的机制。

3.3. 外膜孔蛋白数量的减少或缺失

拟杆菌外膜孔蛋白的变化也是目前可能的耐药机制之一。细菌的外膜孔(OMPs)是一种底物特异性结构，氨基酸、小肽和一些抗生素(包括碳青霉烯类抗菌药物)经其进入细菌细胞。降低 OMPs 的表达或修饰可以降低细菌对这些抗生素的敏感性[66] [67]。目前有报道称，45 kDa 类孔蛋白可能与脆弱拟杆菌耐药性相关[68]，而 70 kDa 孔蛋白可能与对 β-内酰胺类药物的耐药性相关[69]。然而，迄今为止，外膜孔蛋白与抗生素耐药性之间仍无明确相关性的证据。

3.4. 外膜蛋白和脂多糖的构成改变

脂多糖已被证明影响细菌外膜的整体通透性，并与孔蛋白通道形成一系列屏障[70] [71] [72]。通透性降低，伴随孔蛋白含量的改变，已被证明是拟杆菌的耐药的机制之一[73]。Edwards 等人[74]对脆弱拟杆菌进行脂多糖和外膜蛋白检测，探索其结构特征，结果发现产金属内酰胺酶的菌株外膜蛋白和脂多糖的构成与未检出该酶的菌株有明显不同，反映了两者存在屏障通透性的差异。

3.5. 内源性外排系统突变及过度表达

目前拟杆菌对大多数抗菌药物表现出高度耐药，外排泵的过度表达已被证明是是其耐药的主要机制之一[75] [76]。RND 和 Mate 两种类型的外排泵被认为是导致抗菌药物耐药的主要结构，通过利用 ATP 能量或质子动力(PMF)，将对菌体有害的化合物从细菌细胞中泵出[77] [78]。有研究表明，RND 外排系统可能是革兰氏阴性菌产生多重耐药性的主要原因之一，RND 外排系统是抗菌药物和有毒物质的运输器，其结构包括接头蛋白、膜融合蛋白和细菌外膜中的通道[79]。革兰氏阴性菌的外排系统一般有一个共同的基础结构，包括内膜转运蛋白、外膜通道和周质辅助蛋白。在这个组织中，外排泵通过内膜和外膜，从而使底物从细胞质直接输送到外部环境成为可能[80] [81] [82]。目前，在拟杆菌中鉴定出 16 个 RND 家族外排泵[80] [81] [82] [83]。抗菌药物的联合使用，会诱导拟杆菌多种外排泵过度表达，进而导致多重耐药[84]。Pumbwe [85]等人通过测定外排泵基因的转录产物，检测脆弱拟杆菌 RND 家族外排转运系统(BmeABC1-16)的表达和功能，结果显示，除 bmeB9 外，其余外排泵均有表达，ADB77 BmeB3 和 ADB77 Bme、B1 Bme、B3 Bme、B12 对 β-内酰胺类、氟喹诺酮类的敏感性分别增加 3 倍、5 倍。抗菌药物的最小抑菌浓度(MIC)也有所增加，其中氨苄西林增加 2.6 倍、头孢哌酮增加 3.4 倍、头孢西丁增加 1.8 倍、

四环素增加最为显著，为36.4倍，表明BmeB在脆弱拟杆菌中普遍表达。该研究证实，至少有七个BmeB外排泵可有效排出抗菌药物，其中四个BmeB外排泵与拟杆菌耐药性的形成密切相关。

已有研究表明，Bme-RND家族外排转运系统的运行模式和转录水平取决于分离株的临床来源。即使来自同一个体的不同解剖部位(如血液、脓肿和粪便等)的细菌分离株，也显示出不同的外排泵表达模式[83]。当脆弱拟杆菌暴露于生理水平的胆盐(0.1%~1.3%)后，bme 泵基因的表达也会随之变化。因此，Bme-RND家族的外排系统可能通其他机制使脆弱拟杆菌在胆盐存在下的生存下来。因此，接触胆盐会增强对抗菌药物的耐药性，并可能影响脆弱拟杆菌的发病。

4. 总结

大多数拟杆菌对碳青霉烯类抗菌药物仍较为敏感，但目前已出现敏感性下降及耐药菌株的相关报道，这也提醒我们，在临床工作中，应加强对拟杆菌耐药性的监测，合理使用特殊抗菌药物，严格把握用药指征，避免耐药基因通过移动遗传元件在各菌种中广泛传播。

拟杆菌作为耐药率最高的厌氧菌之一，产生耐药性的机制也最为复杂。不仅如此，拟杆菌携带多种毒力相关的致病岛[86] [87] [88]，可通过“基因共享”向肠道内其他菌种进行水平传递[89] [90]，这些基因编码多种毒力因素，且保持长期稳定，包括对抗菌药物耐药、菌株高粘附性、抑制宿主防御及外排泵等。拟杆菌耐药性的增长，不仅为其临床感染诊疗带来了严峻挑战，更可能诱发耐药基因在其他菌种中的传播，使肠道菌群成为各种耐药因子的储存库[90]。

拟杆菌属细菌对碳青霉烯类抗菌药物耐药主要与cfiA基因编码的B类金属-β内酰胺酶的生成密切相关，此外，目前存在cfiA阳性的亚胺培南耐药拟杆菌，其耐药基因上游没有特定序列(IS)插入，但仍能产生碳青霉烯酶从而导致耐药，这些分离株的存在证实[91]，至少存在两种cfiA基因激活机制[92]。其他可能的耐药机制包括：青霉素结合蛋白(PBP)亲和力改变、外膜孔蛋白的变化、外排系统的过度表达等。拟杆菌对碳青霉烯类等药物耐药机制方面的进一步深入研究，包括开展对拟杆菌耐药性的定期监测[93]、规范抗菌药物的使用、抑制外排系统、在耐药基因激活前根除临床环境中携带沉默cfiA基因的拟杆菌等，将会为控制临床感染、研发新型抗菌药物等提供思路。

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