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CR-hvKP耐药毒力协同进化与治疗策略

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摘　要

肺炎克雷伯菌是社区和医院重要的致病病原菌，其多重耐药问题日益严重。耐碳青霉烯类肺炎克雷伯菌(Carbapenem-Resistant *Klebsiella pneumoniae*, CRKP)与高毒力肺炎克雷伯菌(Hypervirulent *Klebsiella pneumoniae*, hvKP)的感染率持续攀升，对公共卫生领域造成了重大威胁挑战。这两类菌株的特征正在逐渐融合，催生出同时具备碳青霉烯类耐药性和高毒力表型的CR-hvKP。其形成的核心机制在于耐药与毒力的协同进化，通过遗传、生理及宿主微环境等多层面的相互作用，成功突破了传统的适应性代价限制。本文围绕CR-hvKP关于耐药性与毒力协同进化的核心机制展开综述，同时探讨了临床应对的新型治疗策略，以期为阐明CR-hvKP进化规律、遏制其传播及开发新型靶向治疗方案提供关键理论支持。

关键词

肺炎克雷伯菌，碳青霉烯类耐药，高毒力，协同进化，治疗策略

Co-Evolution of Resistance and Virulence in CR-hvKP and Clinical Strategies

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Abstract

***Klebsiella pneumoniae* is an important opportunistic pathogen, and the public health crisis caused by the integration of multidrug resistance and hypervirulence is becoming increasingly severe. The characteristics of Carbapenem-Resistant *Klebsiella pneumoniae* (CRKP) and Hypervirulent Klebsiella**

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pneumoniae (hvKP) are gradually converging, giving rise to the CR-hvKP superbug with both carbapenem resistance and hypervirulent phenotypes. The core of its formation is the co-evolution of resistance and virulence traits, which breaks through the traditional limitation of adaptive cost through multi-dimensional coupling such as genetic recombination, phenotypic regulation, and host microenvironment adaptation. This article systematically reviews the core mechanisms of the co-evolution of resistance and virulence in CR-hvKP, as well as the innovative strategies and practical dilemmas of clinical response, aiming to provide key theoretical support for clarifying the evolutionary rules of CR-hvKP, curbing its spread, and developing new targeted therapeutic regimens.

Keywords

***Klebsiella pneumoniae*, Carbapenem Resistance, Hypervirulence, Co-Evolution, Therapeutic Strategy**

1. 引言

肺炎克雷伯菌(*Klebsiella pneumoniae*, Kp)作为一种临床上常见的革兰氏阴性条件致病菌，广泛存在于自然环境和人体肠道中，是导致血流感染、脑膜炎及肝脓肿等高致死率感染的主要病原体[1]。其致病的毒力因子主要包括菌毛、荚膜、脂多糖(LPS)及铁载体等[2]。在抗生素选择性压力的驱动下，碳青霉烯类耐药的肺炎克雷伯菌(CRKP)和高毒力肺炎克雷伯菌(hvKP)在全球范围内的迅速蔓延，已成为严峻的公共卫生新威胁[3]。传统理论认为，细菌获得耐药性的同时常伴随着毒力减弱的适应性代价[4]。然而，高水平的耐药性与高毒力表型正快速融合到于同一菌株，催生出致命的“超级细菌”——耐碳青霉烯类高毒力肺炎克雷伯菌(CR-hvKP) [5]。这类菌株表现出对碳青霉烯类和作为最后防线的多黏菌素类的交叉耐药性。基因组学研究显示，质粒介导的接合转移及插入序列驱动的基因组重塑是促成协同进化的核心机制。KP 还可以通过靶点修饰、生物膜形成等协同机制进一步强化耐药性和毒力，极大地限制了临床治疗方案的选择。因此，深入了解其分子机制对于临床有效防控至关重要。本文将重点阐述 CR-hvKP 耐药性与毒力协同进化的重要机制，并探讨针对性的临床治疗策略，为该类超级细菌的防控提供参考依据。

2. 基因水平转移与荚膜

耐药基因与毒力基因常位于质粒、噬菌体这种可移动遗传元件上。CRKP 获得毒力因子或者 hvKP 获得碳青霉烯类耐药性是协同进化的普遍机制[6]。大片段质粒的共存可能导致显著的代谢负担，但细菌可以通过适应性进化策略来抵消这种适应性成本[7]。在插入序列 IS26 等可移动元件介导下，原本独立的耐药质粒与毒力质粒可发生同源重组，形成耐药–毒力杂合质粒[8]。例如，中国主要流行的 ST11-KL64 型菌株常携带 IncFII 型杂合质粒，该质粒同时包含 blaKPC-2 碳青霉烯酶基因和完整的 iucABCD 毒力基因簇[9]。Jin 等通过长读长测序技术解析了一株 ST11CRKP 中 pKPC-2 与毒力质粒的融合过程，证实 IS26 在质粒融合中的核心作用，且该融合质粒赋予细菌耐药性和增强毒力而无显著适应性代价[10]。IncFIIK34 型质粒通过强化接合转移装置的表达，高效转移进入 hvKP，同时上调 blaKPC-2 的拷贝数与转录水平，并协助毒力质粒的传播，从而在抗生素压力下赋予宿主菌显著的生长优势[11]。辅助型质粒 IncFIB (Mar)

在 CR-hvKP 发挥着更为灵活的载体角色，其通过提供接合转移所需的 IV 型分泌系统，协助非接合型巨型毒力质粒跨越菌株屏障[12]。mcr 基因与毒力基因的共定位现象进一步促进了这种协同作用。携带 mcr-1、mcr-8 或 mcr-9 的 IncX3、IncFII 及 IncHI2 型多黏菌素耐药质粒可能会装载 rmpA 与 iucA 等关键毒力决定簇[13]。这种遗传配置使多黏菌素耐药–高毒力的复合表型能够通过单次接合事件实现水平传播，从根本上改变了耐药性与毒力进化关系，对依赖多黏菌素作为最后防线的临床治疗策略构成了关键性挑战。

荚膜多糖(CPS)作为 KP 抵御宿主免疫的核心屏障，主要由 wcaJ、wzc、wza 等基因簇共同调控，其机制主要是通过构建物理屏蔽层阻断宿主识别而逃避免疫吞噬[14]。插入序列可以通过调控荚膜的表达，推动耐药基因和毒力基因的融合。IS5 与 ISKpn26 及 ISKpn74 等插入序列通过靶向插入荚膜合成关键基因，驱动细菌在“无荚膜–高接合”与“有荚膜–高毒力”两种状态间可逆的切换[15]。在小鼠肠道长期定植模型中证实，无荚膜突变株因暴露表面抗原而被 LOX-1 介导的吞噬作用大量清除，导致细菌负荷显著下降，无法诱导系统性炎症反应，定植能力严重受损；但在长期定植过程中，部分菌株通过体内 IS5 元件通过自发切除恢复了 wcaJ 基因编码序列，重新获得荚膜合成能力及高毒力表型[14]。此外，荚膜进化可能会促进肺炎克雷伯菌的耐药性和毒力协同作用。在 ST23-K1 菌株中，插入序列元件插入 wcaJ 会导致荚膜合成量减少、毒力降低；但 blaKPC-2 质粒的结合频率会相对提高，进而使菌株同时获得高毒力和高水平的碳青霉烯类耐药性[15]。这种 IS 介导的荚膜相变明显提高了耐药质粒与毒力质粒的接合转移效率，导致多耐药和高毒力基因的快速融合，同时增强了细菌的生长速度和生物膜形成能力，提升其环境适应能力。

3. 外排泵与双组份系统的调控

在肺炎克雷伯菌中，外排泵系统与双组份调控系统(TCS)是调节多黏菌素耐药性的重要机制，是细菌生存和进化的重要策略。RND 家族外排泵 AcrAB-TolC 对细菌生理稳态的维持发挥多重功能。研究表明，acrA、acrB、tolC 基因单独缺失会导致抗生素外排能力下降，并显著降低质粒接合转移频率[16]。外排泵过表达通过激活应激应答因子 RpoS，上调荚膜合成(wza、wzb)与铁摄取(iucA、fepA)相关基因表达，间接促进多种耐药与毒力基因的协同表达[17]。双组份系体系的调控作用同样具有显著的效果。PhoPQ 系统是感知环境刺激(如阳离子抗菌肽、低 Mg^{2+}浓度)的关键传感器，其激活通过 LPS 脂质 A 修饰(如氨基阿拉伯糖添加)介导多黏菌素耐药，同时参与了调控铁代谢等相关毒力因子表达[18]。在限制性 Mg^{2+}环境中，PhoQ 自身磷酸化并激活 PhoP，再通过调控下游靶基因网络影响细菌在宿主内的适应性，但其对铁载体合成基因的直接调控机制尚需进一步阐明[19]。CrrAB 系统也具有双重调控功能。McConville 等通过 CRISPR-Cas9 系统对临床 CRKP 分离株的等基因突变研究显示，crrB 错义突变能够诱导明显高于 mgrB 缺失的高水平多黏菌素耐药，还可以通过激活磷酸戊糖途径(PPP)增强细菌的毒力。crrB 与 mgrB 双突变株可以表现出叠加效应，其感染死亡率显著高于任一单突变株，尽管其在体外表现出生长适应性代价。[20]。这种看似矛盾的高毒力–低适应表型源于碳代谢重编程——PPP 的激活为 LPS 生物合成提供了必需的 NADPH 和碳中间体，同时转录组分析显示双突变株中荚膜调控基因 barA 和 rcsA 显著上调。这些研究共同探索了双组份系统突变如何通过“耐药–毒力”双重调控重塑细菌的宿主适应策略，为理解 CR-hvKP 的临床威胁提供了机制基础。

4. 微环境选择压力

宿主微环境内抗生素压力与免疫应答的协同作用，共同推动耐药与毒力表型的协同进化。碳青霉烯类抗生素的直接杀菌作用筛选出耐药的突变体，通过诱导耐药基因的表达间接促进铁载体及荚膜合成基因的表达，从而在资源竞争层面驱动毒力因子的协同富集[21]。宿主免疫系统的吞噬清除压力推动 CR-

hvKP 通过精细调控荚膜合成，平衡耐药性与毒力的适应性。这种双重适应性促进细菌在微环境中表现出更强的生存和定植能力。Song 等通过纵向追踪同一患者体内的 ST11-KL64 型 CR-hvKP 种群动态，发现早期的高黏度菌株通过合成大量荚膜多糖来抵抗吞噬作用而逃避免疫清除；在持续免疫压力作用下，上游 ISKpn26 插入序列的缺失导致荚膜基因表达下调，菌株转变为低黏度表型，通过增强黏附与生物膜形成能力实现长期定植[22]。这种表型的转变表明了 CR-hvKP 在宿主内通过牺牲急性毒力换取持续感染能力的进化策略。宿主微环境内的营养限制进一步强化了耐药和毒力基因的协同表达。铁离子是细菌增殖的必需微量元素，当细菌处于缺铁环境时，其通过 Fur-RcsAB 双效调控系统同时激活铁载体合成基因(iucA、entC 等)及耐药相关基因的表达[23]。铁载体合成系统与碳青霉烯耐药系统的共上调使细菌在抢夺宿主铁营养的同时能够维持抗生素抗性，实现营养获取与生存防御的功能协同[24]。抗生素选择压力下的进化轨迹还呈现出显著的地理分化特征，分子流行病学研究显示，中国 ST23 型 CR-hvKP 的碳青霉烯酶基因分布呈现明显的南北地理隔离，北方地区以 blaNDM 为主，而南方地区则以 blaKPC 为主[25]。

5. 生物膜进化平台

生物膜是 CR-hvKP 在医疗器械及宿主组织中持续存在的主要生存模式，是基因水平转移的关键场所，其独特的微环境物理化学特性构成了耐药与毒力协同进化的选择压力[26]。生物膜基质(EPS)中的高黏度多糖网状结构通过限制抗生素渗透直接增强耐药性，屏蔽补体攻击与吞噬细胞识别间接降低了高毒力表型的代谢成本，从而使高耐药及高毒力的表型突破适应性代价的约束[27]。c-di-GMP 信号网络的调控是连接生物膜形成与耐药–毒力耦合的核心机制。该第二信使在生物膜成熟过程中不断累积，通过激活荚膜多糖合成基因(pgaABCD、yjbF)促进基质合成，还可以通过 PmrAB 双组份系统上调脂多糖修饰基因协同诱导多黏菌素耐药[28]。在高生物膜形成状态下，高 c-di-GMP 水平通过 CRP 调控抑制 ArcZ 表达，从而维持高毒力所需的铁摄取能力[29]。生物膜内的基因转移加速为质粒融合提供了合理场所，并且生物膜内紧密排列的空间和稳定的微环境(pH 梯度、氧张力分层)能够显著提高接合转移频率。在导管相关感染模型中，携带 mcr-1 的 IncX3 质粒与携带 iuc 的毒力质粒在生物膜内的共转移率可达 5.7×10^{-3}，远高于浮游状态[30]。持留菌(Persister)状态与毒力维持的协同进一步巩固了这种进化优势。生物膜深层的营养匮乏和代谢停滞诱导细菌进入持留状态，此状态下毒素–抗毒素系统(TA modules)的激活不仅赋予多药耐受性[31]，还可以低水平维持毒力基因的持续表达。当解除抗生素压力后，这些持留菌复苏并释放更高毒力子代，如此反复则形成“耐药储备库–毒力爆发”的循环模式。

6. 创新治疗策略

6.1. 外排泵抑制及毒力调控疗法

外排泵抑制剂(EPI)通过阻断抗生素外排与毒力调控双重机制发挥协同作用，新型 EPI 如 PAβN 衍生物、青蒿琥酯等通过恢复碳青霉烯及多黏菌素对耐药菌的活性，逆转多药耐药并增强毒力[32]。肺炎克雷伯菌对多黏菌素的耐药性可被外排泵抑制剂氰化物-3-氯苯腙抑制或逆转[33]。针对 mcr 基因的小分子抑制剂(如紫檀芪 pterostilbene、和厚朴酚 honokiol 等天然化合物)，可特异性抑制磷酸乙醇胺转移酶活性，恢复多黏菌素敏感性[34] [35]。然而，EPI 靶向选择性不足会导致潜在毒性，还会出现药代动力学不匹配及耐药诱导风险，且天然化合物缺乏标准化生产工艺，导致目前尚无 EPI 获批上市。

6.2. 抗生物膜疗法

生物膜破坏剂(如 DNase I)与胰蛋白酶联用可降解生物膜基质中的 eDNA 和蛋白成分，与美罗培南联用可使最低生物膜清除浓度(MBEC)降低至少 2.5 倍，显著提高对耐碳青霉烯类高毒力肺炎克雷伯菌(CR-

hvKP)生物膜内细菌的清除效率[36]。光动力疗法(aPDT)通过光敏剂(如亚甲蓝)产生的单线态氧破坏生物膜结构并杀灭持留菌[37]。但抗生物膜疗法在临床应用上面临着深部感染灶给药困难、光穿透深度限制及体外模型与体内疗效差异等挑战。

6.3. 免疫调节与营养支持疗法

维生素 D3 通过非基因组途径调节先天免疫应答。研究显示，25(OH)D 水平>38 ng/mL 与上呼吸道感染发生率降低 2 倍相关[38]。在危重症脓毒症患者中，维生素 D 缺乏是死亡的独立危险因素(风险增加 1.6 倍)，而补充维生素 D3 (50,000~90,000 IU/mL)可直接抑制 KP 等多种病原体生长，并通过下调 Th1/Th17 炎症反应减轻组织损伤[39]。间充质干细胞(MSC)疗法通过免疫调节与组织修复双重机制改善 CR-hvKP 感染预后。在难治性耐药细菌啮齿模型中，多次输注经细胞因子预激活的脐带 MSC 可显著改善肺顺应性与氧合指数，降低支气管肺泡灌洗液中中性粒细胞计数及细菌负荷[40]。其机制涉及通过 IL-1β 信号促进 M2 型肺泡巨噬细胞极化，增强细菌清除能力的同时减轻急性肺损伤[41]。尽管如此，使用维生素 D 治疗疗效个体差异大且大规模试验未证实总体获益；MSC 疗法则受限于产品标准化困难、免疫原性风险及高昂制备成本。

6.4. RNA 干预与噬菌体疗法

小 RNA (sRNA)调控网络为抗毒力治疗提供了精准干预靶点，但其不杀菌特性可能导致感染复发风险。对 ArcZ 的过表达质粒或稳定性 RNA 模拟物可作为新型抗菌佐剂，ArcZ 通过碱基配对直接抑制 mlaA/fbp 翻译过表达降低 HMV 和毒力[42]。噬菌体疗法展现出对 CRKP 的精准清除潜力。针对 ST258 等流行克隆的裂解性噬菌体具有较高的杀伤活力[43]，可特异性识别 OmpK36 孔蛋白等细菌表面抗原[44]。噬菌体与抗生素(如环丙沙星、美罗培南)联用可产生显著的协同杀菌效应，抑制生物膜形成并降低耐药突变频率[45]。在泛耐药肺炎克雷伯菌(PDX-KP)临床个案中，噬菌体与美罗培南、头孢他啶/阿维巴坦联合应用成功治愈感染[46]，为难治性感染提供了可行的替代方案。在实际应用中，sRNA 易被核酸酶降解而缺乏成熟递送系统，其抗毒力作用具有不稳定性；同时噬菌体疗法也面临着监管框架缺失与耐药进化风险等困境。

7. 总结与展望

CR-hvKP 所呈现的耐药与毒力协同进化现象，实际上反映了肠杆菌科细菌在强选择压力下的适应性进化新范式。这种进化并非简单的基因叠加，而是通过质粒融合、插入序列介导的基因组以及宿主内微环境选择等多维度机制实现的表型整合。从分子层面看，AcrAB-TolC 外排泵、双组份调控系统以及 c-di-GMP 信号网络构成了连接耐药与毒力的关键节点；在生态层面，生物膜微环境、免疫压力与营养限制共同筛选出兼具多重耐药与高毒力特征的适应性克隆。当前临床面临的核心困境在于传统诊断手段难以捕捉异质性耐药亚群以及“沉默”耐药基因的动态变化，多黏菌素与碳青霉烯交叉耐药的出现使得治疗选择严重受限。快速检测技术的突破是解决这一识别瓶颈的关键。基质辅助激光解吸电离飞行时间质谱(MALDI-TOF MS)具有检测速度快、准确率高及成本低等特点，新型算法拓展其直接检测碳青霉烯酶(如 KPC、NDM)及高毒力标志物(如 rmpA、magA)的能力，但无法区分携带与表达状态，对混合感染中低频耐药亚群的敏感性也不足。快速分子诊断技术(如 Xpert Carba-R、FilmArray)实现了对耐药基因与毒力因子的多重 PCR 检测，检测时间可缩短至 1~2 小时，然而其依赖已知基因靶点进行检测，难以发现新型变异，且无法提供活菌药敏信息。微流控芯片与数字 PCR 技术的结合可提升对异质性耐药亚群的检测灵敏度，但高昂的成本及复杂操作限制了临床常规应用。只有建立从快速筛查(MALDI-TOF MS)到精准基因

分型(NGS)的分层诊断体系，实现感染早期高危克隆的识别与风险分层，后续的靶向干预才具备临床可操作性。尽管外排泵抑制剂、RNA 靶向干预及噬菌体疗法在体外与动物模型中展现出良好前景，但其临床转化仍受限于体内药效学特性、宿主免疫清除及规模化生产等现实瓶颈。针对未来的防控策略，需建立贯穿“识别–干预–监测”全周期的技术体系：在诊断维度，整合单细胞测序与数字 PCR 技术以追踪低频耐药突变及毒力基因表达异质性；在治疗维度，基于时空多组学数据设计靶向生物膜基质或持留菌状态的联合方案；在公共卫生维度，构建跨区域的基因组监测网络以实时追踪 ST11、ST23 等高危克隆的传播动态。这种多技术协同、跨学科整合的研究路径，或将为突破当前治疗僵局提供新的可能性。

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