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Review 综述

抗生素抗性菌的适应性代价及其防控策略研究进展

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摘　要：微生物的抗生素抗性(antibiotic resistance, AR)问题已成为全球公共卫生安全面临的重大挑战。微生物获得 AR 后常伴随适应性代价，通常在无抗生素环境中其群落竞争力弱于敏感菌，这使得抗生素抗性基因(antibiotic resistance genes, ARGs)成为细菌的负担。基于此，本文详细阐述了适应性代价的产生机制与测量方法，举例说明了不同获取方式下 ARGs 介导的适应性代价，着重介绍了染色体介导和质粒介导的 ARGs 在适应性代价方面的差异及分子机制，最后提出了基于适应性代价的抗生素抗性菌(antibiotic resistance bacteria, ARB)防控策略。本文揭示了抗生素抗性与细菌适应性之间的权衡生物学规律，为解决由 ARB 及 ARGs 引发的全球公共卫生安全问题提供了防控思路。

关键词：抗生素抗性菌；适应性代价；抗性机制；水平基因转移；防控

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Research progress in the fitness cost and prevention and control strategies of antibiotic resistant bacteria

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Abstract: Antibiotic resistance (AR) in microorganisms has become a crucial challenge to global public health security. The acquirement of AR in microorganisms is often accompanied by a fitness cost. Typically, in an environment without antibiotics, the bacterial community with AR shows weaker competitiveness than susceptible bacteria, which makes antibiotic resistance genes (ARGs) a burden for bacteria. This article elaborates on the mechanisms underlying the generation of fitness costs and the corresponding measurement methods, provides examples to illustrate the fitness costs mediated by ARGs under different acquisition methods, and introduces the differences in fitness costs between chromosome-mediated and plasmid-mediated ARGs as well as their molecular mechanisms. Finally, it proposes prevention and control strategies for antibiotic resistant bacteria (ARB) based on fitness costs. This article reveals the biological law of the trade-off between antibiotic resistance and bacterial fitness and provides ideas for preventing and controlling the global public health security issues caused by ARB and ARGs.

Keywords: antibiotic resistant bacteria; fitness cost; resistance mechanism; horizontal gene transfer; prevention and control

抗生素在养殖业和人类临床的大量使用导致抗生素抗性基因(antibiotic resistance genes, ARGs)污染问题日益严峻，对畜禽健康养殖和公共卫生安全构成威胁[1]。Naghavi 等[2]开展的一项覆盖全球 204 个国家和地区的研究表明，2021 年因抗生素抗性菌(antibiotic resistance bacteria, ARB)感染问题直接或间接导致多达 127 万人和 495 万人死亡，预计到 2050 年这一数字将达到 191 万人和 822 万人。如何控制 ARGs 的传播，从而降低其对人和动物的健康风险已成为热点问题。

细菌通常可通过 2 种主要方式传播 ARGs，即通过亲代复制的垂直基因转移(vertical gene transfer, VGT)和可移动遗传元件(mobile genetic elements, MGEs)介导的水平基因转移(horizontal gene transfer, HGT)[3-4]。细菌获得 ARGs 虽能抵抗药物，但通常会产生一定的适应性代价，即在无抗生素环境下 ARB 相对于敏感菌表现出明显的竞争劣势[5]。适应性代价会影响 ARGs 在菌群中的传播，例如降低其接合转移能力，并在停用抗生素后加快 ARGs 的丢失速度[6]。适应性代价的研究可为抑制 ARB 提供新线索，但当前仍面临诸多挑战。例如，适应性代价的精确测量方法、适应性代价与抗生素抗性(antibiotic resistance, AR)的关系以及分子机制仍不明确。解决这些问题对于控制 ARB 至关重要。本文将探讨适应性代价的产生机制和测量方法，说明不同获得方式下 ARGs 介导的适应性代价，介绍染色体和质粒介导 ARGs 的适应性代价差异及分子机制，最后提出临床应用的启示和未来研究方向，以期为从适应性代价角度遏制 ARB 提供科学思路。

1 抗生素抗性菌的适应性代价

1.1 适应性代价的定义及产生机制

适应性是指细菌通过适当调节自身代谢以适应生存环境，并具备较好繁殖能力的过程，通常涉及生长力、侵袭力、致病力的变化[7]。细菌在获得 ARGs 后能够适应抗生素胁迫下的环境，在有抗生素的环境中继续生长繁殖并持续存在，其竞争能力优于敏感菌株；然而在无抗生素环境中 ARGs 反而成为细菌的负担，导致其生长代谢、运动能力、毒力、生物膜形成能力下降，这就是 ARB 的适应性代价[5]。因此，研究适应性代价对于理解菌群中 AR 的发展和持久性至关重要，是决定 ARGs 在环境中存在和传播的关键因素[8]。

适应性代价的产生机制与 ARGs 的获得方式以及抗性机制密切相关。菌株除通过 VGT 获得 ARGs 外，还可通过 2 种主要途径获得 ARGs：(1) 通过基因突变获得 ARGs[3]；(2) 通过 HGT 获得 ARGs[4]。通过基因突变获得的 ARGs 通常会使细菌的基因编码效率降低、相应表达蛋白的活性降低，扰乱细菌的正常代谢或生物功能，导致细菌的整体适应能力下降，从而造成适应性代价[9]。在 HGT 途径中 MGEs 介导的 ARGs 传播通常会产生多维度适应性代价：(1) 抗生素抗性质粒的接合转移过程复杂，需要供体与受体大量蛋白的协调表达和调控，且会大量占用细胞器并消耗能量[10]；(2) 携带 ARGs 的质粒在胞内的复制、转录和翻译均需消耗额外的能量和资源，使细菌产生额外的遗传和代谢负担[11-12]；(3) 在某些情况下，整合酶催化整合子与基因盒之间的重组反应，可能引发非典型位点的重组事件，导致宿主基因组不稳定[13]；(4) 转座子可通过产生有害突变和破坏配子发生，从而对其宿主施加适应性代价[14]。ARGs 的抗性机制包括降低抗生素的渗透性、抗生素的主动运输、抗生素靶标改变与保护、抗生素的灭活与修饰以及靶标旁路途径[15]，由于这些抗性机制的分子机制不同，细菌所表现的适应性代价也存在差异。

1.2 适应性代价的测量方法

细菌适应性代价的测量方法(图 1)主要包括生长曲线(growth curves)法和竞争试验法。生长曲线法主要是在体外相同条件下单独培养抗性菌和敏感菌，测定吸光度并绘制生长曲线图，以确定不同菌株的生长能力，并通过比较二者的生长速度差异来测量适应性代价[16]。竞争试验是将抗性菌和敏感菌共同培养，比较二者在相同环境下的生长和存活能力，通过测定一定时间内二者的数量和比例变化，计算相对适应性 (relative fitness, RF) 或选择系数 (selection coefficient, S)来测量适应性代价。竞争试验主要包括 2 种：(1) 体内竞争试验，通常在实验动物或设计的动物感染模型内进行培养，通过感染动物或模型来测量 ARB 的适应性代价[17]；(2) 体外试验，通常在培养基中进行，将抗性菌与敏感菌按一定比例混合，在无抗生素的条件下进行共培养以竞争营养资源[18]。在开展生长曲线测定和竞争实验的基础上，为系统评估适应性代价，需进一步测定生长代谢、运动能力、毒力、生物膜形成等指标。

竞争试验法广泛用于测量适应性代价，是测量适应性代价的“黄金标准”[5]。相较于测量生

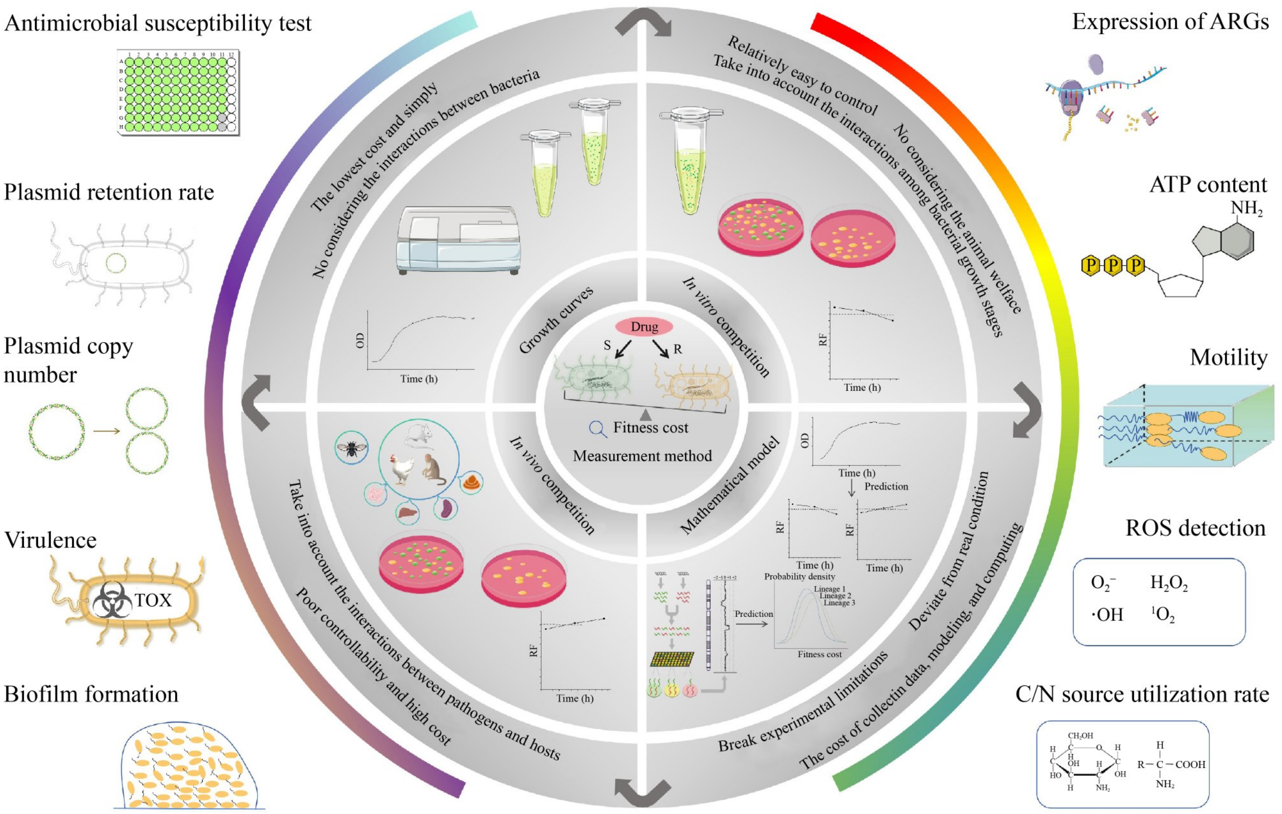

图1　适应性代价的测量方法

Figure 1　Methods for measuring fitness cost.

长曲线，竞争试验考虑了菌株之间在不同生长阶段的相互作用，并能多方面描述菌株全部生长周期的生物学特性[19]。体外竞争试验通常在培养基中进行，实验条件相对容易控制、操作方便、易于实现且无需考虑动物福利，同时可快速进行，因而较为常用[20]；相较于体外竞争试验，体内竞争试验相对不可控、成本高，但可得到真实感染情况下的适应性变化，对于研究病原体和宿主之间的相互作用具有重要意义，是评估安全性和有效性的最佳选择[20]。对比二者的实验结果存在巨大差异，例如，Evangelopoulos 等[21]发现大多数 D-环丝氨酸抗性菌在小鼠体内试验时检测到适应性显著降低，仅通过体外试验无适应性代价的表现，无法发现宿主对 ARB 的胁迫作用。蔡文慧[22]通过体内外实验发现，携带 H-NS 蛋白的 lncX1 型 *tet*(X4) 阳性质粒在小鼠体内具有很高的适应性，且普遍优于体外的研究结果。刘德俊[23]通过体外生长试验发现，弯曲杆菌属(*Campylobacter*)携带 *ermB* 基因后生长、定殖能力降低；而在肉鸡体内竞争试验中，抗性菌在接种初期表现出菌毛合成异常和能量代谢失衡，导致适应性降低。

除经典的适应性代价测量方法外，还可以根据流行病数据建立数学模型来衡量适应性代价，其能在一定程度上突破实验限制，从而客观反映抗生素使用与抗性变化的联系。例如，Ram 等[24]开发出一种基于单一培养物和混合培养物的生长曲线，能够预测混合培养物相对生长的方法；Helekal 等[25]将多谱系流行病学模型与系统发育合并理论结合，根据基因组数据估计 ARB 的适应性代价。此外，数学模型可以根

据适应性代价的高低预测 ARGs 下降的速率，但由于某些细菌表现为无适应性代价以及补偿性进化(compensatory evolution)途径的存在，导致数学模型法的参数计算无法考虑真实情况的所有因素，存在统计学上的偏差，使模型不能满足实际情况[26]，并且开发数学模型用于适应性代价评估依赖较大的数据集和计算成本，这些因素都限制了模型开发。

1.3 不同获得方式下 ARGs 介导的适应性代价

由于细菌获得 AR 的方式和抗性机制多种多样，且其表现的适应性代价不尽相同，AR 与适应性代价之间存在复杂的关系。本节总结了近年来关于细菌 AR 与适应性代价的相关研究(表 1)，这些研究通过测定生长曲线、开展竞争试验以及构建动物模型等途径，以测定和计算生长曲线(growth curves)之间的显著差异(*P*)、相对适应度(relative fitness, RF)、选择系数(*S*)等指标的方式评价了不同细菌、不同抗生素抗性机制下的适应性代价。其中，细菌通过转化和胞外囊泡方式获得 AR 而引起的适应性代价的研究较少，未在表 1 中列举。

获得 ARGs 会影响细菌的运动能力、毒力、ARGs 的传播速度和竞争能力，使细菌表现出适应性代价。在由基因突变产生的 ARGs 中利福平抗性基因 *rpoB* 突变显著延长表皮葡萄球菌(*Staphylococcus epidermidis*)的复制周期[27]，铜绿假单胞菌(*Pseudomonas aeruginosa*)的多药物外排泵基因 *nfxB* 突变导致能量代谢负荷增加[28]，耻垢分枝杆菌(*Mycobacterium smegmatis*) *rv2752c* 突变通过降低 RNA 聚合酶转录效率引起全局基因表达下调，从而使细菌生长速度变慢[29]。在细菌通过 HGT 获得的 ARGs 中，适应性代价表现为携带 β-内酰胺类酶基因 $bla_{\text{CTX-M-14}}$、bla_{NDM} 和 $bla_{\text{CTX-M-55}}$ 导致大肠埃希氏菌(*Escherichia coli*)丧失接合转移能力[30]以及毒力[31]和生长速度[38]下降；携带 *sul3* 导致大肠埃希氏菌运动能力下降[34]；转座子介导粪肠球菌(*Enterococcus faecalis*)获得万古霉素抗性基因 *vanA* 增加了细菌的基因表达负担[35]；携带 dfrA1-sat2-aadA1 抗性基因盒的大肠埃希氏菌生长速度下降[36]。

部分细菌获得 ARGs 后并未表现出显著的适应性代价，甚至适应性得到了提高。例如，铜绿假单胞菌 DNA 旋转酶基因 *gyrA*、*gyrB* 的抗性突变[28]和大肠埃希氏菌通过接合转移获得喹诺酮类抗性基因 *qnrA*、*qnrB*、*qnrS*[32]；沙门氏菌(*Salmonella*)通过接合转移获得磷霉素抗性基因 *fosA7* 也表现出无适应性代价[33]；大肠埃希氏菌通过转座子获得磺胺类抗性基因 *sul1* 和 *sul2*[34]。通过噬菌体转导获得 ARGs 提高了细菌的适应性，酿脓链球菌(*Streptococcus pyogenes*)携带 Φm46.1 噬菌体转导的大环内酯类和四环素类抗性基因 *mef*(A)、*tet*(O)[37]，以及大肠埃希氏菌携带 P1 噬菌体转导的 β-内酰胺类酶基因 $bla_{\text{CTX-M-55}}$[38]，均提高了细菌的生长速率。

2 染色体和质粒介导的 ARGs 的适应性代价差异及分子机制

ARGs 会给细菌带来适应性代价，深入解析适应性代价背后的分子机制有助于更加全面、系统地认识 ARB 的特性。在抗生素胁迫下，细菌可通过染色体基因突变和 HGT 方式获得 ARGs，其中质粒是 MGEs 介导 ARGs 发生 HGT 的重要载体[39]。因此，本节将聚焦于染色体和质粒介导的 ARGs 的适应性代价。由于 ARGs 种类和抗性机制不同，染色体和质粒介导的 ARGs 的适应性代价有所区别(表 2)。

2.1 染色体介导的 ARGs 的适应性代价

位于染色体上的 ARGs 引起的适应性代价与抗性机制相关联。目前已知的抗生素抗性机制包括降低外膜渗透性、抗生素的主动外排和修饰抗生素靶标等。

表1 不同获得方式下ARGs介导的适应性代价

Table 1 The fitness cost of ARGs under different acquisition methods

Access method of ARGs	Species	ARGs	Resistance mechanism	Characteristics	Fitness cost	Reference
Genetic mutation	*Staphylococcus epidermidis*	*rpoB*	Prevent the interaction between rifampicin and the β-subunit of RNA polymerase	The growth rate decreases	RF: <1.0	[27]
	Pseudomonas aeruginosa	*nfxB*	Regulators of multidrug efflux pumps	A large amount of energy is consumed, and the growth rate decreases	Growth curves: P<0.000 1	[28]
		gyrA, *gyrB*	Prevent fluoroquinolones from binding to DNA-modifying subunits of DNA gyrases	No fitness cost	RF: 1.012 (*gyrA*), 1.003 (*gyrB*)	
	Mycolicibacterium smegmatis	*rv2752c*	Encoding a bifunctional RNase J protein with β-lactamase and ribonuclease activities	Decreased transcription efficiency and reduced growth rate	RF: 0.87	[29]
Conjugation	*Escherichia coli*	*bla*$_{CTX\text{-}M\text{-}14}$	Enzymes that hydrolyze penicillin and third-generation cephalosporins	Some bacteria lose their conjugative ability	RF: 0.985	[30]
		bla$_{NDM}$	Enzymes that hydrolyze carbapenem drugs	Decreased virulence and loss of plasmids	RF: 0.813 006	[31]
		qnrA, *qnrB*, *qnrS*	Protect DNA gyrase and topoisomerase IV from inhibition by quinolone drugs	No fitness cost	RF: 1.030 (*qnr*A), 1.056 (*qnrB*), 1.016 (*qnrS*)	[32]
	Salmonella	*fosA7*	Produce fosfomycin-modifying enzymes	The growth rate is not affected	Growth curves: P=0.844 1	[33]
Transposon	*Escherichia coli*	*sul1*, *sul2*, *sul3*	Dihydropteroate synthase with low affinity for sulfonamide drugs	The motility is decreased, and the growth rate is reduced (*sul3*)	S: 0.021>0 (*sul1*), 0.019>0 (*sul2*), −0.087<0 (*sul3*)	[34]
	Enterococcus faecium	*vanA*	The encoded protein alters the synthesis of cell wall peptidoglycan precursors	The growth rate decreases	Growth curves: P<0.001	[35]
Integrator	*Escherichia coli*	dfrA1-sat2-aadA1	Type II integrons carry gene cassettes with a multi-resistance pattern	The growth rate decreases	S: −0.068<0	[36]
Transduction	*Streptococcus suis*	*mef*(A), *tet*(O)	Efflux pump proteins and ribosome protection proteins	The growth rate increases	Growth curves: the logarithmic phase (2 hours earlier) and the OD_{690} peak (3 hours earlier and being 0.25 higher)	[37]
	Escherichia coli	*bla*$_{CTX\text{-}M\text{-}55}$	Enzymes for multiple β-lactam drugs	The growth rate and elevated plasmid loss rate increases (P1)	RF: <1 (No P1), >1 (P1)	[38]

表2 染色体和质粒介导的ARGs的适应性代价分子机制

Table 2 Molecular mechanisms of chromosome- and plasmid-mediated fitness cost

Vector	Mechanism	Drug	ARGs	Impacted cost pathway	Fitness cost	Reference
Chromosome	Reduced permeability	The extended-spectrum	*ompC/F*	Impaired nutrient absorption→DNA methylation→DNA binding to proteins	Arrested the growth and replication of bacteria	[40-41]
			ompC/F	Decreased expression of *csgA/B* →impaired curli synthesis	Decreased biofilm formation	[42-43]
	Active transport of antibiotics	The extended-spectrum	—	Overexpression of efflux pumps	High energy burden	[15]
			mexABOprM, *mexCDOprJ*	Impact on the *rhl* QS system→reduced phenazine synthesis; lack of MexA	Decreased virulence	[44]
			mexEFOprN	Pumping out PQS precursors→delayed production of PQS signaling molecules	Impaired initiation of PQS function, decreased virulence	[45]
			mexEFOprN	H^+ antiport→intracellular H^+ accumulation	Imbalance of pH homeostasis	[46]
			ade group	Downregulated expression of pili and membrane structural proteins	Decreased biofilm formation	[47]
			acrABTolC	Promotion of QS signal AHL efflux→binding to membrane receptor SdiA	Promotion of biofilm formation	[48]
	Target modification	Aminoglycosides	*rrs*	A1408G mutation in 16S rRNA gene→no impact on the ON/OFF switching of the A site	No fitness cost	[49]
			rrs	A1408C/U mutations in 16S rRNA gene→affect the ON/OFF switching of the A site	Bacterial death	[49]
		Rifampicin	*ropB*	Alteration of the conserved β subunit of RNA polymerase	Decreased transcription efficiency	[6,50]
Plasmid	Inactivation and modification of the drug	β-lactams	$bla_{\text{KPC-2}}$	Downregulated expression of virulence genes *iucA*, *magA*, and *rmpA2*	Decreased virulence	[51]
			$bla_{\text{FOX-4/8}}$	Overexpression of AmpC enzyme →abnormal peptidoglycan metabolism→interference with cell wall integrity	Decreased virulence	[52]
			bla_{NDM}	Downregulation of locomotion, ATP synthesis, and DNA replication	Decreased motility and replicative capacity	[11]
		Tetracyclines	*tet*(X4)	Downregulated expression of *atlR* →inability to inhibit the copy number of plasmids	Decreased biofilm formation and virulence	[53]

(待续)

(续表2)

Vector	Mechanism	Drug	ARGs	Impacted cost pathway	Fitness cost	Reference
			tetX	Increased ATPase activity and protein synthesis	Increased metabolic burden	[54]
			tet(X4)	Encoded the H-NS protein→inhibits *tet*(X4) expression	No fitness cost	[55]
	Active transport of antibiotics	Tetracyclines	*tetH*	Downregulated expression of fimbrial genes *fimA* and *fimC*	Decreased motility	[56]
			tetA	Decreased K^+ uptake efficiency of the Trk system	High energy consumption	[57]
		Quinolones	*qepA2*, *oqxAB*	*gyr*A/B mutations that induce the target modification mechanism	Enhanced fitness	[58-59]
	Target modification	Glycopeptides	*van*	Modification of peptidoglycan→defect in sporulation	Decreased infectivity	[60]
		Aminoglycosides	*armA*	Resistant methylation of A1405 in 16S rRNA gene	No fitness cost	[61]
			armA	Interference with the endogenous methylation of C1402 by RsmI	Affects ribosome function	[61]
			npmA	Resistant methylation of A1408 in 16S rRNA gene	No fitness cost	[61]
			npmA	Block the activity of RsmF on C1407	Reduces the accuracy of translation	[61]
		Macrolides	*cfr*	Expression of *cfr*→resistant methylation of A2503 in 16S rRNA gene	No fitness cost	[62]
			cfr	Co-expression of *erm*B and *cfr*→dimethylation of A2508	Obstruction of the export tunnel for nascent peptide synthesis	[62]
		Polymyxins	*mcr*-1	Modification of lipid A→obstruction of LPS synthesis	Decreased virulence	[63]
			mcr-1	Modification of LPS→downregulation of *waa* and *rml*→downregulation of LPS core and O-antigen synthesis	Increased membrane permeability and membrane depolarization	[64]

细菌通过下调孔蛋白通透性来降低外膜渗透性，从而减少各种抗生素进入细胞，这是引起革兰氏阴性菌多重抗性的主要原因之一[65]。例如，常见的 *ompC/F* 孔蛋白基因表达下调将导致细菌吸收各种物质受阻，生长缓慢[40]。当氨基酸缺乏，RelA 蛋白感知空载 tRNA 时细菌会过表达鸟苷四磷酸以增强 DNA 甲基化酶催化复制起点与终点的 GATC 甲基化，该甲基化序列与 SqeA 蛋白结合而引发复制停滞[41]。孔蛋白表达下调会引起细菌 *csgA* 和 *csgB* 基因表达下调，进而导致卷曲菌毛(curli)合成下降[42]，最终使生物膜形成受到抑制[43]。

细菌染色体编码的外排泵能将多种抗生素排至胞外，使细菌具有多重抗性，这些外排泵主要是抗性结节分化家族(resistance nodulation division, RND)，且常见于革兰氏阴性菌。细菌外排泵的过表达不仅会增加能量消耗，还会泵出细菌代谢物，如群体感应(quorum sensing, QS)信号，影响菌群的代谢[15]。例如，铜绿假单胞菌过表达 *mexABOprM* 和 *mexCDOprJ* 会减少吩嗪类毒力因子的合成，并影响 QS 系统 *rhl*，进而引起 MexA 蛋白缺乏，导致毒力下降[44]；铜绿假单胞菌过表达 *mexEFOprN* 编码的外排泵 MexEF-OprN 会泵出 HHQ 分子(PQS 前体)导致 PQS 信号分子产生延迟，且降低细菌的毒力[45]；此外，该外排泵可作为质子反向转运体，其过表达可导致细胞内 H^+积累，从而影响胞内 pH 的稳态，对细菌造成伤害[46]。不同外排泵的过表达对生物膜形成能力的影响不同，鲍氏不动杆菌(*Acinetobacter baumannii*)过表达 *ade* 类外排泵会引起 CsuA/B、CsuC 和 FimA 菌毛蛋白以及 OmpA 外膜结构蛋白下调，从而导致生物膜形成能力下降[47]；鼠伤寒沙门氏菌过表达 *acrABTolC* 会促进 QS 信号 AHL 与 SdiA 膜受体结合，进而促进生物膜形成[48]。

细菌可修饰或改变抗生素的靶标从而使抗生素失效，这类情况主要涉及氨基糖苷类和利福平药物。染色体介导的 rRNA 基因位点突变的适应性代价更为严重。例如，16S rRNA 基因的 A1408 位点突变为嘌呤 G 时无明显的适应性代价；若突变为嘧啶 C/U 则会导致氨酰基-tRNA 解码位点(A 位点)形成稳定的碱基堆叠，难以完成 ON/OFF 切换，使翻译受到抑制，最终造成细菌死亡[49]。*rpoB* 突变介导 RNA 聚合酶的保守结构改变，虽然阻断了利福平与 β 亚基结合，但也损害了细菌的转录水平[6,50]。

2.2 质粒介导的 ARGs 的适应性代价

质粒介导的 ARGs 的适应性代价也与抗性机制相关。细菌编码可对抗生素的结构进行修饰或降解的酶，从而使抗生素失去活性[15]，此类基因在 β-内酰胺类抗生素中较常见，如 pLVPK(IncFII)-$bla_{\text{KPC-2}}$[51]、pUCP-FOX-8(IncQ)-$bla_{\text{FOX-4/8}}$[52]、p210704-1(IncC)-bla_{NDM} 以及 p210744-5(IncX3)-bla_{NDM}[11]，在四环素类抗生素中也较常见，如 pUC19-*tetX*[53-54]以及 *tet*(X4)[55]。细菌表达 β-内酰胺酶可造成细菌的 *iucA*、*magA* 和 *rmpA2* 毒力基因下调[51]以及 AmpC 酶高表达，干扰细胞壁完整性，导致成毒力下降[52]，还会使细菌的运动和复制能力下降[11]。催化四环素氧化的四环素灭活酶，如 *tet*(X)家族，可引起 *atlR* 基因下调，无法抑制质粒的拷贝数，导致细菌生物膜形成和毒力下降[53]，因而提高 ATP 酶活性和蛋白质合成，增大代谢负担[54]。此外，在大肠埃希氏菌携带的 20 个不同 *tet*(X4)阳性质粒中大部分质粒表现出适应性代价，但 pRF154-1(IncFII)、pRS3-1(IncFIB)和 pRF55-1(IncX1)这 3 个质粒显著促进了生物膜的产生，IncFIA 和 IncX1 型质粒表现出毒力增强，可能是这些质粒携带了生物膜形成和毒力基因[55]。

质粒可携带特定药物的外排泵基因，其过表达会引起适应性代价。对于携带四环素类药物外排泵基因的情况，嗜油不动杆菌(*Acinetobacter oleivorans*)过表达 pAST2-*tetH* 会引起 *fimA* 和 *fimC* 菌毛基因下调，导致运动性缺陷[56]；大肠埃希氏菌携带并表达 pBR322-*tetA*，因 Trk 转运系统对 K^+的吸收效率降低会增加能量消耗[57]。对于携带喹诺酮类药物外排泵的情况，大肠埃希氏菌表达 pBK-CMV-*qepA2* 表现为无适应性代价，当该基因引起位于染色体上的 *gyrA* 和 *parC* 突变时细菌的相对适应性降低(RF<1)，并通过 *marR* 缺失进行补偿[58]；而大肠埃希氏菌携带 pHNGC59(IncF)-*oqxAB* 和 pHNFD436(IncX3)-*oqxAB* 时相对适应性低(0.873 和 0.764)，当这引起位于染色体上的 *gyrAB* 突变时相对适应性却升高(RF>1)[59]。

质粒携带修饰抗生素靶标[如肽聚糖、核糖体和脂多糖(lipopolysaccharide, LPS)]的 ARGs，其适应性代价与修饰位点有关。革兰氏阳性菌

表达 pJAK112-*van* 基因可修饰肽聚糖与糖肽类抗生素结合的 D-Ala-D-Ala 位点，但因其孢子形成缺陷而导致感染能力下降[60]。pGB2(IncP-1)-*armA* 与 pGB2(IncP-1)-*npmA* 对 16S rRNA 基因的 G1405 和 A1408 位点进行抗性甲基化时无适应性代价，但这会干扰 A 位点 C1402 和 C1407 的内源甲基化，降低核糖体翻译效率[61]。pJAK112-*cfr* 的表达对 23S rRNA 基因 A2503 位点的抗性甲基化无适应性代价，但当 *ermB* 启动子驱动 *ermB* 与 *cfr* 基因共表达时会导致 A2508 位点发生二甲基化，这 2 个位点位于核糖体的肽链出口隧道，会干扰翻译功能[62]。pBBR1 MCS-5-*mcr*-1 介导革兰氏阴性菌的 LPS 的脂质 A 被带正电荷的残基(如磷酸乙醇胺或氨基阿拉伯糖)修饰，从而阻止多黏菌素破坏细菌的细胞壁，但会引起脂质 A 的合成受损[63]。Lu 等[64]对大肠埃希氏菌过表达 pHNSPH24(IncFII)-*mcr*-1 的转录组学研究发现，*waa* 和 *rml* 基因下调引起细菌 LPS 核心和 O 抗原合成下调，导致细胞膜通透性增强和膜去极化，此外还影响碳水化合物代谢、氧化应激与 DNA 损伤，以及 ABC 转运蛋白下调。

3 基于适应性代价的 ARB 防控策略

3.1 适应性代价的靶向干预

利用适应性代价干预抗性菌的核心思路是通过靶向调控相关基因的表达水平人为增加其生存成本，从而在无抗生素压力的环境中加速 ARB 的淘汰(图 2)。(1) 根据调控基因的靶向代谢物类似物的错误代谢诱导来加剧适应性代价：携带他伐硼罗抗性基因 *leuS* 的大肠埃希氏菌无法分离非亮氨酸与亮氨酸 tRNA 之间的错误连接，导致蛋白质合成异常，最终表现为生长缓慢，因此采用高度敏感的亮氨酸类似物(如正缬氨酸)能提高其错误率以增强其适应性代价[66]。携带利福平抗性的 *rpoB* H526Y 突变体大肠埃希

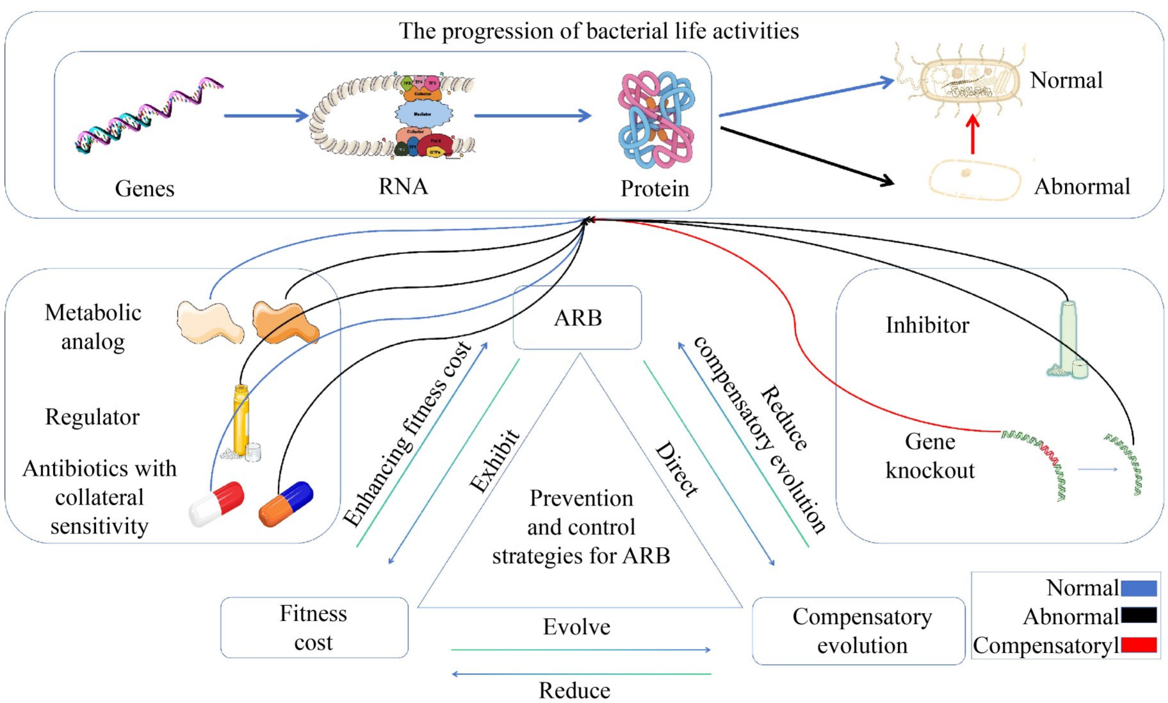

图2 ARB的防控策略

Figure 2 Prevention and control strategies for ARB.

氏菌，其 *upp* 基因参与尿嘧啶的回收利用，使转录效率显著升高，干扰细菌正常的转录调控，因此使用高度敏感的尿嘧啶类似物(如 5-氟尿嘧啶)能够干扰抗性菌的转录以加剧其适应性代价[67]。(2) 通过调节调控基因来加剧适应性代价：抗利福平药物的 *rpoB* H526Y 突变体大肠埃希氏菌，其 *gpp* 基因的编码产物能降解信号分子 ppGpp，使高转录效率无法被有效抑制，基于该菌的 RNA 聚合酶对 ppGpp 不敏感的特性，抑制 *gpp* 基因不会调控细菌转录效率，反而会使其细胞壁合成缺陷，从而加剧了适应性代价[67]。*mcr*-1 表达会诱导活性氧(reactive oxygen species, ROS)产生，ROS 会激活 *dinB*，通过负反馈抑制 *mcr*-1 的转录和翻译，从而增强大肠埃希氏菌的适应性，所以通过抑制 *dinB* 能降低 *mcr*-1 阳性菌的毒性和适应性[68]。(3) 利用细菌对抗生素的附带敏感性(collateral sensitivity)，即当细菌因基因突变或适应环境而对某种药物产生抗性时会表现出相应的适应性代价，反而对另一种不同作用机制的药物变得更加敏感的特性[69]。例如，*nfxB* 突变体铜绿假单胞菌过表达 MexCD-OprJ 外排泵从而产生对喹诺酮药物的抗性，但 MexD 蛋白会竞争性替代 MexXY-OprM 外排泵的 MexY 蛋白，而 MexX 蛋白相互作用，这减弱了 MexXY-OprM 外排泵对特异性底物氨基糖苷类抗生素的外排功能[70]。大肠埃希氏菌发生 *rfaH*、*rfaG* 和 *envZ* 基因突变，从而产生对头孢菌素药物的抗性，但也表现出苏氨酸-tRNA 连接酶合成缺陷和外膜不稳定性的适应性代价，使细菌对博来霉素药物的抗性下降[71]。金黄色葡萄球菌(*Staphylococcus aureus*)的 *apmA* 基因表达对安普霉素产生抗性，但也导致编码青霉素结合蛋白 PBP2a 的 *mecA* 基因表达下调、β-内酰胺酶活性降低和质子动力势紊乱引起外排泵活性丧失的适应性代价，使细菌对 β-内酰胺类药物的抗性下降[72]。

3.2 补偿性进化的分子阻断策略

补偿性进化是指 ARB 通过基因突变或非突变途径来提高适应性，从而降低或消除适应性代价，是细菌适应性进化的一种方式，在有无抗生素存在的情况下均可发生，主要包括二次突变、正向异位显性效应、基因重复和非突变性补偿 4 种类型，这增加了控制 ARB 的难度[73-74]。因此可以靶向补偿性进化的位点，设计药物或进行基因敲除加以干预(图 2)。例如，Balbontín 等[75]发现，发生双抗性突变的细菌容易引起转录-翻译冲突而产生 R 环，其可被通过补偿性进化的细菌表达的 Rnase HI 降解，因此可通过该酶抑制剂 RHI001 或基因敲除来抑制细菌 DNA 断裂修复。Olivares Pacheco 等[46]发现，RND 外排泵过表达会导致胞内 H^+积累，需要通过增大耗氧量以及表达硝酸盐呼吸链进行代谢补偿以将其消除，因此可通过降低氧气和硝酸盐的供应，以及使用硝酸盐呼吸链抑制剂来阻断该补偿机制。Wen 等[76]通过代谢组学分析发现，在亚最低抑菌浓度(minimum inhibitory concentration, MIC)下的强力霉素抗性大肠埃希氏菌通过下调丙酮酸以减少旁路碳代谢，下调毛果芸香碱以抑制次级代谢，从而减缓适应性代价，因此可通过下调二者的表达来阻断该补偿途径。Freihofer 等[77]发现结核分枝杆菌(*Mycobacterium tuberculosis*)发生 16S rRNA 基因的 A1408G 位点突变会引起生长缓慢的适应性代价，其可通过增强 *tlyA* 基因表达以促进 C1409 位点甲基化，从而降低适应性代价，因此通过使用卷曲霉素可诱导该基因失活。

4 总结与展望

细菌通过基因突变或水平基因转移获得 ARGs 时普遍伴随代谢负担、运动性、生物膜形成能力和毒力下降等适应性代价。适应性代价是自然环境中阻碍 ARGs 传播的关键生物学因素。本文围绕适应性代价进行了系统总结：阐述了适应性代价的核心产生机制及经典测量方法，明确了不同测量手段的优势与局限；针对 ARGs 的不同获得方式、不同载体(染色体、质

粒)系统讨论了其对适应性代价的差异化影响及机制；基于上述机制，提出了根据适应性代价的靶向干预与补偿性进化的分子阻断这 2 种 ARB 防控策略，为从“适应性权衡”角度遏制 ARGs 传播提供了科学依据。

先前的研究多聚焦于细菌的 AR 问题，而对人类社会而言，目前更迫切需要比研发新型抗生素更简便、低成本和高效的方法。因此可以从 ARB 的适应性机制入手解析适应性代价的具体表现，挖掘影响适应性代价的关键因素，并基于适应性代价机制设计干预策略，尤其是针对致病菌的 AR 问题及其携带的高风险 ARGs (如万古霉素、替加环素、碳青霉烯类抗生素抗性基因等)所引起的适应性代价。

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