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Review 综 述

致病性葡萄球菌 *cfr* 基因介导的多重耐药机制研究进展

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摘 要：葡萄球菌是临床常见致病菌及食源性致病菌，可在食品原料加工、包装及运输过程中污染食品，引起人体多种严重感染，其耐药性的不断增强对公共卫生安全产生了重大的威胁。葡萄球菌中 *cfr* (chloramphenicol-florfenicol resistance)基因编码的甲基转移酶，可引起细菌核糖体 RNA 的甲基化，从而阻碍或减弱多种化学结构不同的抗生素与肽基转移酶活性中心(peptidyl transferase center，PTC)的结合，导致葡萄球菌多重耐药表型的出现。噁唑烷酮类药物–利奈唑胺是继万古霉素后治疗耐药革兰氏阳性菌所致感染的最后一道防线，*cfr* 基因的出现大大加速了利奈唑胺耐药性的传播。*cfr* 基因广泛分布于多种致病性葡萄球菌中，*cfr* 基因与各类型可转移元件(质粒、转座子和整合相关元件等)密切关联的遗传环境是其广泛传播的结构基础。在 *cfr* 基因水平传播的过程中，食源性致病葡萄球菌作为中间者扮演着重要的角色。本文就近年来国内外对致病性葡萄球菌中 *cfr* 基因的分布状况、耐药机制、遗传环境、传播机制等进行综述，以期为防控致病性葡萄球菌的传播提供参考，以遏制多重耐药菌的进一步传播。

关键词：致病性葡萄球菌；*cfr* 基因；耐药机制；遗传环境；传播机制

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Mechanism of *cfr* gene-mediated multiple drug resistance in pathogenic *Staphylococcus*

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Abstract: The foodborne pathogenic *Staphylococcus* is common in clinical settings. It contaminates food during the raw material processing, packaging, and transportation, thus causing a variety of serious human infections. However, the drug resistance of this species has been on the rise, posing a huge threat to public health. The methyltransferase encoded by the *cfr* (chloramphenicol-florfenicol resistance) gene in *Staphylococcus* can cause methylation of bacterial ribosomal RNA, thus blocking or weakening the binding between multiple antibiotics with different chemical structures and peptidyl transferase center (PTC). This explains the development of multiple drug resistance in this species. Linezolid, an oxazolidone, is regarded as the last line of defense after vancomycin in the treatment of infections caused by drug-resistant Gram-positive bacteria. *cfr* gene accelerates the spread of linezolid resistance. This gene is ubiquitous in a variety of pathogenic *Staphylococcus* bacteria and the close relationship of the gene with various mobile elements (plasmids, transposons, integration-related elements, etc.) is the structural basis for its wide spread. In the horizontal transfer of *cfr* gene, foodborne pathogenic *Staphylococcus* plays an important role as an intermediary. This study reviews the distribution, resistance mechanism, genetic environment, and transfer mechanism of *cfr* gene in pathogenic *Staphylococcus*, which is expected provide a reference for prevention and control of the spread of pathogenic *Staphylococcus* and the control of further spread of multidrug resistant bacteria.

Keywords: pathogenic *Staphylococcus*; *cfr* gene; resistance mechanism; genetic environment; transmission mechanism

葡萄球菌广泛存在于自然界中，以共生微生物的形式定殖于人类鼻腔中，是少数家畜(如牛、家禽)皮肤微生物群的一部分，是引起人及动物多种感染的重要致病菌。葡萄球菌在创口、动物鼻腔中定殖，在临床引起严重的感染(皮肤和软组织感染、肺炎、感染性心内膜炎、骨关节感染、中枢神经系统感染、血流感染和中毒性休克)[1−2]。葡萄球菌亦是常见的重要食源性致病菌，其可在食品中大量繁殖，在特定条件下产生多种毒素[3]，人及动物摄取了含有大量葡萄球菌污染的食品后，引起感染，导致食物中毒等疾病[4]，是危害食品安全与人类健康最重要的风险来源之一[5]。

葡萄球菌耐药性严重。现阶段，细菌耐药性问题已经成为全球关注的焦点问题。据英国《全球抗菌药物耐药回顾》估计，全球每年因耐药性感染的死亡人数超过 70 万，在欧洲和美国每年有至少 50 000 人死于耐药性感染，若不

及时遏制其发展，预计截止到 2050 年，全球每年将有 1 000 万人死于耐药菌感染，远高于目前因癌症死亡人数[6]。据报道在美国每年预计有超过 24 万人因感染葡萄球菌致病[7–8]。世界卫生组织发出遏制耐药细菌的呼吁：迫切需要在“One Health”指导下，在整个生态系统中(包括环境−食品−人等多个环节)采取统一行动以遏制耐药细菌的蔓延[9]。

耐药基因是细菌产生耐药性的重要因子，多重耐药基因更是在细菌多重耐药性中扮演着重要的角色。葡萄球菌中质粒编码的多重耐药基因 *cfr* (chloramphenicol-florfenicol resistance，*cfr*)可同时介导包括治疗多重耐药阳性菌的最后一道防线−恶唑烷酮类抗生素在内的五类结构不同的抗生素(氯霉素类、林可酰胺类、截短侧耳素类和链阳菌素 A 类)耐药，且位于可转移元件上的 *cfr* 基因可在不同种属间转移，*cfr* 基因已经成为抗生素治疗的严重威胁[10–11]。*cfr* 基因的出现进一步加剧了葡萄球菌耐药性的传播，葡萄球菌耐药问题愈加严峻。

1 *cfr* 基因及其耐药机制

2000 年利奈唑胺获得美国食品和药品管理局(Food and Drug Administration，FDA)批准，用于治疗革兰氏阳性球菌引起的感染，包括由耐甲氧西林金黄色葡萄球菌(methicillin-resistant *Staphylococcus aureus*，MRSA)引起的疑似或确诊的医院获得性肺炎 (hospital acquired pneumonia，HAP)、社区获得性肺炎 (community-acquired pneumonia，CAP)以及耐万古霉素肠球菌(vancomycin-resistant *Enterococcus*，VRE)感染[12]，利奈唑胺是继万古霉素后治疗耐药革兰氏阳性菌所致感染的新型恶唑烷酮类药物，并且作用显著。利奈唑胺作用于细菌 50S 核糖体亚基的肽基转移酶活性中心(peptidyl transferase center，PTC)，抑制 mRNA 与核糖体的结合，干扰细菌蛋白质的合成，发挥抗菌作用[13–14]。2000 年，Schwarz 等[11]在牛源松鼠葡萄球菌的耐药质粒 pSCFS1 中发现一新型耐药基因 *cfr*，其编码 349 个氨基酸，可介导氯霉素和氟苯尼考耐药。进一步的研究表明，*cfr* 基因在金黄色葡萄球菌和大肠埃希氏菌中均可提高多种不同化学结构药物的最小抑菌浓度(minimum inhibitory concentration，MIC)。*cfr* 基因可同时介导以下 5 类不同化学结构抗生素耐药：氯霉素类(包括氯霉素和氟苯尼考)、林可酰胺类(包括克林霉素)、恶唑烷酮类(包括利奈唑胺)、截短侧耳素类(包括泰妙菌素和沃尼妙林)和链阳菌素 A 类(包括普那霉素II、维吉尼亚霉素 M 和达福普汀)，该表型被命名为 $PhLOPS_A$[15]。同时，*cfr* 基因还可减弱十六元环大环内酯类抗生素与核糖体的亲和力，降低细菌对十六元环大环内酯类抗生素的敏感性[16]。

截至目前 *cfr* 基因的起源仍未确定，但 *cfr* 基因所编码的自由基 S-腺苷-L-甲硫氨酸(SAM)甲基转移酶 Cfr，具有自由基 SAM 甲基转移酶的显著特征(图 1)[17–20]。Cfr 在进化关系上与 SAM 家族中 RlmN 接近(图 1，3)[18-19]，同时 Cfr 蛋白的 SWISS-MODEL 同源模型与 RlmN 具有最高相似度(图 1A–C)。RlmN 是一种甲基转移酶，负责 23S rRNA 核苷酸 A2503 的 C2 位置甲基化[21–22]。而进一步的结合足迹实验和 MALDI-TOF MS 显示 Cfr 蛋白可在细菌 50S 核糖体亚基 23s rRNA 核苷酸的 A2503 (C2 和 C8)及 C2498 位点甲基化(图 1E)[19–20]。氯霉素类、林可胺类、截短侧耳类、恶唑烷酮类和链阳菌素 A 类药物均结合于细菌核糖体的 PTC，且其靶位点均在 A2503 附近，Cfr 在 A2503 的 C8 位点的甲基化导致以上几类抗生素靶位点构象的变化，阻遏了抗生素与靶位点的结合，导致多重耐药的出现(图 1D)[20]。同时，Cfr 介导的 A2503 甲基化

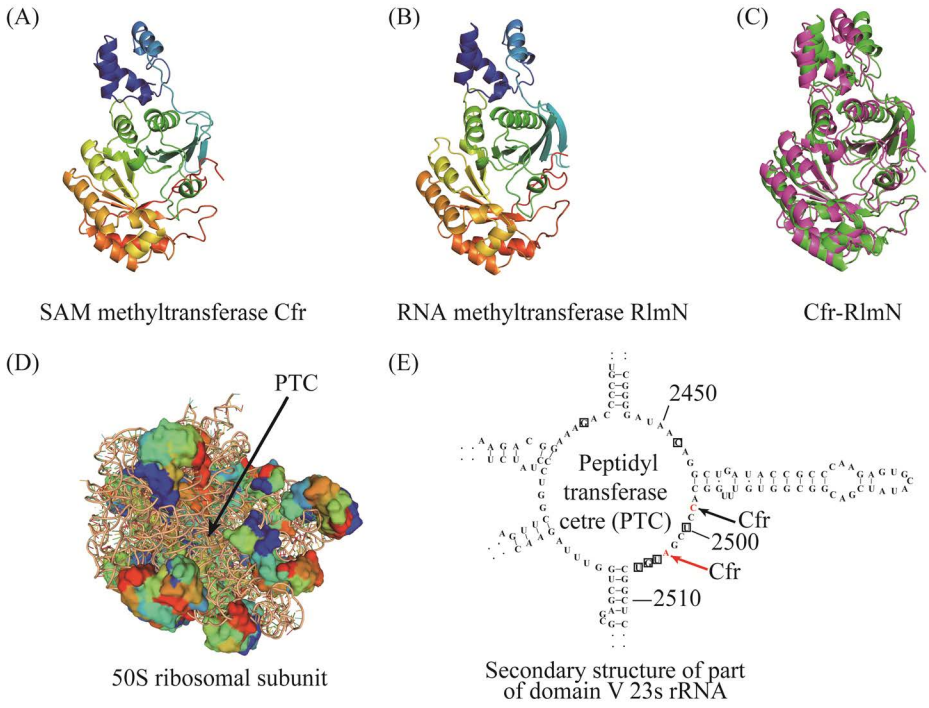

图 1　甲基转移酶(Cfr 和 RlmN)及 Cfr 作用位点(23s rRNA 的 V 域)结构图[17–19]

Figure 1　Structure of methyltransferase (Cfr and RlmN) and Cfr target sites (V domain of 23S rRNA)[17–19]. A: predictive structures of SAM methyltransferase Cfr; B: predictive structures of RNA methyltransferase RlmN; C: comparison of Cfr and RlmN prediction structures (Cfr-purple, RlmN-green); D: X-ray structure of the 50S ribosomal subunit; E: the secondary structure of part of domain V 23S rRNA.

干扰了十六元环大环内酯类抗生素螺旋霉素和交沙霉素侧链与核糖体的结合，介导十六元环大环内酯类抗生素耐药[16]。

以上研究表明，Cfr 蛋白对核糖体 RNA 甲基化，通过靶位点的保护阻止了多种抗生素与其靶位点的结合，使细菌中蛋白质合成得以正常进行，从而介导了葡萄球菌多重耐药表型。

2　*cfr* 基因的分布

多重耐药基因 *cfr* 分布极为广泛(表 1)。自 *cfr* 基因在 2000 年于松鼠葡萄球菌(*Staphylococcus sciuri*)中首次发现以来，截至目前，在德国、丹麦、美国、哥伦比亚、墨西哥、西班牙、爱尔兰、意大利、中国、印度、巴西、葡萄牙、比利时和越南等多地致病菌中均报道了 *cfr* 基因的存在(表 1)。这些致病菌包括葡萄球菌(*Staphylococcus*)[23–28]、肠球菌(*Enterococcus*)[29–32]、芽孢杆菌(*Bacillus*)[33–34]、普通变形杆菌(*Proteus vulgaris*)[35]、大肠杆菌(*Escherichia coli*)[36]、溶乳酪细球菌(*Macrococcus caseolyticus*)[37]、*Jeotgalicoccus pinnipedialis*[37]、猪链球菌(*Streptococcus suis*)[38]以及摩氏摩根菌(*Morganella morganii*)[39]等。其中 *cfr* 基因主要分布在葡萄球菌属中[40]，包括多种葡萄球菌在内(*S. sciuri*、*S. epidermidis*、*S. cohnii*、*S. saprophyticus*、*S. warneri*、*S. simulans*、*S. hominis*、*S. arlettae*、*S. haemolyticus*、*S. equorum*、*S. lentus*、*S. capitis*、*S. chromogenes*、*S. kloosii*、*S. simulans*、*S. lugdunensis*、*S. aureus* 和 MRSA)(表 1)[28,41]。最近我们首次在零售肉制

表 1 *cfr* 基因在葡萄球菌中的流行情况及其遗传背景

Table1 Prevalence and genetic background of *cfr* gene in *Staphylococcus*

Bacteria	Source	Date of isolation/publication	Country	Gene location	Genetic background
S. lentus, *S. simulans*, *S. sciuri*, *S. aureus*,	Cattle, swine	1997-2000/ 2000-2006	Germany[11,25,45]	pSCFS1, pSCFS3	IS*21-558-cfr*-ΔTn*558* (Tn*558*-like); *lsa (B)-cfr-pre/mob-erm* (33)-*spc-tnpC*-Δ*tnpB-rep*,
S. lentus, *S. aureus*, MRSA	Swine, patients	2001-2005/2014	Germany[25], America[46], Columbia[41,47]	pSCFS3, p1128105, chromosome	Tn*558*-like, Δ*rep*-Δ*tnpB-cfr-rec-pre/mob*-Δ*rep*, *erm* (B)-*cfr*-IS*21-558-erm* (B)
S. warneri, *S. simulans*	Pig	2006/2006	Denmark[48]	pSCFS6	*tnpA-tnpB*-Δ*tnpC*-IS*21-558-lsa* (B)-*cfr*-IS*21-558*-ΔTn*558*
S. aureus, *S. epidermidis*,	Patients	2007/2013	America[26,49]	pSCFS3, p7LC, p004-737X,	Tn*558*-like, IS*256-aacA-aphD*-IS*Enfa4-cfr-orf1*-IS*Enfa4*,
S. epidermidis, *S. aureus*, MRSE,	Patients	2008/2013	America[28], Spain[50–52], Italy[53]	pSA737, pSCFS3-like, pSCFS7-like, plasmid	Δ*rep*-Δ*tnpB-cfr-rec-pre/mob*-Δ*rep*, Tn*558*-like
S. cohnii, *S. epidermidis*, MRCoNS, *S. haemolyticus*, *S. cohnii*	Patients	2009/2010	Mexico[54] China[55]	Plasmid, pSS-02-like	Δ*rep*-Δ*tnpB-cfr-rec-pre/mob*-Δ*rep*
MRSA, MRSE, *S. cohni*, *S. arlettae*, *S. saprophyticus*, *S. equorum*	Patients, animal, milk	2010/2015	Spain[56–57], Italy[58], China[59–60]	pERGB, pSP01.1, pSS-(01-03), pBS-01, pMSA16	IS*21-558-cfr*-IS*431-ant (4)-Ia-tet* (L)-*dfrK*, *res-tnp-cfr*-IS*21-558-lsa (B)*-Tn*552like*, Δ*pre/mob-cfr*-Δ*tnpB-rep*-Tn*917*, *rep*-Δ*pre/mob-cfr-pre/mob-erm* (C), Tn*558*-like, IS*256-aacA-aphD*-IS*Enfa4-cfr-orf1*-IS*Enfa4*-Tn*558*, *rep-erm* (A)-Δ*pre/mob-cfr*-Δ*pre/mob*
S. aureus, MRSP, MRSA, CoNS, *S. capitis*, CoNS, *S. lentus*, *S. sciuri*, *S. cohnii*, *S. haemolyticus*, *S. rostri*, *S. simulans*, *S. arlettae*	Patients, dog, pig, chicken, duck, workers, environment, slaughterhouse	2011/2018	America[61], Portugal[62], China[27,63–65]	p2823634, p25ZB12, plasmid, chromosome, pHNKF3, pHNCR35, pHNZT2	Tn*558*-like, IS*256-aacA-aphD*-IS*Enfa4-cfr-orf1*-IS*Enfa4*, *rep*-Δ*pre/mob-cfr-pre/mob*
S. epidermidis, *S. aureus*, MRSA, *S. capitis*, *S. cohnii*,	Patients, pig	2012/2019	Germany[66], Ireland[67], Brazil[68], Portugal[69], China[27,63,70–72], Korea[73]	p12-00322-like, pSCFS3-type, pM12/0145, pM13/0401, p45547X, p6ZB3, pN3, p2ZX3, p2ZG3, p5ZG14, p5ZX13, pMHZ, pHK01, pRM01, pRA01, p432	Tn*558*-like, IS*257like-cfr*-IS*21-558-lsa (B)*-IS*257like-res*, *tnpA-tnp-cfr-tnpC-orf138-fexA*, *istBlike-tnp-cfr*-IS*21-558-lsa* (B), *rep*-Δ*pre/mob-cfr-pre/mob-erm* (B), IS*Enfa4-cfr-orf1*-IS*Enfa4*, IS*256like-cfr*-IS*256like*

(待续)

(续表 1)

S. epidermidis, MRSA, *S. cohnii*, *S. capitis*, *S. delphini*, *S. sciuri*, *S. chromogenes* *S. aureus*	Patients, porcine, duck, pig, fecal,	2013/2021	Ireland[74], China[42,71–72,75–79], Korea[73]	Plasmid, pLRSA417, pSR01, pSS-02, pSCFS7-like, chromosome, pWo28-3	IS*256-aacA-aphD*-IS*Enfa4-cfr-orf1*-IS*Enfa4*, IS*Enfa4-cfr-orf1*-IS*Enfa4*,*cfr-orf1*-IS*Enfa4* (integrate into *mec* Complex), Tn*558*-derivative, *fex* (A)-*orf138-aacA-aphD*-IS*257-aadD-ble*-IS*21-558-cfr-res-tnpA*, ΔIS*1216-aacA-aphD*-IS*256-cfr*-IS*256*, Tn*558*-like,
CoNS, MRSA, MRSH, MRSE, *S. haemolyticus*, CoNS, *S. capitis*, *S. cohnii*, *S. equorum*, *S. sciuri*, *S. simulans*, *S. capitis*, *S. delphini*, *S. aureus*	Calves, pig, veterinarian, patients, chicken, pork, duck	2014/2021	Germany[40,80], Ireland[81], India[82], China[27,42–43,72,83–84], Korea[73]	p13-00130, p13-00131, p13-00882, pSEM13-0451, pSAM13-0401, p13L105, pG350, pB289, pYFC28, pHNTLD18, pHNTLKJC2, pWo35-20, pWo28-3, pWo28-1, pWo27-9, chromosome	Tn*558*-like, *tnpA-tnp-cfr-tnpC-orf138-fexA*, *rep-pre/mob-*Δ*lsa* (B)-*cfr-pre/mob-erm* (T), *aacA-aphD*-IS*Enfa4-cfr-orf1*-IS*Enfa4*, *erm* (C)-Δ*pre/mob-cfr-pre/mob-rep*, Tn*558*-derivative (chromosome), *tnpA-res-cfr*-IS*21-558-ble-aadD*-IS*257-aacA-aphD-orf138-fexA-optrA*, *tnpA-res-cfr*-IS*21-558-ble-aadD*-IS*257-aacA-aph D* (chromosome)
S. aureus, MRSA, *S. arlettae*,	Patients, fecal, dumplings	2015/2019	Italy[85–86], China[87–88], Korea[73]	Chromosome, chromosome-Tn*6644*, pSA-01, p2868B2	IS*Enfa5-cfr*-IS*Enfa5* (chromosome), IS*431-rep-*Δ*pre/mob-cfr-pre/mob-erm* (C)-*repU-*Δ*pre/mob-tet* (L)-IS*431*, Tn*558*-like
MRSA, MRSE, MRSH, *S. epidermidis*, *S. hominis*, *S. lugdunensis*, *S. cohnii*, *S. aureus*	Patients, chicken, pig, wound, blood, animals	2016/2021	Spain[89], China[27,90], Korea[73], China[91]	pSCFS7-like, p26FS31, p25FS24, p25FS35, pHB119, pHYB6, pH29-46	*Erm* (A)-Δ*pre/mob-cfr-pre/ mob-rep*, Tn*558*-like, IS*256-aacA-aphD*-IS*256-cfr-orf1*-IS*256-fexA*
MRSA, *S. aureus*, *S. epidermidis*, *S. pasteuri*, *S. cohnii*	Patients, sputum, pig, environment	2017/2022	Belgium[92], China[90], Korea[73,93],	pSA12	Tn*558*-like
S. haemolyticus, *S. cohnii*	Patients	2018/2020	Vietnam[94]	pLRSA41-like	IS*256-aacA-aphD*-IS*Enfa4-cfr-orf1*-IS*Enfa4*
MRSA, *S. aureus*	Pig	2019/2021	Spain[95], Italy[96]	Chromosome	Tn*558*-like
MRSA	Pig	2020/2020	Spain[97]	Plasmid	Tn*558*-like

MRSA: methicillin-resistant *Staphylococcus aureus*; MRSH: methicillin-resistant *Staphylococcus haemolyticus*; MRSP: methicillin-resistant *Staphylococcus pseudintermedius*; MRSE: methicillin-resistant *Staphylococcus epidermidis*; CoNS: coagulase-negative *staphylococci*; MRCoNS: methicillin-resistant coagulase-negative *staphylococci*; Bright green: mobile genetic elements related gene.

品来源的海豚葡萄球菌(*S. delphini*)中发现了 *cfr* 基因的存在，并且具有新的遗传结构，将会在下面详细论述[42]。携带 *cfr* 基因的致病性葡萄球菌的来源极为广泛，主要为临床患者及食源性动物，包括养殖场、屠宰场、以及零售肉制品[28]，而这些食源性动物则可能随着食物链成为人的食品来源，暗示着携带 *cfr* 基因的致病性葡萄球菌随食物链传播的可能(表 1)[43–44]。值

得注意的是,许多 *cfr* 基因的研究结果来自我国。这些观察结果表明，*cfr* 基因的传播和扩散要比预想的更为广泛，由 *cfr* 基因介导的耐药情况亦更为严重。

cfr 基因传播范围如此之广泛，与其遗传环境和传播机制密切相关。

3 *cfr* 基因遗传环境及传播机制

致病菌形成耐药性的重要原因是耐药基因的转移，探究致病菌耐药基因的遗传环境及其动态转移过程、耐药性微进化趋势，是阐明自然条件下致病菌获得耐药性的关键，不仅可以为我们合理使用抗生素提供理论基础，还可为防控耐药性致病菌提供良好的分子靶标。

结构决定功能，*cfr* 基因的传播机制即隐藏在其遗传结构中。*cfr* 基因广泛分布于质粒(表1)。葡萄球菌中已发现的 *cfr* 基因大多数和其他耐药基因共存在质粒上，*cfr* 基因上下游存在有一些插入序列或转座子元件,可介导 *cfr* 基因及其共存的耐药基因的转移。*cfr* 基因首次发现于松鼠葡萄球菌中的 pSCFS1 质粒上[11]，随后被陆续发现于质粒 pSCFS1 (*S. simulans*)[25]、pSCFS3 (*S. aureus* 和 *S. lentus*)[25]、pSCFS6 (*S. warner* 和 *S. simulans*)[48]、pSCFS3-like (MRSA)[61]、pSS-01 (*S. cohnii* 和 *S. saprophyticus*)[60]、pSS-02 (*S. saprophyticus*、*S. sciuri*、*S. cohnii* 和 *S. arlettae*)[60,98]、pSS-03 (*S. saprophyticus*、*S. cohnii*、*S. arlettae* 和 *S. sciuri*)[60]、pSS-04 (*S. sciuri*)[98]、pJP2 (*S. rostri*)、pBS-01 (*S. cohnii*、*S. saprophyticus* 和 *S. sciuri*)[60]、p7LC (*S. epidermidis*)[49]、p004-737X (MRSA)[49]、pSCFS7 (MRSA)[99]、pERGB (MRSA)[56]、pSA1900 (*S. aureus*)[28]、p1128105 (MRSA)[46]、pSP01 (*S. epidermidis*)[100]、pWo28-3 (*S. sciuri*)[78]、pWo35-20 (*S. sciuri*)[84]、pSA-01 (*S. arlettae*)[87] 以及染色体(MRSA、*S. hyicus*、*S. cohni*、*S. arlettae*、*S. saprophyticus*、*S. sciuri* 和 *S. lentus*)[25,48–49,60,77,98]。对上述遗传环境进行对比分析发现，目前在致病性葡萄球菌中 *cfr* 基因遗传环境具有以下特点：

(1) *cfr* 基因存在于质粒上，亦有定位于染色体上，均伴有可转移元件包括插入序列、转座子以及 *pre*/*mob* 基因；

(2) 可转移元件与 *cfr* 基因的转移密切相关；

(3) *cfr* 基因与其他耐药基因共存；

(4) *cfr* 基因的传播方式有水平传播(包括接合、转化及转导)和垂直克隆传播，以水平传播为主；

Kehrenberg 等[25]的研究发现 *fexA* 与 *cfr* 基因共同定位于葡萄球菌 pSCFS3 质粒上，与插入序列 IS*21-558* 耦合，插入到 Tn*558*，IS*21-558* 在质粒间重组过程中形成 Tn*558* 与 IS*21-558* 复合结构 Tn*558*-like。*cfr* 与移动遗传元件的关联可能有助于它们的传播，如有研究[48]发现质粒 pSCFS6 中的 2 个 IS*21-558* 元件之间可形成具有基因转位(transposition)特征的微环结构(minicircle)，此含有 *cfr* 基因的独立环状结构，进一步通过重组整合至特定位点,介导 *cfr* 基因的转移。在临床源葡萄球菌 pSCFS7 质粒和动物源葡萄球菌 pSCFS3、pSS-02 质粒上的 *cfr* 基因具有相同的 *cfr* 遗传环境[25,60,99]。而我们在 1 株食品源的 MRSA 菌株中的质粒 p2868B2 上亦发现了具有相同遗传环境的 *cfr* 基因,且此质粒亦具有转移的潜力。同时我们在食品源海豚葡萄球菌中发现 *cfr* 基因和另外 4 个 ARGs (antibiotics resistance gene，ARG)定位在一个新型的 Tn*558* 转座子 Tn*558*-derivative 上(图 2)[101]。亦检测到了具有转位活性的微环结构(minicircle of Tn*558*-derivative)，暗示 *cfr* 基因具有利用 Tn*558*-derivative 进一步转移的可能。Tn*558*-like 和 IS*21-558* 复合结构利用其转位功能携带 *cfr* 基因在耐药菌中传播与扩散。

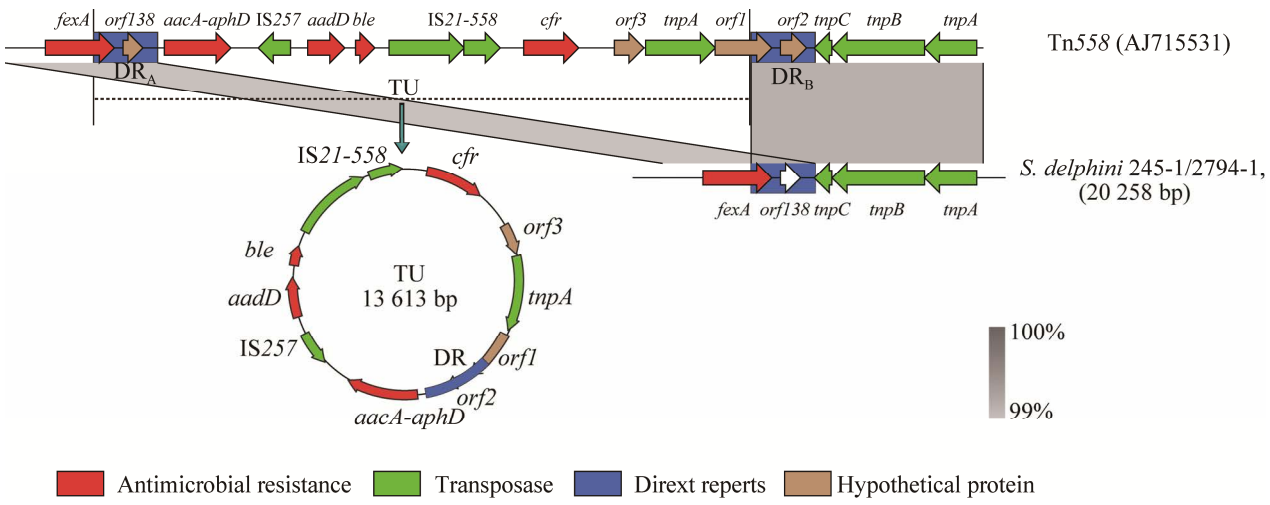

图 2　Tn*558*-derivative 中 *cfr* 基因环境及直接重复序列(DRs)介导的可转移单元(Tu)的形成[42]

Figure 2　The environment of the *cfr* gene on chromosomes of *Staphylococcus delphini* and the formation of translocatable unit (TU) mediated by direct repeats (DRs)[42].

除了位于 Tn*558*-like 及其相关的 IS*21-558* 插入元件之外，IS*256*、IS*257*、IS*431*、IS*Enfa4* 及 IS*Enfa5* 亦与 *cfr* 基因的转移密切相关(表 1)。Liu 等[87]发现在阿尔莱特葡萄球菌中位于 pSA-01 质粒上的 *cfr* 基因上下游分布有 3 个重复的 IS*431* (IS*431*A、IS*431*B、IS*431*C)插入序列，IS*431*A 和 IS*431*B 之间及 IS*431*B 和 IS*431*C 可能同时形成环状结构，其中的耐药基因可以通过相同的 IS 元件所介导的位点特异性重组被环化移动[102]，介导 *cfr* 基因在质粒间和质粒内的重组中转移。具有类似特征活性的插入序列还包括 IS*256*[98]、IS*257*[100]、IS*Enfa5*[86]和 IS*1216*[86]等。另一组涉及质粒重组及转移的基因 *pre*/*mob* 与 *cfr* 基因构成 Δ*pre*/*mob*-*cfr*-*pre*/*mob* 的遗传结构，此结构在多个质粒中均有存在(表 1)[27,60,65]。

值得注意的是，一些位于染色体上的 *cfr* 基因，因其上下游经常伴有其他的重复序列(耐药基因或直接重复序列)，*cfr* 亦可通过类似于 IS 介导重组环化的方式，脱离染色体发生转移。位于 MRSA 染色体上的 *cfr* 基因的上下游存在 2 个相同的耐药基因 *erm*(B) (介导 macrolide-lincosamide-streptogramin B 抗性，MLS_B)，2 个相同的 *erm*(B)通过环化重组，形成含有 *cfr*-*istAS*-*istBS*-*erm*(B)的微环，并从染色体上环化脱离[41]。相同的 *erm*(B)基因环化重组介导 *cfr* 水平转移现象亦存在于表皮葡萄球菌多重耐药质粒 pSP01 中[100]。存在于 *cfr* 基因上下游的同向重复序列(包括上面提及的插入序列及耐药基因)通过一种新的重组环化的机制[103–104]，形成可转移的单元(translocatable unit，TU)，促进 *cfr* 基因在质粒之间以及染色体上的转移[105]。

我们在 2 株海豚葡萄球菌中发现的 *cfr* 基因和另外 4 个 ARGs 定位在 1 个新型的 Tn*558* 转座子上(图 2)，而此新型的 Tn*558*-derivative 转座子内部存在两段方向相同的 1 326 bp 的重复序列(duplicated region，DR)，这两个相同的 DR 可以介导 TU 的形成，而 TU 序列中包含的多重耐药区与 *S. sciuri* 中质粒 pWo28-1 以及 *S. rostri* 中质粒 pJP2 (KC989517.1)的序列具有 99%的核酸相似度[78]。与传统的由插入序列或耐药基因组成的重复序列不同，此重复序列则是由部分 *fexA* (430bp)序列和 *orf138* 所组成。携带有 *cfr*

基因的 TU 可脱离染色体，表明 *cfr* 基因可能随着由重复序列介导的重组环化而转移，而 DR 在介导抗性基因转移过程中扮演着重要的角色。尽管 *cfr* 并未处在一个自由质粒中，但它仍然存在于一个高度不稳定/可移动的区域，并且可通过此区域中重复序列的重组产生可移动环，使得 *cfr* 仍然可以从染色体脱离，可能进一步地转移扩散。

cfr 与其他耐药基因共存于同一葡萄球菌的质粒或染色体上，导致复合耐药及高水平耐药表型的出现。Kehrenberg 等[25]研究发现 *fexA* 与 *cfr* 基因共同定位于葡萄球菌中 pSCFS3 质粒上，携带有 *cfr* 和 *fexA* 质粒 pSCFS3 的原始菌株和转化菌株具有高水平的氟苯尼考耐受性。Smith 等[16]在 MRSA 临床株 CM05 中发现，*erm*(B)和 *cfr* 在 CM05 的染色体中组成一个 *mlr* 操纵子，由 *erm*(B)启动子所控制，组成型表达。*erm*(B)和 *cfr* 基因分别编码的两种甲基转移酶联合作用导致 23S rRNA 核苷酸中 A2058 和 A2503 的 2 个特定核苷酸的修饰，协同增强了对十六元环大环内酯类抗生素的抗性。更多的研究表明 *cfr* 与多种耐药基因，包括 *optrA*、*fexA*、*aadD*、*ble*、*aacA-aphD*、*tet* (L)、*dfrK*、*lsa* (B)、*erm*(A)、*lnu* (B)、*optrA*、*fos* (D)和 *poxtA* 等共存于葡萄球菌中同一质粒或染色体耐药区域[56,58–59,78,84,86–87,106]，亦有 *cfr* 基因插入至葡萄球菌盒式染色体 *mec* 复合体中的结构[77]。同时携带 *cfr* 与其他耐药基因的多重耐药质粒/区域的出现，可能反映了 *cfr* 基因遗传环境的进化趋势，即趋向于耐药性集合的方向，其背后的推动因素可能为抗生素的选择压力，即抗生素对耐药基因的共选择加剧了 *cfr* 与其他多种耐药基因的共存。

耐药基因的传播扩散有 2 种方式：随亲本的垂直克隆传播和借助可移动元件(包括质粒、转座子、插入序列、噬菌体等)水平传播。研究表明 *cfr* 基因的扩散存在克隆传播[72,107–109]，而且大量的研究[43,78,87]表明，*cfr* 可通过水平转移的方式(自然转化、接合、转导)传播。Cafini 等[110]发现携带有 *cfr* 基因 pSCFS7-like 质粒的葡萄球菌可在种内、种间、MRSA 与 MRSA 间接合转移，亦可以借助噬菌体转导以及自然转化转移，表明 *cfr* 基因不仅能接合传播，而且可以通过噬菌体介导的转导传播。此外还有前面所提及的转座子 Tn*558* 及 Tn*558*-like 的转座作用，插入序列(IS*21-558*、IS*256*、IS*257*、IS*Enfa4*、IS*Enfa5* 和 IS*1216*)及重复序列(如 *erm*(B)和 DR)通过同源重组形成含有 *cfr* 及其他 ARGs 的微环或 TU 结构，在不同质粒之间以及质粒和染色体之间的转移方式。

由于 *cfr* 基因可通过染色体的垂直传播和通过移动元件发生水平转移，导致 *cfr* 基因可在不同来源的葡萄球菌之间发生转移与扩散。在 *cfr* 基因传播的过程中，食源性葡萄球菌作为中间环节，既是耐药基因的接受者，也是耐药基因的天然携带者或散播者[110]，食品源的葡萄球菌作为 *cfr* 基因的储存库和传播工具，被认为是 *cfr* 基因进入人体最直接的载体。*cfr* 阳性葡萄球菌不断在家畜、环境、食品和人源临床样品中被检出[25,50,86,107]，并且在不同来源 *cfr* 阳性菌株中，具相似(甚至相同)耐药质粒以及亲缘关系极为接近的菌株进化关系[27]，表明摄入受污染的肉类可能会导致致病性耐药细菌在食物、动物和人类之间的传播[111]，已经发生了携带 *cfr* 基因的质粒在猪和人的葡萄球菌之间的传播[55]。而 Wang 等[65]在对猪、工人、屠宰场和生猪市场分离的葡萄球菌中 *cfr* 基因分布的研究中发现，不同来源分离得到的 *S. simulans* 的 PFGE 谱系具有高度相似性，表明携带 *cfr* 的 *S. simulans* 已在猪、人、环境和动物源性食品中

存在克隆传播。Cuny 等[40]发现，在同一农场的猪源 *S. kloosii*、人源 *S. cohnii* 以及医院兽医源 *S. epidermidis* 中质粒上的 *cfr* 基因遗传结构完全相同，进一步表明 *cfr* 基因存在随食物链/接触链在生态系统中传播的可能性。携带 *cfr* 基因的致病性葡萄球菌在养殖场、屠宰场、零售肉类及临床患者[40,65,83,90]中的大量出现和传播令人担忧，其通过食物链从食品转移到人，并可能在社区甚至医院中引起进一步的人-人传播。*cfr* 基因在不同来源的致病性葡萄球菌分离株间的广泛流行以及在环境-食品-人中的传播，导致致病性耐药葡萄球菌在整个生态系统中的迅速扩散，加剧了多重耐药致病性葡萄球菌的泛滥，使得致病性葡萄球菌耐药问题愈演愈烈，对食品安全及公共卫生安全构成了严重的威胁。

综合以上研究结果，虽然 *cfr* 基因位于不同类型、大小的质粒及染色体上，但具有很多相似的遗传结构，且与可转移元件具有密切的关系，表明可转移元件在 *cfr* 基因的转移中扮演着重要的角色，促进了 *cfr* 基因在致病性葡萄球菌中的转移及传播。而其可转移元件关联 *cfr* 基因水平转移的原动力可能来自细菌种属间的基因交流，而此种基因的交流在抗生素的选择压力下，使获得抗性基因的菌株获得生存优势，占据更高的生态位，导致致病性耐药葡萄球菌的扩散。

4 类 *cfr* 基因

自 *cfr* 基因在 *S. sciuri* 质粒上首次发现以来，一系列的类 *cfr* 基因陆续在一些致病性菌株中被发现。这些类 *cfr* 基因包括 *cfr* (B)、*cfr* (C)、*cfr* (D)和 *cfr* (E)，其所编码的蛋白与 Cfr 蛋白序列同源性均低于 80% (图 3)[112]。其中 *cfr*(B)首次被发现于 *C. difficile* 11140508 中的 Tn*6218*-like 转座子上[113–114]，并且随后的研究[115]表明 Cfr (B)具有与 Cfr 蛋白质相同的功能。而后 *cfr* (B)基因亦在临床 *Enterococcus faecium*[116]分离株中被检测到，并且其遗传环境与首次报道的 *C. difficile* 中一致。*cfr* (C)基因亦在 *Clostridium difficile* 和 *Campylobacter* 中发现，并介导 $PhLOPS_A$ 耐药表型，且具有多种整合接合元件 (integrative and conjugative elements，ICEs)与 *cfr* (C)基因相关联[117–118]。另外，*cfr* (D)和 *cfr* (E)也分别在 *Enteroccocus faecium*[119]和 *Clostridium difficile*[112]中发现，并进一步确认 Cfr (C)和 Cfr (E)的甲基化功能。已检测到的类 Cfr 蛋白具有 Cfr 蛋白相同的功能，可介导 $PhLOPS_A$ 耐药表型。并且类 *cfr* 基因与可转移元件(Tn 及 ICEs)相关联，不同来源的类 *cfr* 基因遗传环境相似，表明存在水平转移的可能性。

5 展望

近年来关于 *cfr* 基因在致病性葡萄球菌中引起的多重耐药的情况越来越严重，Cfr 对核糖体的甲基化修饰导致作用于 PTC 上的多种药物的抗性，这些药物中的任何一种均可对 *cfr* 的存在产生选择压力；由于 *cfr* 基因获得的适应代价很低[120]，具有较高的传播势能，进一步加剧了其在致病性葡萄球菌中的传播，同时在动物源及食品源 *cfr* 基因可能通过食物链或者环境传递给人类，可能出现社区传播，进而在整个生态系统中扩散，对公共卫生安全构成巨大的挑战。目前关于 *cfr* 基因的耐药机制、遗传环境及传播机制的研究已经取得了较大的进展，但还有以下几点有待进一步的探究：(1) *cfr* 基因的来源仍不清楚，其生物学来源有待进一步研究，(2) *cfr* 基因的生物学进化方向不清晰，其可能的进化方向待深入解析，(3) 防控携带 *cfr* 基因的致病耐药葡萄球菌的方法有限，目前仅限于对其检测和监控，未曾有适合于临床的防控手段。同时考虑到

我们虽然无法根除细菌耐药性，但可以通过减少对耐药性的选择压力进而减少耐药菌/基因的产生与传播。鉴于此种现状，对未来发展提出以下建议：(1) 以整个生态作为一个整体，在“One Health”思想指导下，通过多方位联动，对动物养殖及人医临床中相关抗生素(包括氯霉素类、林可酰胺类、截短侧耳素类、链阳菌素 A 类、大环内酯类和氨基糖苷类)药物规范、谨慎使用。(2) 开发多种针对耐药性致病菌的新型防控手段，如利用噬菌体、食药用菌(抗菌肽)、抗体制剂、益生菌(拮抗剂/细菌素)开发新型抗菌剂，及开发新型靶向消除耐药菌/基因的技术(图 4)[121–124]。(3) 同时

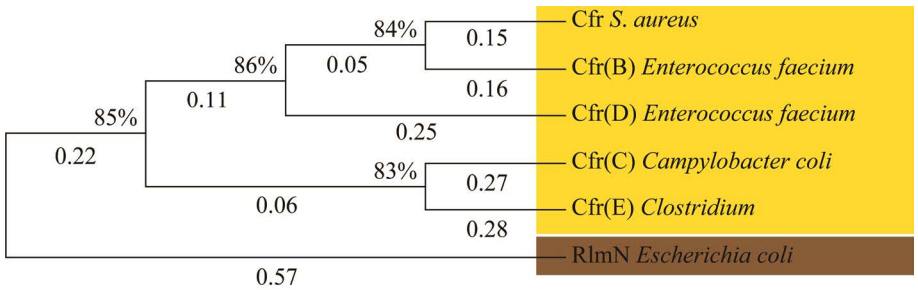

图 3 Cfr、类 Cfr 及 RlmN 蛋白进化关系[112]

Figure 3 The relationship of Cfr, Cfr-like, and RlmN protein[112].

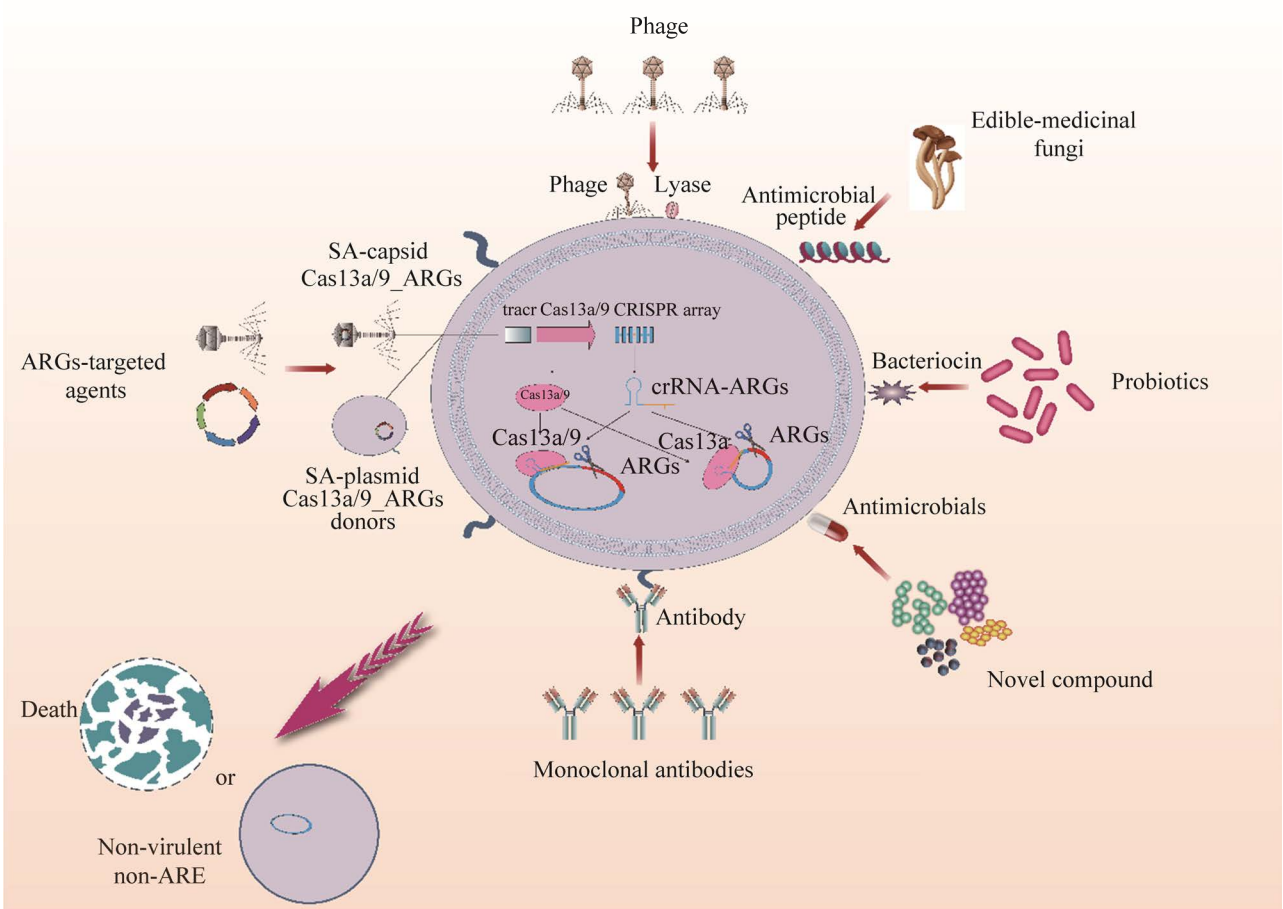

图 4 耐药性致病葡萄球菌防控策略[121–124]

Figure 4 Prevention and control strategy of drug-resistant pathogenic *Staphylococcus*[121–124].

进行细菌耐药性的科普宣传亦极为重要，减少人们日常抗生素的盲目滥用。(4) 加强对 *cfr* 基因在整个系统中分布状况的监控，进一步研究其传播链条，寻找耐药菌/基因传播的关键靶点。(5) 增强在食源性动物养殖及加工环节的监测与控制，切断致病性耐药菌/耐药基因的传播链，有效控制多重耐药菌株的发生与流行；同时也为动物养殖、临床合理用药以及多重耐药致病菌对人与动物健康的风险评估提供数据参考。

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