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Review 综 述

耐药细菌中交互敏感现象研究进展

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Li Qian, Zhu Kui. Advance in collateral sensitivity in drug-resistant bacteria. *Acta Microbiologica Sinica*, 2022, 62(5): 1688–1697.

摘　要：细菌耐药性是全球亟待解决的重要公共卫生问题之一，耐药病原菌对人类和动物健康构成极大威胁。交互敏感性、附带敏感性(collateral sensitivity)是指耐药细菌在进化过程中出现的对一类抗菌药物耐药，而对另一类或几类抗菌药物更加敏感的现象。利用交互敏感策略限制甚至逆转细菌耐药性以恢复其对抗菌药物的敏感性是细菌耐药性研究的热点。本文综述了细菌交互敏感的最新研究进展，主要从交互敏感性的概念、表型及机制研究等方面进行阐述，以期为防控和治疗耐药病原菌感染提供新思路。

关键词：交互敏感性；抗菌药物；细菌耐药性；抗菌机制

Advance in collateral sensitivity in drug-resistant bacteria

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Abstract: Antibiotic resistance is one of the global conundrums. Multi-drug resistant (MDR) bacteria-associated infections pose a great threat to the health of both human and animals. Collateral sensitivity is a phenomenon that the bacteria developed resistance to one antibiotic display increased susceptibility to a second antibiotic. Collateral sensitivity has been intensively explored to restrict and/or reverse the evolutionary trajectory of resistance bacteria in the past years. This review mainly

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focuses on the concept, phenotypes, and molecular mechanisms of collateral sensitivity, to shed light on the development of alternative approaches to treating MDR bacteria.

Keywords: collateral sensitivity; antibiotic; antibiotic resistance; antibacterial mechanism

抗菌药物的不合理使用导致细菌耐药性问题日益严重,是全球高度关注的公共卫生问题之一。2014 年报道全球每年大约 70 万人因细菌耐药性而死亡，如果不加以控制，到 2050 年细菌耐药性每年将导致 1 000 万人死亡，并使全球 GDP 损失超过 100 万亿美元[1–4]。为遏制细菌耐药性的发生和发展，现已经提出了多种应对策略。目前，新型抗菌化合物及增效剂的研发仍是对抗耐药菌的主要策略[5]。例如，一种广谱抗菌药物增效剂 SLAP-S25 能与多类抗菌药物协同使用，从而恢复临床常见革兰阴性耐药菌对抗菌药物的敏感性[6–7]。同时，宿主导向的抗菌治疗和抗菌药物替代物等也是目前的研究热点和难点[8–12]。虽然这些策略将为长期应对细菌耐药性提供理论依据及技术支持,但大多数项目仍处于临床前研究，无法迅速治疗耐药病原菌感染。因此,迫切需要找到新的应对策略以减缓耐药菌导致的临床上无药可用的窘境[13]。

耐药菌的交互敏感性(collateral sensitivity，也称附带敏感性)是细菌耐药性进化过程中的一种常见表型,是细菌改变其遗传物质或者生理生化特性来适应某一类抗菌药物压力时产生对另一类或者几类抗菌药物敏感性升高的现象[14]。交互敏感性的研究将为耐药菌防控策略提供新的突破口。采用交互敏感的抗菌策略可以通过利用药物之间的特定相互作用来增加耐药病原菌对现有抗菌药物的敏感性。因此，利用细菌的交互敏感性不仅可以在菌株已经产生耐药性后实现有效治疗，还可以提高现有抗菌药物的疗效，延长其使用寿命，实现临床上迅速、高效的治疗策略[15–16]。此外，深入研究细菌交互敏感机制将有利于进一步揭示耐药菌株的产生与形成规律，为靶向耐药菌的新型抗菌药物提供理论基础[17]。在本文中,我们探讨了耐药细菌中交互敏感性的最新研究进展，重点介绍了交互敏感性的概念、表型以及分子机制,以期为研发新的抗菌策略提供新思路。

1 交互敏感性

细菌在抗菌药物持续使用时会通过改变自身遗传特性等方式进化出耐药性,通常表现为合成抗菌药物水解酶、抗菌靶点突变、合成外排泵蛋白和改变自身代谢途径等。复杂的耐药机制和抗菌机制之间产生了关联和矛盾,形成交互敏感和交叉耐药(cross resistance)。例如，质子动力势的强弱与外排泵蛋白的活性紧密相关,当细菌通过大量表达外排泵活性蛋白产生耐药性时,又不可避免地使依赖质子动力势的药物进入胞内的量增多,这种生理功能的矛盾性导致细菌产生交互敏感(图 1A)。另外，*cfr* 耐药基因会使抗菌靶点发生甲基化修饰从而使作用在此位点的 5 类抗菌药物(噁唑烷酮类、截短侧耳素类、链阳霉素类、林可胺类以及酰胺醇类)出现交叉耐药的现象[18]。交互敏感性可以指导研发设计新型抗菌药或合理的联合用药方案来对抗耐药菌。研究表明，74%的实验室耐药菌株都表现出对一类或多类药物的敏感性增强[19–21]。因此，在细菌耐药性的进化过程中,交互敏感性是一种常见且值得关注的现象。

交互敏感性的概念最早是用来解释癌细胞在长期化疗后出现的对药物敏感性变化[22]。细菌中交互敏感性的描述最早报道于 1952 年，

Bryson 和 Szybalski 观察到大肠杆菌菌株在获得氯霉素抗性后对多黏菌素 B 变得敏感[23]。近年来，在细菌耐药性发展迅速而新型抗菌药物逐年减少的危机下，关于耐药菌交互敏感性表型及机制的研究逐渐成为热点[13,24]。在抗菌药物的选择性压力下细菌出现耐药性突变频率大大增加，这种突变往往不会给细菌造成很大适应性代价，并且突变菌株可在特定抗菌药物或者无抗菌药物压力时存活并持续传播相关基因。但某些耐药性突变可能会造成细菌自身结构或者生理功能的改变，使其对另一类药物趋向于敏感，产生交互敏感现象(图 1B)。因此，揭示耐药细菌交互敏感性的产生及形成规律将有助于预判和逆转细菌的耐药性，制定合适的给药方案，提高耐药细菌的防控效率[25–26]。

2 交互敏感研究进展

2.1 交互敏感现象研究概述

交互敏感是细菌耐药性进化过程中一种常见的现象，在大肠杆菌[27]、沙门菌[28]、铜绿假单胞菌[29–30]、鲍曼不动杆菌[31]、金黄色葡萄球菌[30]和其他多种病原菌中均有报道[32–34]。2009 年，研究人员发现实验室菌株及临床分离大肠杆菌菌株都存在交互敏感现象，并对交互敏感现象进行更深入的探究。梳理菌株的交互敏感和交叉耐药网络是当前广泛采用的研究方法，可以为临床长期使用药物治疗提供数据参考[35]。例如，使用交叉耐药网络中的药物进行治疗时即可预测到耐药性后期发展轨迹，以及时调整用药策略，避免诱导出高水平耐药及无效治疗的可能性。相反，基于交互敏感网络的药物组合的顺序治疗可以减少高水平耐药发展的可能性，并且可以预见到一类抗菌药物耐药后的治疗方案。这些研究表明，交叉耐药和交互敏感网络可为治疗最初选择抗菌药物及预测耐药性发展轨迹奠定基础。除此之外，还可通过菌株基因组进化分析推测交互敏感产生机制[36–37]。例如，通过构建数学模型模拟计算来判断葡萄球菌及粪肠球菌等菌株的交互敏感性[38–40]，并以此来判断菌株的耐药发展方向。

2.2 交互敏感机制研究进展

目前，关于交互敏感机制的研究尚处于起步阶段(图 2)。在细菌遗传物质改变介导的交互敏感性方面取得了一些进展，可以总结为 3 点：(1) 耐药基因片段介导的交互敏感；(2) 基因突变引起的交互敏感；(3) 耐药质粒导致的交互敏感。

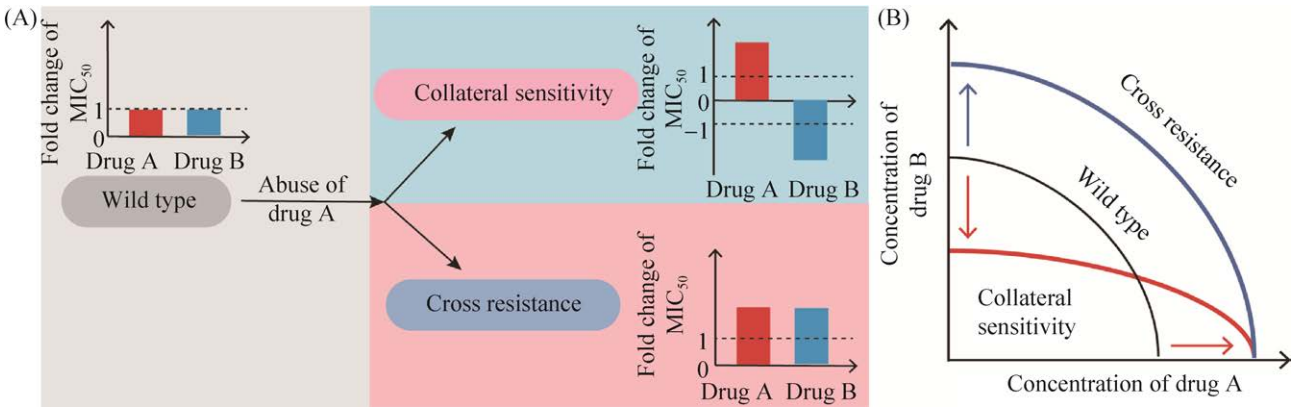

图 1 交互敏感性与交叉耐药性模式图

Figure 1 Scheme of collateral sensitivity and cross resistance in bacteria. A: scheme of cross-resistance and collateral sensitivity; B: the change of antibiotic sensitivity.

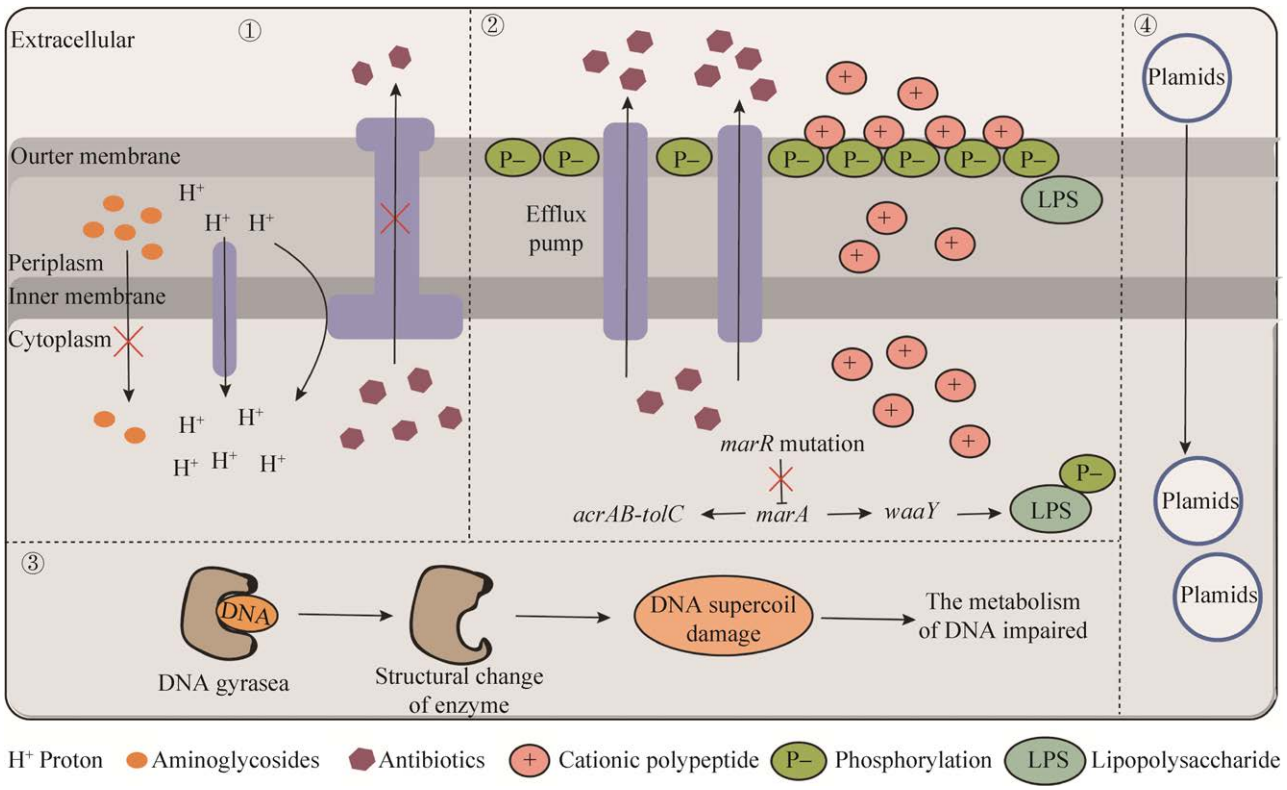

图 2　细菌交互敏感机制图

Figure 2　Molecular mechanism of collateral sensitivity in bacteria. Modes of action of collateral sensitivity of ①: aminoglycoside antibiotics resistant bacteria to other antibiotics; ②: MDR bacteria to antimicrobial peptides; ③: quinolone antibiotics resistant bacteria to other antibiotics; ④: plasmid-mediated resistance.

此外，还有一些其他机制介导交互敏感的研究，如转录重编程导致细菌中其他生物学功能发生改变[41–42]。

首先，耐药基因除了可以引起细菌产生耐药表型外，还可以引起其他生物学效应，导致细菌产生交互敏感现象(表 1)。例如，氨基糖苷类抗菌药物常需要利用细菌的质子动力势(proton-motive force，PMF)进入胞内，发挥抗菌作用。因此，氨基糖苷类抗菌药物耐药的大肠杆菌可以通过降低 PMF 使氨基糖苷类药物的胞内累积量减少而实现耐药；但 PMF 降低会导致质子依赖的外排泵的活性降低，导致其他多类抗菌药外排减少，胞内抗菌药物含量升高，进而导致细菌生长被抑制[43]。相应地，细菌表达四环素耐药基因 *tet* 增加外排泵蛋白表达，四环素外排增多，引起四环素耐药；但高效的外排泵反而提高了胞外氨基糖苷类抗菌药物进入菌体内的效率，从而引起细菌对氨基糖苷类抗菌药物的敏感性增加[44]。

此外，基因突变也是产生交互敏感现象的重要机制。耐药基因以及其他基因突变均有可能导致基因功能改变，促进细菌产生交互敏感现象(表 1)。例如，喹诺酮类耐药菌株通过耐药基因突变改变自身的 DNA 拓扑异构酶的结构，减弱了酶与喹诺酮类药物的亲和力产生耐药[45]。但耐药菌 DNA 超螺旋结构的改变，从根本上影响了整个基因组的转录，最终使细菌无法应对其他抗菌药造成的损害而死亡。同时，在探究了产广

表 1　细菌的交互敏感表型及其机制

Table 1　Phenotypes and mechanisms of collateral sensitivity in bacteria

Species	Resistance	Collateral sensitivity	Mechanism	*In vitro*/*vivo*	References
E. coli	Aminoglycosides	β-lactam antibiotics	Reduction of PMF in aminoglycoside-resistant isolates diminish the activity of PMF-dependent major efflux pumps, leading to susceptibility to β-lactam antibiotics	*In vitro*	[43]
	Mecillinam	Cefotaxime	Three non-synonymous of CTX-M-15 increase resistance against mecillinam that confer susceptibility to cefotaxime	*In vitro*/*vivo*	[46]
	Multi-antibiotics	Cationic antimicrobial peptide	*marR* mutant increase the expression of efflux pump inducing multi-resistance, while it facilitates the interaction of antimicrobial peptides via modulation of the LPS phosphorylation pathway	*In vitro*/*vivo*	[47]
	Azithromycin	Colistin	Plsmid-mediated collateral sensitivity	*In vitro*/*vivo*	[48–49]
P. aeruginosa	Ciprofloxacin	Gentamycin	*nfxB* mutation in ciprofloxacin resistant bacteria up-regulates the transporer protein (MexC) that confer susceptibility to gentamycin	*In vitro*/*vivo*	[50]
	Gentamycin	Penicillin	Unclear	*In vitro*/*vivo*	[51]
	Ceftazidime	Tobramycin	Unclear	*In vitro*/*vivo*	[52]
MRSA	Methicillin	Meloxicillin-piperacillin-tazobactam (ME/PI/TZ)	ME/PI/TZ disrupt PBP2α to recover sensitive to β-lactam antibiotics	*In vitro*/*vivo*	[53]

谱 β-内酰胺酶 CTX-M-15 大肠杆菌的交互敏感机制时发现，具有交互敏感表型菌株中的 CTX-M-15 都有 3 个错义突变，导致其对美洛西林或哌拉西林-他唑巴坦的耐药性增加，但突变的水解酶与几种头孢菌素药物亲和力减弱，因而细菌恢复对头孢菌素药物的敏感性[46]。此外，细菌可通过调节细菌外膜脂多糖(lipopolysaccharide，LPS)来实现对抗菌肽的交互敏感。具体来讲，*marR* 基因突变上调了 AcrAB-ToIC 外排泵的表达，增加对多类抗菌药物的耐药性；*marR* 基因突变同时上调了 LPS 磷酸化激酶 WaaY，LPS 的磷酸化增加了细菌外膜表面负电荷，增强了靶向外膜的阳离子抗菌肽的敏感性[47]。

最新研究表明耐药质粒可以介导耐药菌交互敏感性的形成(表 1)。2021 年首次发现水平转移的耐药质粒可以导致大肠杆菌产生交互敏感现象[48–49]，证明了耐药质粒转移到大肠杆菌内后对一些抗菌药物敏感性升高。该研究结果不仅为治疗质粒介导的耐药菌株提供了新思路，还将以往从基因片段的角度揭示耐药菌交互敏感性形成机制拓展到耐药质粒，为后继相关机制的研究提供了新的方向。我们课题组前期通过构建交互敏感网络，发现耐万古霉素的屎肠球菌(VRE_{fm})和对新型海洋源抗菌化合物 equisetin 耐药的金

黄色葡萄球菌都表现出交互敏感现象[40]。此外，我们证明磷酸化的 VanR 通过结合相似的启动子序列，共同调控万古霉素耐药基因簇与核糖体保护蛋白 MsrC 的表达，介导 VRE_{fm} 对截短侧耳素类药物的交互敏感[54]。

2.3 交互敏感性在临床菌株中的研究进展

近年来，随着对交互敏感现象的研究越来越深入，研究对象逐渐从实验室菌株逐渐拓展到临床菌株。如何将交互敏感规律应用于临床菌株来控制耐药菌的进化，提高现有抗菌药的使用效率，延长其使用寿命是解决问题的关键。利用交互敏感现象指导临床用药有以下几方面优势：(1) 可以用相对较低剂量的抗菌药物抑制病原菌生长，阻断病原菌感染进程；(2) 基于交互敏感性的治疗策略可以优化抗菌药治疗组合，提高治疗慢性感染的成功率[55–56]；(3) 利用交互敏感抗菌药物组合实现周期性循环用药，逆转病原菌的耐药性，提高现有抗菌药物的使用效率[57–59]。

基于耐药菌交互敏感性设计的药物组合可以实现相对较低剂量的抗菌药物防控耐药病原菌。例如，美罗培南耐药的大肠杆菌可与呋喃妥因表现出交互敏感，对呋喃妥因的 MIC 下降了 64 倍，较低剂量的呋喃妥因就能抑制耐药大肠杆菌的生长[60]。同时，通过构建交互敏感网络筛选出的抗菌药物组合可以治疗临床慢性感染，延缓甚至逆转耐药菌的进化方向。研究表明，由铜绿假单胞菌引起纤维性囊肿病人在已经出现对药物耐药的情况下，使用通过构建交互敏感网络筛选的抗菌药物组合，可以清除喹诺酮类药物耐药的绿脓杆菌亚群，实现有效治疗[50]。此外，利用交互敏感药物组合实现循环用药来治疗耐药菌的感染，并可根据使用的药物组合控制和预测耐药性发展方向，提高现有抗菌药物的使用效率。以临床分离大肠杆菌为研究对象，对常用的 23 种抗菌药物进行交互敏感药物组合筛选，获得几百种组合并最终确定庆大霉素和头孢呋辛可实现循环用药治疗[21]。之后，基于交互敏感的药物组合被陆续报道可以有效控制临床分离菌株，包括 MRSA 和致病性大肠杆菌等病原菌[61–62]。这些研究进一步证明了交互敏感性指导的给药方案在治疗临床感染中潜力巨大。

相较于交互敏感现象在实验室条件下的深入研究及其揭示的不同耐药性机制和抗菌药物作用之间的新联系，临床上开展交互敏感性的研究和应用仍处于初级阶段，还需更多的临床数据来指导药物组合的设计和合理用药[63–65]。但须强调，基于耐药病原菌交互敏感性的药物组合及联合用药策略将为未来临床合理用药提供理论基础和技术支撑，是破解临床上面对耐药菌感染而出现无药可用窘境的新突破口。

3 总结与展望

尽管目前在交互敏感性的研究上取得了长足的进步，但仍有两个方面亟待开展深入研究。(1) 耐药细菌交互敏感性的分子机制尚不清楚。已有许多研究表明，交互敏感现象广泛存在于大肠杆菌、金黄色葡萄球菌、铜绿假单胞菌和表皮葡萄球菌等细菌中，但其形成机制的研究大多是集中在细菌遗传物质方面的研究，具体机制还有待进一步阐明。由于能产生交互敏感现象的菌种较多，而菌种之间差异非常大，且产生交互敏感的药物组合和机制各不相同，所以进一步阐明其具体机制存在一定难度。阐明交互敏感分子机制，揭示病原菌耐药进化的规律，高效预测细菌耐药发生发展方向，从而制定合理给药方案或靶向设计新药，提高耐药病原菌的治疗效率。(2) 如何利用交互敏感设计抗菌药物组合。虽然关于耐药菌交互敏感的研究已经从实验室菌株拓展到临床菌株，但总体研究还处于初级阶段。基于交互敏感机制设计的药物组合在临床使用需要

更加严谨的临床试验研究的数据支持。目前还缺乏评价这类药物组合药效的临床用药标准和评价体系，仍需要更系统的前瞻性临床治疗研究来检验其提高疗效或降低耐药发生率的能力。

综上所述，在细菌耐药性日益严重而新型抗菌药物匮乏的现状下，利用耐药菌交互敏感性策略将为防控耐药菌提供新的方向。期待早日阐明耐药菌的交互敏感性现象的产生机制及形成规律，为合理用药和治疗耐药病原菌感染提供新思路和强有力的技术支持。

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