Chapter 23
Role of Plasmid-Encoded Drug Efflux Pumps in Antimicrobial Resistance

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Abstract Plasmids, as extrachromosomal genetic mobile elements, have been widely documented to mediate high-level bacterial resistance to all major clinically relevant antibiotics and antiseptic agents. The first drug efflux pump discovered in bacteria is plasmid encoded. Naturally occurring drug resistance plasmids are diverse and belong to different incompatibility groups. Multidrug resistance determinants often coexist on the same plasmids with strong linkages to mobile elements such as integrons or transposons. Thus, plasmids play a critical role in the evolution of resistance and in the dissemination of resistant bacteria, which poses a major challenge to antimicrobial therapy. This chapter provides an up-to-date overview of the plasmid-mediated genetic and biochemical mechanisms of antimicrobial resistance with an emphasis on plasmid-encoded drug efflux pumps in major pathogens.

Keywords Antimicrobial resistance • Antiseptic • Multidrug resistance • Plasmid • Integron • Transposon • Efflux pumps

23.1 Introduction

The term plasmid was proposed in 1952 by Joshua Lederberg to be referred to as "a generic term for any extrachromosomal hereditary determinant" [1]. Being extrachromosomal genetic elements, plasmids replicate independently and occur commonly in bacteria. To date, numerous plasmids have been characterized in detail, which include in-depth understanding of the complete nucleotide sequences, gene products, and their functions. Such functions include plasmid transfer elements, metabolic/catabolic degradation enzymes, virulence determinants, and, frequently, antimicrobial resistance genes. The role of plasmids (initially known as "R factor")

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in drug resistance was recognized soon after the beginning of the antibiotic era [2, 3]. In fact, plasmid-mediated resistance is often of high level and thus threatens effective antimicrobial therapy [4, 5]. Plasmids not only possess independent replicons but may also contain other mobile genetic elements (e.g., insertion sequences, integrons, and transposons) [6] and, hence, provide an important means for both vertical and horizontal gene transfer that assist the widespread of resistance within or across bacterial species or genus of different geographical regions. Plasmids make a major contribution to resistance especially in organisms such as the ESKAPE pathogens (i.e., *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species); epidemic resistance plasmids have been found globally [7]. Moreover, resistance plasmids that simultaneously carry multiple resistance determinants have been observed frequently [8, 9]. These plasmids can also encode virulence factors and enhance bacterial biofilm formation or colonization in the host, thus contributing greatly to the pathogenicity [10, 11]. It is necessary to mention that there is a very large amount of studies on plasmid-mediated resistance, a topic that has been regularly reviewed over past decades [5, 12–20]. This chapter provides an up-to-date description of plasmids' contribution to current antimicrobial resistance crisis with an emphasis on the role of plasmid-encoded drug efflux pumps.

23.2 Overview of Plasmid-Mediated Antimicrobial Resistance

The significance of plasmid contribution to antimicrobial resistance cannot be overstated since many plasmids from different incompatibility groups, either conjugative or nonconjugative, have been found to confer resistance to all major classes of antimicrobial agents in both Gram-positive and Gram-negative bacteria [5, 15, 19]. These resistance plasmids are widely present in various environments. Plasmid-encoded products exhibit different biochemical mechanisms of resistance, including drug inactivation, modification of drug targets, and drug efflux (Table 23.1).

23.2.1 Genetic Characteristics of Resistance Plasmids

Like any plasmids, resistance plasmids carry replication elements for their independent maintenance. They vary in size (small to mega-plasmids), incompatibility groups, and host ranges [49, 50]. For example, a small plasmid of *Staphylococcus aureus* is only about 2.8 kb and carries a drug transporter gene [51], while mega-plasmids are >100 kb carrying multiple resistance determinants and mobile genetic elements [31]. Some of them have a broad host range and can replicate in different species. They may carry genes for plasmid transfer and become conjugative [49]. The plasmids may encode a single or multiple drug resistance determinants, their

Table 23.1 Examples of plasmid-mediated resistance to major antimicrobial drugs

Antimicrobial resistance	Plasmid (GenBank accession)	Origin of bacterial species	Mechanisms	Reference
β-Lactams	pRSF1030 (RSF1030OR)	*Salmonella* Panama	TEM-1 narrow-spectrum β-lactamase	[21]
	pR997	*Proteus mirabilis*	SHV-1 narrow-spectrum β-lactamase	[22]
	pMG211	*E. coli*	PSE-1 β-lactamase	[23]
	pRGN238 (J02967)	*E. coli*	OXA-1 β-lactamase	[24]
	pMVP-3 (X92506)	*E. coli*	CTX-M-1 extended-spectrum β-lactamase	[25, 26]
	pMVP-2 (X91840)	*K. pneumoniae*	CMY-2 AmpC β-lactamase	[27]
	pAK9373 (D50438)	*S. marcescens*	IMP-1 metallo β-lactamase	[28]
	pKpANDM-1 (FN396876)	*K. pneumoniae*	NDM-1 metallo β-lactamase	[29]
Aminoglycosides	pCTX-M-3 (AF550415)	*C. freundii*	ArmA aminoglycoside methylase	[30]
	pNDM-CIT (JX182975)	*C. freundii*	AadA2 aminoglycoside acetyltransferase	[31]
	pRH-1238 (KR091911)	*Salmonella* Corvallis	AAC(6′)/Aad aminoglycoside acetyltransferases, and AphA6; StrA/B aminoglycoside phosphotransferases	[32]
Amphenicols	pC194 (NC_002013)	*S. aureus*	Cat chloramphenicol acetyltransferase	[33]
	pSCFS1 (AJ249217)	*S. aureus*	Cfr methylase	[34–36]
Fluoroquinolones	pMG252 (AY072035)	*K. pneumoniae*	QnrA DNA gyrase protection protein	[37]
	(DQ303918)	*E. coli*	AAC(6′)-Ib-cr	[38]
	pHPA (AB263754)	*E. coli*	QepA efflux pump	[38]
Fosfomycin	p1E1C (JF411006)	*E. coli*	FosA3 thioltransferase	[39]
Glycopeptides (vancomycin)	pLW1043 (AF017171)	*S. aureus*	VanA	[40]
Macrolides-lincosamides-streptogramins	pE194 (NC_005908)	*S. aureus*	Erm methylase	[41]
Oxazolidinones-amphenicols	pE349 (KP399637)	*E. faecalis*	OptrA efflux pump	[42]

(continued)

Table 23.1 (continued)

Antimicrobial resistance	Plasmid (GenBank accession)	Origin of bacterial species	Mechanisms	Reference
Pleuromutilins-lincosamides-streptogramins	pSA-7 (NG_041699)	*Staphylococcus cohnii*	Vga(E) efflux pump	[43]
	pV7037 (NG_041616)	*S. aureus*	Lsa(E) efflux pump	[44]
Polymyxins	pHNSHP45 (KP347127)	*E. coli*	Mcr-1 phosphoethanolamine transferase	[45]
Rifamycins	In53 (AF205943)	*E. coli*	Arr-2 ADP-ribosyltransferases	[46]
	pTNN01 (AJ277027)	*K. pneumoniae*	Arr-3 ADP-ribosyltransferases	[47]
Sulfonamides/ trimethoprim	pRH-1238 (KR091911)	*Salmonella* Corvallis	SulI /SulII dihydropteroate synthase; Dfra7 dihydrofolate reductase	[32]
Tetracyclines	pOZ100 (L12241)	*Neisseria gonorrhoeae*	Tet(M) ribosomal protein	[48]
	pR100 (NC_002134)	*S. flexneri*	TetA(A) efflux pump	[8]

regulatory genes, and other mobile genetic elements such as insertion sequences, integrons, and transposons [5, 28, 29, 49, 52]. These multiple resistance-associated elements form gene cassettes that occur widely in resistance plasmids. An early reported plasmid, R100, of *Shigella flexneri*, is about 94 kb and contains the *tetA* gene (for tetracycline resistance) in the transposon Tn10, *cat* for chloramphenicol resistance in Tn9, and *aadA1* for aminoglycoside resistance, *sul1* for sulfonamide resistance, and *mer* operon genes for mercury resistance in Tn21 [8]. In another example, the 140-kb plasmid of *Klebsiella pneumoniae* that encodes a gene for the NDM-1 β-lactamase also contains mobile elements (insertion sequences IS26 and class 1 integron) and many other resistance genes including *arr-2* (for rifamycin resistance), *ereC* (erythromycin resistance), *aadA1* (aminoglycoside resistance), *cmlA* (chloramphenicol resistance), *qacEΔ*1 (defective antiseptic resistance), and another gene for an efflux pump [53]. A recent study of a 187-kb plasmid of *Salmonella enterica* Corvallis demonstrated the presence of 15 resistance gene determinants comprising of $bla_{\text{NDM-1}}$, $bla_{\text{CMY-16}}$, *fosA3*, *sulI*, *sulII*, *strA*/*B*, *aac*(*6′*)-*Ib*, *aadA5*, *aphA6*, *tetA*(A), *mphA*, *floR*, *dfrA7*, and *merA* genes that provide resistance to β-lactams (including carbapenems), aminoglycosides, amphenicols, fosfomycin, macrolides, sulfonamides, trimethoprim, and tetracyclines [32]. Of note, this plasmid is considered to originate from Asia and to have been transferred to Germany through a migratory wild bird [32]. Moreover, resistance plasmids may also carry virulence genes and play a critical role in pathogenicity, as shown in the example of a multidrug resistance (MDR) plasmid of *Salmonella* [54]. Current identification

and characterization of plasmids, facilitated by the whole genome sequencing availability together with the bioinformatics analysis, continue to provide insights on the diversity of resistance plasmids derived from various environments [55, 56].

23.2.2 Genetic and Biochemical Mechanisms of Plasmid-Mediated Resistance

β-Lactams Resistance to β-lactams in Gram-negative bacteria is mostly caused by β-lactamases [57], which are encoded by chromosomes or plasmids (Table 23.1). There are more types and numbers of plasmid-encoded β-lactamases than those of chromosomal β-lactamases. Most Ambler class A β-lactamases are produced by plasmids and contain many TEM, SHV, and CTX-M enzymes [57, 58], most of which are extended-spectrum β-lactamases (ESBLs) that hydrolyze aztreonam and oxyimino-cephalosporins and can be inhibited by β-lactamase inhibitors (clavulanate, sulbactam, and tazobactam) [57, 59]. Many CTX-M-producing plasmids are MDR plasmids [60, 61]. Class A enzymes also include *K. pneumoniae* carbapenemases (KPCs) that pose a major threat to antimicrobial therapy [62], and these enzymes are also frequently encoded by plasmids [63, 64]. Numerous class B metallo β-lactamases are encoded by plasmids. Perhaps the most noticeable example in recent years is the global spread of NDM-1-encoding plasmids that also contain multiple drug resistance determinants [29, 65]. One major substrate class for these metalloenzymes is carbapenems [29]. A strain harboring both a NDM-1 plasmid and a KPC plasmid was also recently noted [66]. While often encoded by chromosomes, class C AmpC enzymes are also frequently encoded by plasmids, such as the CMY enzymes that are widely distributed in isolates of humans and animals and can particularly hydrolyze cephamycins and oxyimino-cephalosporins [67–69]. Class D OXA β-lactamases are mostly encoded by plasmids and can be divided into several subgroups [70], including carbapenem-hydrolyzing OXA-type carbapenemases [62, 70, 71].

Aminoglycosides Three types of aminoglycoside-modifying enzymes exist and are aminoglycoside *N*-acetyltransferases, *O*-nucleotidyltranferases, and *O*-phosphotransferases, which play a major role in aminoglycoside resistance. Many of them are encoded by plasmids in both Gram-positive and Gram-negative bacteria [72]. Copresence of aminoglycoside resistance genes with other resistance determinants are frequently observed on the same plasmids [8, 32, 44, 73]. Plasmid-encoded methyltransferases such as ArmA, RmtA, and RmtB alter the aminoglycoside binding site of 16S rRNA of the 30S ribosomal subunit and are increasingly seen as a key mechanism of aminoglycoside resistance [49, 58, 74, 75].

Amphenicols Resistance to chloramphenicol and thiamphenicol is mainly mediated by drug-specific chloramphenicol acetyltransferases through drug inactivation. This mechanism can be inducible due to the mRNA structural changes in the 5′-untranslated region of the *cat* gene in the presence of an antimicrobial to enhance

the translation of the *cat* mRNA [33]. These enzymes are often encoded by MDR plasmids containing resistance gene cassettes [76, 77]. Plasmids also mediate non-enzymatic resistance mechanism through amphenicol-specific drug exporters named CmlA or FloR [78, 79] or multidrug exporters such as OptrA [42] (see details in the section on drug efflux pumps). A third mechanism is related to chloramphenicol-florfenicol resistance (Cfr) protein that is encoded by plasmids [34] and is able to methylate 23S rRNA, resulting in reduced binding of amphenicols, lincosamides, oxazolidinines, pleuromutilins, and streptogramins to their ribosome targets [35, 36]. The first described *cfr*-bearing plasmid was an MDR transposon plasmid that also contained *erm*(*33*) for inducible resistance to macrolide-lincosamide-streptogramin B and a streptomycin resistance gene [80]. A novel *cfr*-containing plasmid was found to carry *blaZ* β-lactamase gene, *msr*(*A*) efflux gene, and heavy metal resistance genes [81]. Another plasmid-borne chloramphenicol-florfenicol resistance gene termed *fexA* was also reported with an unknown mechanism of resistance [82]. *cfr*- and *fexA*-carrying resistance plasmids are widely present in staphylococci [83]. A *cfr*-carrying plasmid from *Enterococcus faecalis* was also described [84]. More recently, the *fexA* or *fexB* combination with plasmid-borne *optrA* transporter gene was observed in enterococci of human and food animal sources [42, 85].

Fluoroquinolones While enzymatic inactivation of quinolones by an aminoglycoside-fluoroquinolone acetyltransferase is due to the AAC(6′)-Ib-cr-encoding plasmids, *qnr*-containing plasmids provide quinolone resistance via a target protection mechanism [20, 37, 86–88]. Plasmids carrying *AAC*(*6′*)*-Ib-cr* or *qnr* genes are widely disseminated in numerous *Enterobacteriaceae* and often exist as part of a resistance gene cassette to cause MDR [20, 37, 55, 58]. Additionally, contribution of the QepA and QepA2 transporters to fluoroquinolone resistance will be described in the next major section.

Fosfomycin This agent is increasingly being recognized for its role in therapy against multidrug-resistant pathogens [18, 89]. However, plasmid-borne *fos* genes have been well documented to be responsible for fosfomycin resistance in both Gram-positive and Gram-negative bacteria [90, 91]. The *fos*-encoded thioltransferases cause enzymatic inactivation of fosfomycin [90]. *fos* genes are divided into various groups such as *fosA*, *fosB*, and *fosC*. Of importance, *fos* genes are also frequently observed in MDR plasmids [60, 92]. *fosA3*-containing plasmids of *E. coli* from China and the USA also carry CTX-M-65 β-lactamase gene and *rmtB* methylase gene as well as insertion sequences [39, 91]. Another conjugative plasmid derived from extensively drug-resistant *Enterobacter cloacae* carries *fosA3*, NDM-1 β-lactamase gene, and *armA* aminoglycoside resistance gene [93].

Glycopeptides Transferable resistance to vancomycin and teicoplanin is well recognized [40, 94–98]. Several vancomycin resistance determinants such as *vanA* are associated with mobile genetic elements (e.g., typically Tn*1546*), which also exert an important role in the evolution of vancomycin resistance. For example, plasmid pLW1043 of *S. aureus* encoded six copies of the IS256 transposase, vancomycin

resistance-associated *vanRSHAXYZ* genes, and other resistance genes *dfrA* (for trimethoprim resistance), *qacC* (antiseptic resistance), *aacA-aphD* (aminoglycoside resistance), and *blaZ* (β-lactam resistance) [40]. Van resistance determinants (such as *vanA*, *vanB*, and *vanC*) cause replacement of the terminal D-alanine of the cell wall peptidoglycan precursors with D-lactate or D-serine and consequently result in reduced binding of drugs to the peptidoglycan precursors [99]. In enterococci, in response to a pheromone peptide, pheromone-responsive plasmids help acquisition of resistance genes [100], although pheromone produced by commensal enterococci can also result in killing of multidrug-resistant enterococci [101].

Lincosamides and Macrolides Plasmid-mediated transferable resistance to these classes of agents is well known [52, 102–104]. One example is the plasmid-mediated inducible resistance to three structurally unrelated classes of antimicrobials, macrolides, lincosamides, and streptogramin B [41, 105]. These plasmids contain genes encoding erythromycin ribosome methylases (Erm) that lead to the posttranscriptional modification of the 23S rRNA by the adenine-*N6* methyltransferase. The binding site in the 50S ribosomal subunit for erythromycin overlaps the site of other macrolides, lincosamides, and streptogramin B, resulting in cross-resistance to three antimicrobial classes [106]. The expression of *erm* genes can also often be inducible by an antibiotic such as erythromycin due to a deregulation of posttranscriptional attenuation [107]. In addition to Erm ribosomal methylases, several other macrolide resistance proteins are also encoded by plasmids such as Ere esterase or Mph phosphotransferase (that cause macrolide inactivation) and Mef, Mel, and Msr exporters [31, 52, 104, 108]. The different resistance determinants play synergistic roles in raising macrolide resistance level [52]. A newly reported plasmid-containing methylase-encoding *erm*(*T*) conferred a ≥128-fold increase of the MIC values of azithromycin, erythromycin, clindamycin, and lincomycin [109]. The role of efflux pumps Mef, Mel, and Msr exporters in macrolide resistance [31, 108] will be described below in the section on drug efflux pumps.

Oxazolidinones, Pleuromutilins, and Streptogramins The abovementioned *cfr*-encoding plasmids also mediate resistance to oxazolidinones due to the modification of 23S rRNA and the overlapping mode of action of these agents with that of amphenicols [36, 81, 110]. A new plasmid-borne gene dubbed *optrA* which encodes an exporter is involved in resistance to oxazolidinones and amphenicols (see Drug Efflux Pumps section below) [42, 85]. Either Lsa(E)- or Vga(E)-containing plasmids mediate resistance to pleuromutilins, lincosamides, and streptogramins [43, 44].

Polyketides The plasmid-borne *mupA* gene mediates high-level resistance to mupirocin (≥120-fold MIC increase) in *S. aureus*, in contrast to chromosomal mutation-related low-level resistance (2- to 32-fold MIC increase) [111]. The *mupA* gene encodes a modified isoleucyl tRNA synthetase. Diversity of *mupA*-containing plasmids has been noted, and these plasmids often contain mobile genetic elements and can be conjugative [111, 112].

Polymyxins Until recently [45], resistance to polymyxins had been only known to be caused by chromosomal mutations that affect structure of lipopolysaccharide, the primary target of polymyxins [113]. For instance, the changes from chromosomally encoded PhoPQ and PmrAB systems can modify the lipopolysaccharide-related outer membrane barrier and subsequently mediate resistance to polymyxins [114–116]. The newly discovered colistin resistance plasmid named pHNSHP45 was isolated from *E. coli* of pig origin and was conjugatively transferred to and maintained in *K. pneumoniae* and *P. aeruginosa* [45]. It produced, respectively, 8- to16-fold and four- to eightfold increases in the MIC values of colistin (mostly to 8 μg/ml) and polymyxin B (to 4 μg/ml) for various transconjugants. This plasmid contains a gene dubbed *mcr-1* that encodes a phosphoethanolamine transferase for modification of lipopolysaccharide structure via the addition of phosphoethanolamine to lipid A [45]. The *mcr-1* gene was found to be in *E. coli* isolates, respectively, derived from 15 %, 21 %, and 1 % of raw meat, animal and human inpatient samples [45].

Rifamycins Plasmids encoding ADP-ribosyltransferases [46, 47] or efflux pumps [117] have been reported to confer rifamycin resistance via drug inactivation or extrusion. The *arr* genes are often located in a resistance gene cassette containing integron [46, 47].

Sulfonamides and Trimethoprim Resistance to these anti-folate agents is also frequently attributable to plasmids carrying *sul* genes or *dfrA* genes, which encode, respectively, dihydropteroate synthase and dihydrofolate reductase to provide an alternate folate metabolic pathway [118]. These resistance genes often exist as part of mobile drug resistance gene cassettes [119]. For instance, *sul* is one of the many resistance genes encoded by the mega-plasmid that produces NDM-1 metallo β-lactamase described earlier [29]. *sul* genes are among those frequently identified resistance genes in various environments [120]. The vancomycin resistance plasmid pLW1043 described earlier in this chapter also carries *dhfr* gene for trimethoprim resistance [40].

Tetracyclines Resistance to tetracyclines is often mediated by plasmids in both Gram-positive and Gram-negative species with involvement of active efflux systems (see next section below) and ribosomal protection [121]. The latter includes *tet*(*M*), *tet*(*O*), and *tet*(*Q*) determinants encoding proteins that reduce tetracycline binding to its target [48, 122].

Biocides and Disinfectants These agents such as benzalkonium chloride and chlorhexidine are frequently used in hospital infection control or in preserving food products. Exposure to biocides may also select resistance to clinically used antimicrobial agents [123]. Resistance to these agents is attributed to multiple mechanisms including efflux pumps [124, 125]. Plasmid-mediated resistance to biocides constitutes a major mechanism and include efflux pumps such as Qac pumps to be discussed in the next section.

23.3 Plasmid-Encoded Drug Efflux Pumps

The first drug efflux pump discovered in bacteria, i.e., tetracycline-specific Tet efflux pump, is plasmid encoded [126–128]. The discovery of this mechanism of energy-dependent active extrusion of drugs from bacterial cells was a milestone in resistance studies and expanded our understanding of biochemical mechanisms of resistance. To date, bacteria are known to contain a large number of plasmid-encoded drug efflux pumps that belong to several transporter families and contribute to clinically relevant antimicrobial resistance [125, 129].

23.3.1 Major Facilitator Superfamily

Most known plasmid-borne drug efflux pumps are members of the major facilitator superfamily (MFS), whose characteristics are described in Chap. 2 and have been also reviewed elsewhere [130–132].

Tet Efflux Pumps These pumps are widely found in both Gram-positive and Gram-negative bacteria and include more than two dozen members such as Tet(A) to Tet(E), Tet(G), Tet(H), Tet(J), Tet(K), Tet(V), Tet(Y), Tet(Z), Tet(30), Tet(31), Tet(33), Tet(35), Tet(38), Tet(39) to Tet(43), TetAB(46), and Tet(47) (http://faculty.washington.edu/marilynr/tetweb1.pdf. Accessed on March 20, 2016). A number of plasmid-borne *tet* genes have been revealed to encode Tet efflux pumps that mediate high-level resistance to tetracyclines [129, 133]. The different Tet proteins may vary in their substrate specificities. Many Tet pumps such as Tet(A) confer resistance to chlortetracycline, oxytetracycline, and tetracycline but not the lipophilic minocycline. However, the latter is subject to the extrusion by Tet(B) pump [122]. Glycylcyclines were developed to counter the effect of Tet efflux pumps (and ribosomal protection) and are not the substrates of these pumps [134]. *tet*-containing plasmids often carry other resistance genes such as *sul*, *floR*, and *strA*/*strB* [135] and may also have *tetR* gene (typically seen in various transposons such as Tn10) [135–138] that encode a repressor (the prototype of the TetR repressor family [139]) to inhibit the expression of *tet* efflux gene. Tetracycline binds TetR and thus induces expression of the efflux pump [137].

FloR Pump This pump confers resistance to amphenicols [34, 140]. The gene *floR* was first found in a transferable R plasmid in florfenicol-resistant fish pathogen *Pasteurella piscicida* [141] and subsequently was also located in MDR plasmids isolated from a number of animal-derived bacteria including *Salmonella* [78], *E. coli* [60, 138, 140, 142], *Actinobacillus pleuropneumoniae* [143], *Aeromonas salmonicida* [144], *Haemophilus parasuis* [145], and *Mannheimia haemolytica* [146].

Mef Pumps These pumps include Mef(A), Mef(B), and Mef(I), are encoded by conjugative genetic elements including plasmids, and provide inducible macrolide resistance in streptococci [77, 147, 148] or *E. coli* [119]. The *mef* genes are generally part of the MDR integron/transposon-containing gene cassettes [77, 119]. A *mef* gene and an ABC exporter-encoding gene *mel* was also found to form an operon on mobile genetic elements to produce dual efflux pumps Mef and Mel that are inducible by erythromycin [147, 149].

QacA and QacB Pumps Resistance to antiseptics such as monovalent quaternary ammonium compounds (e.g., benzalkonium chloride) and divalent cations (e.g., chlorhexidine) is frequently mediated by MDR plasmids containing *qac* efflux pump genes such as *qacA* and *qacB* [150–153]. *qac* plasmids are widely distributed in methicillin-resistant *S. aureus* [154–156]. In fact, a description of the *qacB*-containing plasmid dates back to 1951. It was the earliest known *S. aureus* plasmid encoding a drug efflux pump [157]. *qacA* and *qacB* genes differ only by six to nine bases; yet, their proteins produce different phenotypes with QacA displaying higher activity in the efflux of divalent cations [158, 159]. The initially discovered *qacA* gene was located on a 28-kb plasmid (called pSK1) [160] which provided resistance to multiple biocides including quaternary ammonium compounds, chlorhexidine, and the intercalating dyes acriflavine and ethidium bromide [153]. A *qacB* plasmid of *S. aureus* also contains *aacA-aphD* aminoglycoside-modifying enzyme genes, *fosB* fosfomycin resistance gene, cadmium resistance protein gene, and transposase gene [161]. Several variants of plasmid-encoded QacB have been described with one variant being able to confer staphylococcal resistance to fluoroquinolones (fourfold increase of norfloxacin and ciprofloxacin MICs, but no change in levofloxacin MIC values) [159]. It is important to note that a repressor gene dubbed *qacR* is often located upstream of either *qacA* or *qacB* gene and transcribed divergently. QacR negatively controls the expression of *qacA* or *qacB* by binding to the DNA upstream of *qacA* or *qacB*. Certain lipophilic cations can bind to QacR and thus derepress or induce the *qacA* or *qacB* expression [152].

Qep Pumps These pumps including QepA and QepA2 are encoded by MDR plasmids that are mostly of *E. coli* origin and confer fluoroquinolone-specific resistance [20, 162, 163]. Cloned *qepA* provides resistance to ten fluoroquinolone agents of various generations (2- to 16-fold MIC increase) in a hypersusceptible *E. coli* host with virtually no impact on susceptibility to non-fluoroquinolone agents including ampicillin, erythromycin, kanamycin, acriflavine, benzalkonium, crystal violet, deoxycholate, ethidium bromide, rhodamine 6G, and sodium dodecyl sulfate [162]. QepA pump plays a synergistic role with the chromosomal fluoroquinolone resistance mechanism to raise the resistance level [164]. The *qepA* or *qepA2* gene often coexists in the same plasmids with transposon elements and other resistance genes including $bla_{CTX\text{-}M}$, *aac(6′)-Ib-cr*, and/or *qnr* genes [165, 166].

23.3.2 Resistance-Nodulation-Cell Division Superfamily

The drug efflux systems of the resistance-nodulation-cell division (RND) superfamily are generally chromosomally encoded and are predominately found in Gram-negative bacteria, and their importance in MDR is examined in various chapters of this book. Since the RND pump systems are typically a tripartite efflux complex requiring three gene products, the discovery of RND pump genes on plasmids was quite surprising. However, there is an increasing occurrence of plasmid-encoded multicomponent efflux systems including RND pumps.

OqxAB In 1999, a 52-kb plasmid named pOLA52 was obtained from a swine *E. coli* isolate that was resistant to olaquindox, an animal feed additive [167]. This plasmid encoded two gene products (dubbed OqxAB) exhibiting high homology to AcrAB efflux proteins (that are, respectively, a periplasmic adaptor protein and a pump). The plasmid also has another open-reading-frame downstream of *oqxAB* with a divergent transcriptional direction that encodes a repressor (OqxR) [168, 169]. Although lacking an OM protein gene from the plasmid, OqxAB function requires chromosomally encoded TolC protein, which is also an indispensable component of most chromosomal RND systems of *E. coli* (see Chap. 9). Like most chromosomal RND pumps, OqxAB also displays a broad substrate specificity that includes chloramphenicol, fluoroquinolones, nalidixic acid, trimethoprim, olaquindox, benzalkonium chloride, and sodium dodecyl sulfate (cloned *oqxAB* genes increase the MIC values of these agents by 8- to128-fold) [167, 170]. pOLA52 also carries virulence genes such as those for type IV secretion system. Similar to pOLA52 MDR transferable plasmid, newly identified *oqxAB* plasmids carry other resistance genes such as a CTX-M gene or *floR* gene [61, 171]. These plasmids are mostly observed in *E. coli* [61, 172–175] but also in other *Enterobacteriaceae* such as *Salmonella* spp. and *K. pneumoniae* [171, 176–178]. The *oqxAB-oqxR*-containing chromosome of *K. pneumoniae* has been considered as a possible source of plasmid-borne *oqxAB* [179]. Still, additional Gram-negative bacteria such as *Enterobacter aerogenes*, *E. cloacae*, and *Serratia marcescens* were also recently found to contain *oqxAB-oqxR* genes, but the *oqxAB* expression in these bacteria was minimal and appeared not to contribute to quinolone resistance [169]. A newly available study further revealed that plasmid-mediated OqxAB is also involved in resistance to nitrofurantoin and facilitates to high-level nitrofurantoin resistance [180].

SilCBA/CusCBA A 180-kb mega-plasmid, pMG101, was isolated from a multidrug-resistant *Salmonella* derived in 1973 from a severe burn patient in the USA [181, 182]. The plasmid conferred resistance to silver salts (8- to 16-fold silver nitrate MIC increase), ampicillin, chloramphenicol, streptomycin, and tetracycline [181]. Being an MDR plasmid, pMG101 produces three gene products

SilCBA with high homology to an RND system comprised of the antiporter SilA, membrane fusion protein, and outer membrane channel protein SilC. It also encodes an ABC transporter SilP and periplasmic metal-binding protein SilE as well as a two-component regulatory system SilRS [182]. SilABC and SilP likely play a synergistic role in the extrusion of silver salts. pMG101 is the earliest known RND pump encoded by an MDR plasmid. However, the complete nucleotide sequence of this plasmid is not available. Using gene-specific primers, amplification of *silCBA*, *silE*, *silP*, and *silRS* was obtained from several plasmids of silver-resistant *E. cloacae* isolates of human and veterinary origin [183]. The same group also reported the detection of *silE* in methicillin-resistant *S. aureus* and other staphylococci with yet undetermined location of *silE* [184]. These studies warrant the need to investigate the role of *sil* genes in silver resistance, in particular because silver-derived agents are being actively pursued as novel antimicrobials in combating drug resistance.

Recently, a study conducted in China has characterized a 273-kb conjugative IncH1 MDR mega-plasmid named pEC5207 that was isolated in 2011 from an *E. coli* strain of swine origin [185]. The sequence of this plasmid showed the presence of a cluster of genes (*silP-copG-cusA-silB-cusC-cusR-cusS-silE*) [185] that had an identical arrangement in comparison with a region containing *silP-orf-silA-silB-orf-silC-silR-silS-silE* of plasmid isolated in 1973 from *Salmonella* spp. in the USA [182]. This gene cluster is also present in another MDR 227-kb mega-plasmid pSH111_227 of *Salmonella* origin reported in the USA in 2011 (GenBank accession JN983042) [185]. Specifically, these genes encode RND-type efflux system CusC-SilB-CusA, a two-component regulatory system CusRS, ABC transporter SilP, and silver-binding protein SilE [185]. It is important to note that this plasmid-encoded CusA-SilB-CusF-CusC-CusR-CusS is organizationally identical to the chromosomally encoded CusCFBA-CusRS systems of *E. coli* (see Chap. 9 on *E. coli* efflux pumps). In addition, pEC5207 also contain genes encoding homologs to CopABCE (involved in copper resistance), TerZABCDEF (tellurium resistance), EmrE (SMR-type pump for antiseptic resistance), and CMY-2 β-lactamase (β-lactam resistance), as well as the genes for H-NS regulator and RamA activator. *E. coli* transformants with pEC5207 were demonstrated to confer resistance to silver (80-fold increase of $AgNO_3$ MIC) and copper (1.5-fold increase of $CuSO_4$ MIC) [185]. All these findings with plasmids pMG101, pEC5207 and pSH111_227, and *E. coli* genome suggest the importance of CusCBA-CusRS/SilCBA-SilRS for persistency of *E. coli* or *Salmonella* spp. in diverse environments.

Other RND Systems Plasmid DNAs from uncultured bacteria in wastewater treatment plant contain genes with homologs of chromosomal RND pump genes of *E. coli* and *P. aeruginosa* (especially *mexEF-oprN*) [186]. Several large plasmids have also been found to contain RND pump genes. Two conjugative plasmids of ca. 63 and 67 kb were isolated in 1993 as mercury resistance plasmids due to plasmid-borne *mer* resistance genes. However, these plasmids also encode gene products showing homology to MexEF-OprN components of *P. aeruginosa* [187–189]. *E. coli* carrying one of these two plasmids displayed no altered drug susceptibility to chloramphenicol, nalidixic acid, and trimethoprim. An IncHI1 plasmid from an extremely drug-resistant *Citrobacter freundii* isolated from a patient returning from

India [31] contained genes encoding carbapenemase NDM-1, ArmA 16S rRNA transferase, and an RND system (homologous to AcrR-MexAB-CusC which correspond, respectively, to an efflux expression repressor, a membrane fusion protein, an efflux transporter, and an outer membrane channel protein) [190].

23.3.3 Small Multidrug Resistance Family

The most studied chromosomally encoded efflux pump of this family, EmrE of *E. coli*, mediates resistance to antiseptics (disinfectants or biocides). Similarly, plasmid-encoded small multidrug resistance (SMR) exporters such as Smr, QacC, QacD, QacF, QacH, and QacJ and also involved in biocide resistance. They are mostly found in staphylococci [152, 155, 191–194] but also in Gram-negative bacteria [195]. Smr-type *qac* genes were also found in enterococci and *Listeria monocytogenes* [152]. A plasmid-encoded QacZ from *E. faecalis* confers resistance to quaternary ammonium compounds [196]. A small 2.7-kb Smr pump-encoding plasmid of *S. aureus* confers resistance to quaternary ammonium compounds [51]. An MDR plasmid derived from uncultured bacteria contains an *smr* gene for QacF efflux pump, OXA-2 β-lactamase gene, *aadA4* spectinomycin/streptomycin resistance gene, and *sul1* sulfonamide resistance gene and can be transferred to *E. coli* [197]. A recent review examined the phylogenetic relation of *qac* genes that encode either SMR family pumps or MFS-type pumps with SMR genes grouping into four clusters [152].

23.3.4 ATP-Binding Cassette Superfamily

The transporters of the ATP-binding cassette (ABC) superfamily are widely distributed in bacteria. The abovementioned plasmid pMG101 contains ABC silver exporter gene [182]. Another 48-kb MDR plasmid, pRSB101, from an activated sludge of a wastewater treatment plant contains 20-kb resistance region located in a Tn402-like transposon. This plasmid encodes an ABC-binding protein, an ABC transporter, and a periplasmic membrane fusion protein that may possibly form an efflux complex [198]. In addition, it also encodes *sul1* for sulfonamide resistance, *dhfr1* gene for trimethoprim resistance, *aadA2* for spectinomycin/streptomycin resistance, a $bla_{TLA\text{-}2}$ β-lactamase gene, *mph*(*A*) for macrolide resistance (including *mph*[*R*] regulatory protein gene), and *tet*(*A*) for tetracycline resistance (including *tetR* repressor gene) [198]. In a recent study from the USA that investigated $bla_{CTX\text{-}M}$-containing IncF plasmids of *E. coli*, several MDR plasmids (155- to 172-kb) were shown to contain genes for ABC transporter(s) and ABC transporter ATB-binding protein(s), which were considered as putative virulence factors [199]. To date, multiple plasmid-encoded ABC transporters have been reported and include Lsa(E), Msr(A), Mel, and Vga(E) (Table 23.2). Either Msr(A) or Mel can be coproduced with Mph2 from a macrolide resistance cluster of the same MDR plasmid from *S. aureus* [208] or Gram-negative bacteria (*E. coli*, *C. freundii*, *Providencia stuartii*,

Table 23.2 Examples of major plasmid-encoded drug efflux pumps

Transporter family/pump	Plasmid (GenBank accession)	Bacterial species	Plasmid-borne resistance phenotype (resistance gene)	Reference
MFS				
FloR	R plasmid (NG_034640)	*P. piscicida*	Florfenicol (*floR*), sulfonamides (*dhfrIX*)	[141]
QacA	pSK1 (NC_014369)	*S. aureus*	Antiseptic (*qacR qacA*), aminoglycoside (*aacA-aphD*)	[160]
QacB	pTZ2162 (NC_010419)	*S. aureus*	Antiseptic (*qacR qacB*), aminoglycoside (*aacA-aphD*), fosfomycin (*fosD*), arsenate (*arsCBR*), cadmium (*cadD*)	[161]
QepA	pHPA (AB263754)	*E. coli*	Fluoroquinolones (*qepA*) β-lactams (bla_{TEM-1}), aminoglycosides (*rmtB*)	[38]
TetA(A)	pRH-1238 (KR091911)	*Salmonella* Corvallis	β-Lactams (including carbapenems) (bla_{NDM-1}, bla_{CMY-16}), aminoglycosides (*aac(6′)-Ib*, *aadA5*, *aphA6*, *strA/B*), amphenicols (*floR*), fosfomycin (*fosA3*), macrolides (*mphA*), sulfonamides (*sulI*, *sulII*), tetracyclines (*tetA*(*A*)), trimethoprim (*dfrA7*), mercury (*merA*)	[32]
TetA(B)	pHCM1 (AL513383)	*Salmonella* Typhi	Tetracyclines (*tetR-tetA*(*B*)), chloramphenicol (*cat*), β-lactams (*bla*), sulfonamides (*sulII*), streptomycin (*strA/B*)	[200]
RND				
MexAB-CusC	pNDM-CIT (JX182975)	*C. freundii*	β-Lactams (bla_{MBL}, bla_{NDM-1}), aminoglycoside (*aadA2*, *armA*), chloramphenicol (*cat*), macrolides (*mel*, *mph2*), sulfonamides (*sulI*), trimethoprim (*dfrA12*), antiseptics (*qacEΔ1*), tellurium (*terABCDEFWY*)	[31]
MexCD-OprJ	pB4 (AJ431260)	Uncultured bacterium	β-Lactams ($blas_{NPS-1}$), spectinomycin and streptomycin (*strA/B*), chromate (*chrBAC*)	[201, 202]

Table 23.2 (continued)

Transporter family/pump	Plasmid (GenBank accession)	Bacterial species	Plasmid-borne resistance phenotype (resistance gene)	Reference
OqxAB	pOLA52 (EU370913)	*E. coli*	β-Lactams (bla_{TEM}), carbadox, nitrofurantoin, and olaquindox (*oqxAB*), sulfonamides (*sulI*)	[167, 180, 203–205]
SilCBA	pMG101 (AF067954)	*Salmonella* Typhimurium	Ampicillin, chloramphenicol, streptomycin, tetracycline, silver	[181, 182, 206]
SilCBA/ CusCBA	pEC5207 (KT347600)	*E. coli*	β-Lactams (bla_{CMY-2}), aminoglycosides (*aacA7*), sulfonamides (*sulI*), silver (*silP-cusA-silB-cusC-silE-cusRS*), copper (*copABCE*), antiseptic (*emrE*), tellurium (*terABCDEFWXYZ*)	[185]
SMR				
QacF	pB8 (AJ863570)	Uncultured bacterium	Quaternary ammonium compounds (*qacF*), ethidium bromide (*qacEΔ1*), β-lactams (bla_{OXA-2}), aminoglycosides (*aadA4*), sulfonamides (*sul1*)	[197]
QacZ	pTEF1 (AE016833)	*E. faecalis*	Quaternary ammonium compounds (*qacZ*), aminoglycosides (*aac-6′*)	[196, 207]
Smr	pSM52 (NC_025022)	*S. aureus*	Quaternary ammonium compounds (*smr*)	[51]
ABC				
ABC efflux complex	pRSB101 (AJ698325)	Uncultured bacterium	β-Lactams (bla_{TLA-2}), aminoglycosides (*aadA2*), macrolides (*mph*(*A*), *mph*(*R*)), sulfonamides (*sul1*), trimethoprim (*dhfr1*), tetracyclines (*tet*(*A*), *tetR*)	[198]
Lsa(E)	pV7037 (NG_041616)	*S. aureus*	Pleuromutilins, lincosamides and streptogramins (*lsa*(*E*)), aminoglycosides (*aacA-aphD*, *aadE*), lincosamides (*lnu*(*B*)), macrolides (*ermB*)	[44]

(continued)

Table 23.2 (continued)

Transporter family/pump	Plasmid (GenBank accession)	Bacterial species	Plasmid-borne resistance phenotype (resistance gene)	Reference
Mel	pRSB105 (DQ839391)	Uncultured bacterium	β-Lactams ($bla_{OXA\text{-}10}$), macrolides (*mel*, *mph*), sulfonamides (*sulI*), trimethoprim (*dfrB2*), antiseptics (*qacEΔ1*)	[108]
Msr(A)	pMS97 (AB092817)	*S. aureus*	Macrolides (*msr*(*A*), *mph*)	[208]
OptrA	pE349 (KP399637)	*E. faecalis*	Florfenicol, linezolid, and tedizolid (*optrA*)	[42]
Vga(E)	pSA-7 (NG_041699)	*S. cohnii*	Pleuromutilins, lincosamides, and streptogramins (*vga*(*E*))	[43]

Salmonella Paratyphi B, and *A. baumannii*) [31, 108]. Resistance to three structurally unrelated classes of pleuromutilins, lincosamides, and streptogramins is related to Lsa(E) or Vga(E) ABC transporters [43, 44].

A recent new study described a plasmid (named pE349) of oxazolidinone-resistant *E. faecalis* of human origin [42]. This plasmid, 36 kb in size, is conjugative and encodes an ABC transporter dubbed OptrA that is almost identical to a known putative ABC transporter of *E. faecalis* and *E. faecium*. OptrA shows good phylogenetic clustering with several staphylococcal ABC transporters such as Lsa(E) and Vga(A) that are involved in resistance to lincosamides, pleuromutilins, and streptogramins. Although pE349 also contains the *fexA* gene that confers resistance to amphenicols, the cloned *optrA* gene alone produces resistance to linezolid (four- to eightfold MIC increase), tedizolid (fourfold IMC increase), and florfenicol (16-fold MIC increase) in *E. faecalis* and *S. aureus* [42]. According to current clinical resistance breakpoints for linezolid and chloramphenicol from the Clinical and Laboratory Standards Institute [209], the *optrA*-containing plasmid sufficiently changes the interpretive category from susceptible to resistant for enterococci [42]. Of concern, a further survey of 885 enterococci revealed that *optrA* is five- to tenfold more frequently present in *E. faecalis* and *E. faecium* of food animal origin (20 % and ca. 6 %, respectively) than those of human sources (ca. 4 % and 0.6 %, respectively) [42]. An expanded survey of human hospital-derived 1,159 enterococci in China for the *optrA* gene showed prevalence of *optrA* in 34 (2.9 %) tested isolates that had variable molecular typing characteristics [85].

23.4 Concluding Remarks

Plasmid-mediated high-level resistance to all major clinically relevant antibiotics and antiseptic agents has been well documented, with the first bacterial drug efflux pump being plasmid encoded. More importantly, multiple drug resistance

determinants often coexist on the same plasmids with the presence of various mobile elements (insertion sequences, integrons, and/or transposons). Drug resistance plasmids are not limited to encoding only the single-component drug efflux pumps such as the diverse tetracycline-specific Tet pumps. They are increasingly found to carry genes encoding multicomponent drug efflux systems such as RND transporters involved in MDR. Since plasmids play a critical role in the evolution of resistance and in the dissemination of resistant bacteria, strategies to inhibit plasmid transfer could have potential implications in public health. Indeed, a recent study showed the feasibility to minimize resistance spread by blocking bacterial conjugation via the use of synthetic 2-alkynoic fatty acids [210]. Moreover, the enrichment of plasmid-containing bacteria in the presence of antimicrobial selective pressure again supports the significance of prudent antimicrobial use in any setting. Meanwhile, due to the widespread prevalence of plasmid-mediated resistance to antiseptics in hospitals, appropriate infection control measures including optimized disinfectant or biocide use should be taken into consideration in order to reduce the prevalence and spread of resistant pathogens. Lastly, several plasmid-encoded drug efflux pumps such as FloR, Lsa(E), OqxAB, OptrA, and Vga(E) were first identified in isolates of food animal origin, highlighting the important role of antimicrobial stewardship in veterinary medicine.

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