Genomic Islands in *Staphylococcus*

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Zaaima AL-Jabri and Nada AL-Mebairik

Abstract

Staphylococci are Gram-positive bacteria that have successfully evolved from a normal flora with limited threats to potentially life-threatening pathogens, particularly, *Staphylococcus aureus.* Species of staphylococci have adapted to survive under selective pressure mainly due to their ability to acquire mobile genetic elements (MGEs). Methicillin-resistant *S. aureus* is a common example of this successful evolution not only in hospital setting but also in the community. Recent literature supports that Coagulase-negative staphylococci including *S. epidermidis* are the reservoir for resistance as well as virulence-associated determinants for *S. aureus*. A wide range of MGEs are present in Staphylococci including genomic islands (GI), with staphylococcal chromosome cassette (SCC*mec)* as an example of the most common GI of medical importance, found in 15–20% of the *S. aureus*. The SCC*mec* are mobile entities that have been classified, so far into 14 types. Other GIs with similar characteristics to the SCC element is the Arginine Catabolic Mobile Element (ACME) and Copper and Mercury Resistance (COMER) that form a composite island with SCC*mec* IV, which have been first described in *S. aureus* USA-300 and in *S. epidermidis* as well. Other MGEs, include Insertion sequences and Transposons, plasmids, Integrative and conjugative elements (ICEs), and bacteriophages. MGEs have a

Z. AL-Jabri (✉)
Department of Microbiology & Immunology, College of Medicine and Health Sciences, Sultan Qaboos University, Muscat, Sultanate of Oman
e-mail: zaeema@squ.edu.om

N. AL-Mebairik
Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, King Saud University, Riyadh, Kingdom of Saudi Arabia
e-mail: Nalme.bairik@ksu.edu.sa

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significant survival advantage over their host species as these carry a wide variety of genes that confer resistance to antibiotics, heavy metals, and biocides.

Keywords

Mobile genetic elements · Staphylococci · Staphylococcal chromosome cassette (SCC*mec*)

11.1 *Staphylococcus* Species

Bacteria in the genus *Staphylococcus* are Gram-positive, cocci-shaped bacteria that are arranged in grape-like clusters. Traditionally, *Staphylococcus* species were divided into two major subtypes on the basis of their capability to produce the enzyme coagulase, which is responsible for blood plasma clotting (Foster 1996; Otto 2004). The main and the most pathogenic species, *Staphylococcus aureus*, belongs to the coagulase-positive staphylococci (CoPS) while the coagulase-negative staphylococci (CoNS) comprise most other *Staphylococcus* species. From the CoNS, *Staphylococcus epidermidis* is considered as the most important member that accounts for most of the CoNS infections (Foster 1996; Otto 2004).

11.2 *Staphylococcus aureus*

S. aureus is found as a commensal usually in the nasal carriage, on the skin, and mucous membranes. However, these bacteria are also successful as pathogens and can cause a wide range of diseases from mild skin infections to pneumonia, septicemia, and endocarditis (Malachowa and Deleo 2010; Tong et al. 2015). *S. aureus* pathogenicity and its ability to adapt under selective pressures are mostly attributed to the products of MGEs that confer virulence factors and antibiotics resistance, including the gene conferring methicillin resistance in methicillin-resistant *S. aureus* (MRSA) (Ito et al. 1999; Malachowa and Deleo 2010).

MRSA was reported shortly after the introduction of methicillin, a drug now replaced by flucloxacillin in clinical practice. Over the years, MRSA became one of the most significant causes of nosocomial infections with increasing morbidity and mortality (Ayliffe 1997; Chongtrakool et al. 2006). The healthcare-associated MRSA (HA-MRSA) shows resistance to methicillin by the acquisition of a MGE called the staphylococcal cassette chromosome *mec* (SCC*mec*) (Katayama et al. 2000; Chongtrakool et al. 2006). Additionally, MRSA was isolated from patients with no recent contact with healthcare facilities, thus labeled as community-associated MRSA (CA-MRSA) and differs from HA-MRSA as it contains various types of SCC*mec* and several virulence factors that are rarely identified in HA-MRSA, such as pore-forming toxin and the Panton-Valentine leukocidin (PVL) (Davidson et al. 2008; Herold 1998; Naas et al. 2005; Naimi 2003).

11.3 *S. epidermidis* and Other CoNS

The CoNS comprise species that normally colonize humans and they can cause infections in certain situations. These species include *S. epidermidis, S. haemolyticus, S. hominis, S. capitis, S. saccharolyticus, S. saprophyticus, S. cohnii, S. warneri*, and *S. lugdunensis* (Otto 2004). CoNS also contain species that colonize and infect animals and species that are less or non-pathogenic. However, the main and best-described species is *S. epidermidis* (Otto 2004). This species is considered a commensal bacterium on healthy skin and mucosal surfaces. Although *S. epidermidis* is less virulent than *S. aureus*, severe complications associated with indwelling medical devices can arise from this bacterium. *S. epidermidis* ability for biofilm formation in addition to the medical devices' insertion makes this bacterium a significant nosocomial pathogen, and the leading cause of surgical site infections and bloodstream infections (Cherifi et al. 2013; Lee et al. 2018; Otto 2013).

Interestingly, several previous studies discussed the role of CoNS including *S. epidermidis* as a potential reservoir for resistance-conferring genes and virulence determinants that transfer to *S. aureus* and contribute toward its diversity and pathogenicity (Hung et al. 2015; Otto 2013). For example, the *mecA* gene and the SCC*mec* elements were found and reported earlier to be more frequent in *S. epidermidis* strains in comparison to *S. aureus* strains (McManus et al. 2015; Otto 2013). Additionally, *S. epidermidis* SCC*mec* elements have DNA sequences that are homologous to these elements in *S. aureus*, however, the polymorphous structure of SCC*mec* with novel cassette chromosome recombinase (*ccr*) and *mec* gene complexes that have not been described in *S. aureus* are present in CoNS. This evidence indicates that CoNS including *S. epidermidis* may act as a pool for the SCC*mec* entities (Barbier et al. 2010; Otto 2013). Another example is the ACME mobile element which is found in *S. aureus* USA300-NAE. Some reports show that 52% of global *S. epidermidis* strains harbor the ACME mobile element. On the other hand, some investigations noted that the different types of ACMEs in *S. epidermidis* are similar to those discovered in *S. aureus* USA300. This evidence suggests that *S. epidermidis* is the origin of most ACME-associated genes (Barbier et al. 2011; Miragaia et al. 2009; Otto 2013; Onishi et al. 2013; O'Connor et al. 2018b).

11.4 Mobile Genetic Elements of *Staphylococcus* Species

Among *Staphylococcus* species, the MGEs are best described in *S. aureus* as it has been known as the most virulent species. In fact, the diversity of the MGEs in *S. aureus* contributed to *S. aureus* adaptation and evolution into successful lineages. These MGEs, including plasmids, transposons, ICEs, bacteriophages, and staphylococcal chromosome cassettes (SCCs) found to compose around 15-20% of the *S. aureus* genome (Alibayov et al. 2014; Haaber et al. 2017; Lindsay 2010). This chapter sheds light on some of these MGEs.

11.5 Staphylococcal Cassette Chromosome *mec* (SCC*mec*)

S. aureus and other CoNS show an ability to resist methicillin by the acquisition of the SCC*mec* genomic island. This MGE carries *mecA* which encodes a penicillin-binding protein named PBP2a or PBP2', which is different from the core PBP2. This PBP2a exhibits low affinity to methicillin and most semisynthetic ß-lactam antibiotics (Chongtrakool et al. 2006; Hartman and Tomasz 1984; Pinho et al. 2001). SCC*mec* is a critical mobile element as MRSA has spread worldwide and become the leading cause of both community-acquired infections and healthcare-associated infections (Davidson et al. 2008; Monecke et al. 2016; Naimi 2003; Rolo et al. 2017).

There are essential components that are usually found in the SCC*mec* element. The first one is the *mec* gene complex which contains the *mecA* gene, as well as the regulatory genes; *mecR1* and *mecI* located upstream of *mecA* and IS*431* downstream of *mecA* (Chongtrakool et al. 2006; Ito et al. 2001; IWG-SCC 2009). In addition, the other component is the *ccr* gene complex which contains the *ccrAB* or *ccrC* genes. These site-specific recombinase genes catalyze SCC*mec* element integration into a site-specific attachment sequence in the staphylococcal chromosome called the *attB* and also catalyze the excision of SCC*mec* from the same place (Chongtrakool et al. 2006; IWG-SCC 2009; Noto et al. 2008). Additionally, different accessory genes that encode virulence or resistance determinants can be found in SCC*mec* elements in areas called joining regions (J-regions) (IWG-SCC 2009; Monecke et al. 2016). Interestingly, SCC*mec* elements that lack *ccr* genes have also been reported which are known as pseudo-SCC*mec* elements, and SCC elements without the *mecA* gene but with other characteristic genes have also been identified in staphylococcal genomes (IWG-SCC 2009; Wilson et al. 2016).

There are 14 types of SCC*mec* elements (types I–XIV) which are classified based to the different combinations of *mec* gene and *ccr* gene complexes (Table 11.1).

Table 11.1 SCC*mec* types identified in *S. aureus*

SCC*mec* type	*ccr* gene complex	*mec* gene complex
I	1 (A1B1)	B
II	2 (A2B2)	A
III	3 (A3B3)	A
IV	2 (A2B2)	B
V	5 (C1)	C2
VI	4 (A4B4)	B
VII	5 (C1)	C1
VIII	4 (A4B4)	A
IX	1 (A1B1)	C2
X	7 (A1B6)	C1
XI	8 (A1B3)	E
XII	9(C2)	C2
XIII	9(C2)	A
XIV	5(C1)	A

There are four classes of the *mec* gene complex identified thus far: class A, B, C, and E; while three different *ccr* genes had been discovered: *ccr*A, B, and C. Additionally, the differences in J-regions are used for determining the SCC*mec* subtypes (Baig et al. 2018; IWG-SCC 2009; Urushibara et al. 2019; Wu et al. 2015). Currently, MRSA elements are identified by the chromosome sequence type (ST) and the SCC*mec* type. SCC*mec* types I, II, and III, comprise most of the HA-MRSA whereas CA-MRSA belongs mostly to types IV and V (Kang et al. 2015; Naimi 2003).

11.6 Arginine Catabolic Mobile Element (ACME)

The ACME is a genomic island that is found in many staphylococcal species and shows characteristics that are similar to the SCC element. It was first described in *S. aureus* USA300-NAE as well as *S. epidermidis* strain ATCC12228 (Diep et al. 2006). In *S. aureus* USA300-NAE, ACME forms a composite island with SCC*mec* IV, while in *S. epidermidis* ATCC12228, it exists as a composite island with SCC*pbp4* (Diep et al. 2006; Shore et al. 2011). This mobile element which ranges in size from 31 to 34 kb integrates into the staphylococcal chromosome at the attachment site*; attB* with direct repeat sequences at the flanks which is similar to SCC. The *ccrAB* genes encoded by SCC elements mediate the movement of ACME (Shore et al. 2011; Thurlow et al. 2013). In addition, the presence of several internal direct repeats in ACME has resulted in a stepwise pattern of assembly of this element (O'Connor et al. 2018b).

There are two gene clusters characterized in the ACME element, the *arc* operon and the *opp3* operon (Diep et al. 2008; Granslo et al. 2010). The *arc* operon comprises the regulatory gene (*argR*) and *arcABCD* genes that encode the main bacterial arginine catabolic pathway, an arginine deaminase pathway. The result of this pathway is converting arginine into ornithine, ammonia, carbon dioxide, and ATP, and consequently serves bacterial growth with arginine as the sole source of energy (Diep et al. 2008; Makhlin et al. 2007; O'Connor et al. 2018b). The *opp3* operon consists of *opp-3ABCDE* genes that encode ABC transporter systems (Diep et al. 2006; Granslo et al. 2010; Shore et al. 2011). Moreover, the ACME element has two additional associated genes; the *speG* gene encoding polyamine resistance and *copBL* genes encoding a copper export P1-type ATPase and a putative lipoprotein, respectively. The *copBL* genes are suggested to be a novel copper resistance locus (O'Connor et al. 2018a; Planet et al. 2015; Purves et al. 2018; Rosario-Cruz et al. 2019). On the whole, it is found that the presence of ACME in staphylococcal species increases their fitness and improves their capacity for skin and mucus membrane colonization (Lindgren et al. 2014; Miragaia et al. 2009; Purves et al. 2018).

ACME mobile elements are classified into three distinct types: ACME type I which contain the *arc* and *opp-3* operon, ACME type II contains only the *arc* operon, and ACME type III which contains the *opp-3* operon only (McManus et al. 2017; Shore et al. 2011; Rolo et al. 2012). Recently, two more types of *S. epidermidis* were identified. ACME type IV which carry the *arc* operon, a *kdp*

operon which encodes the ABC transporter, and ACME type V which harbors both the *arc* and the *opp-3* operons, as well as the *kdp* operon (O'Connor et al. 2018a).

11.7 Copper and Mercury Resistance (COMER)

Copper and Mercury Resistance (COMER) is a novel MGE that was first described in the *S. aureus* USA300-SAE strain. Similar to ACME, this mobile element is found adjacent to SCC*mec* IV in the *S. aureus* USA300 chromosome (Planet et al. 2015). COMER element is thought to contribute to copper and mercury resistance. The presence of the copper and mercury resistance coding sequences in the COMER element support this idea. Additionally, the COMER element harbors genes encoding an abortive phage (Abi) infection system. This system is a resistance mechanism which leads to bacterial death after viral infection, thus preventing further dissemination of phages (Almebairik et al. 2020; Dy et al. 2014; Planet et al. 2015; Purves et al. 2018). It could be argued that the COMER element enhances the fitness of USA300-SAE as recently, this strain has been identified in North and South America, Europe and Gulf region (Oman) (Almebairik et al. 2020; Planet et al. 2016; Purves et al. 2018; Al-Jabri et al. 2021).

As in the ACME element, novel copper resistance genes (*copXL*) were detected in COMER, however, those two genes were associated with the *mco* gene (encodes multi-copper oxidase) in the COMER element (Almebairik et al. 2020; Planet et al. 2015; Purves et al. 2018; AL-Jabri et al. 2021). The other characteristic operon in COMER is the *mer* operon that confers mercury resistance. This operon consists of genes involved in the enzyme-mediated reduction of divalent mercury (Hg^{2+}) into the elemental form (Hg^{0}) that is less toxic and then volatilizes from the cell (Osborn et al. 1997). Two types of the *mer* operon have been identified: (i) a narrow-spectrum *mer* operon which confers resistance to inorganic mercurial compounds and (ii) a broad-spectrum *mer* operon which confers resistance to inorganic as well as organo-mercurial compounds (Bruce 1997). This operon encodes proteins for regulation (*merR* gene), transport, and mercuric reductase (*merA* gene). In the broad-spectrum *mer* operon, an additional protein called organomercurial lyase encoded by the *merB* gene is found (Osborn et al. 1997).

COMER elements were also detected in *S. epidermidis* isolates belonging to the ST2 clonal lineage which is associated with multidrug-resistance in hospital settings worldwide. In *S. epidermidis*, this MGE is named COMER-like element because it harbors the *mer/cop* operon as well as the *abi* gene located in COMER element of *S. aureus* USA300. However, there were other genes identified in the *S. epidermidis* COMER-like element which are lacking in COMER USA300, namely the *ars* operon and a type I restriction-modification system. Additionally, the COMER-like element is located immediately adjacent to SCC*mec* III in *S. epidermidis* chromosome, instead of SCC*mec* IV in USA300 COMER element (Almebairik et al. 2020).

11.8 The Mechanism of SCC*mec* Transfer

The excision and integration of SCC*mec* are catalyzed by the Ccr proteins. These proteins mediate the site-specific recombination events between the *attB*-specific site on the chromosome, and one in the circularized SCC*mec* named *attS* (Ito et al. 2004; Misiura et al. 2013; Wang and Archer 2010). This *attB* attachment site is terminally located in a conserved ribosomal methyltransferase gene of orfX, also known as *rlmH* (Boundy et al. 2013). When the SCC*mec* is inserted, it is flanked by direct repeat (DR) sequences and inverted repeat sequences (IRs), at both ends, referred to as *attL* and *attR*. These new pairing sites contain the *attB* sequence which is duplicated during SCC*mec* insertion in the chromosome. When the SCC*mec* excises, *attL* and *attR* sites are reconstituted and reproduce the *attB* in the chromosome and the *attS* in the circular SCC*mec* (Liu et al. 2017; Misiura et al. 2013; Wang and Archer 2010).

Chromosomal SCC*mec* excision is a significant step in its lateral horizontal transfer among *Staphylococcus* species. The excision process can occur spontaneously with a low-frequency rate, less than 10^{-4} in *S. aureus* (Ito et al. 1999; Stojanov et al. 2015). The mechanisms that trigger the excision of the SCC*mec* are still not well understood, however, some studies found that many antibiotics, including ß-lactam antibiotics, could increase the frequency of SCC*mec* excision from the chromosome and consequently increase its transfer (Higgins et al. 2009; Liu et al. 2017).

The mechanism of SCC*mec* elements transfer between staphylococci is still unknown. Some early studies suggest that the movement of SCC*mec* is via a transduction mechanism. However, these studies report conflicting conditions for successful SCC*mec* transduction (Cohen and Sweeney 1970; Scharn et al. 2013; Shafer and Iandolo 1979; Stewart and Rosenblum 1980). Cohen and Sweeney proposed that successful methicillin resistance transfer is mediated by a prophage as well as a penicillinase plasmid in the recipient cell (Cohen and Sweeney 1970). Stewart and Rosenblum suggested that recipient cells require a penicillinase plasmid only (Stewart and Rosenblum 1980). Shafer and Iandolo demonstrated the co-transduction of methicillin resistance with tetracycline resistance via a small plasmid (Shafer and Iandolo 1979). A more recent study with *S. aureus* USA300 showed the successful transduction of SCC*mec* types IV and I via bacteriophages 80a and 29. This study reported that the recipient cell and the homologs of donors require a penicillinase plasmid, in addition to recipients respecting the presence/absence of the ACME element. This study also noted the possibility of truncation, substantial deletions, or rearrangement of the SCC*mec* and ACME in the recipient during the transduction process (Scharn et al. 2013).

11.9 Plasmids

More than 90% of clinical isolates of staphylococci harbor plasmids ranging in size; however, only 5% of staphylococcal plasmids are large multiresistant conjugative plasmids. Small staphylococcal plasmids range from 1 to 10 kb in size (Malachowa and Deleo 2010; Shearer et al. 2011). On the other hand, large multiresistant plasmids of more than 15 kb in size carry antibiotic resistance, heavy metal, and biocide-resistance-conferring genes (Novick et al. 1989; Firth and Skurray 2006; Jensen and Lyon 2009; Shearer et al. 2011).

11.10 Multi-Resistant (Conjugative) Plasmids and their Mobilization System

Larger plasmids carrying multiple resistance genes (20–65 kb) are found in most staphylococci, however, lack mobilization genes (Shearer et al. 2011). In fact, there is a paucity of conjugative genes in most staphylococci. In staphylococci, the conjugative plasmids are classified based on their distinct conjugation-gene clusters. These include examples such as pSK41, pWBG749, and pWBG4 families (Kwong et al. 2017), which were identified in many countries worldwide as associated with many infections including community-acquired MRSA (Archer and Johnston 1983; Diep et al. 2008; Goering and Ruff 1983; Jaffe et al. 1982; Pérez-Roth et al. 2006). These plasmids are capable of transferring from the donor to the recipients at a relatively low frequency (Climo et al. 1996; Helinski 2022; Macrina and Archer 1993). Some conjugative plasmids like pSK41 were found to be integrated into the chromosome (Mcelgunn et al. 2002). The resistance genes are usually carried in small-sized plasmids which are cointegrated between two copies of IS to promote their conduction (Caryl et al. 2004; Climo et al. 1996; Gennaro et al. 1987). An example is IS257/IS431 found integrated within the pSK41/pGO1 plasmids (Kwong et al. 2004), harboring linezolid and high-level resistance to vancomycin (Bender et al. 2014; Clark et al. 2005). Members of pSK41-like family of plasmids carry various resistance-conferring genes including resistance to biocides and antiseptic agents (*qacC*) (Littlejohn et al. 1991), mupirocin (*mupA/ileS2*) (Morton et al. 1995; Pérez-Roth et al. 2010), MLS antibiotics [*erm(C)*] (Diep et al. 2006), trimethoprim (*dfrA*) (Evans and Dyke 1988), tetracycline [*tet(K)]* (Shearer et al. 2011), and linezolid (*cfr*) (Bender et al. 2014). The conjugative plasmids in the pWBG749 family carry penicillin, aminoglycoside as well as vancomycin resistance genes (Panesso et al. 2015; O'Brien et al. 2015; Rossi et al. 2014) and mobilized by SmpP, a putative relaxase and a distinct *oriT*. On the other hand, the conjugative plasmid pWBG637, does not harbor any resistance-conferring genes (E. E. Udo and Grubb 1990). However, pWBG637 has the ability to conjugate with other staphylococcus species including *S. aureus and S. epidermidis* as well as other Gram positives such as *Enterococcus faecalis* strains. The latter plasmid is capable of mobilizing several coresident antimicrobial resistance plasmids through conjugative transfer. The pWBG4 family of conjugative plasmids was first identified in 1985

which harbors a cointegrated Tn*554* containing *erm(A)* resistance gene with *det* conjugation-associated gene (Townsend et al. 1985, 1986; E. Udo et al. 1987). pWBG14, is another conjugative multiresistant-conferring aminoglycoside, macrolide, lincosamide, and spectinomycin resistance. The pWBG4-family plasmid (pSA737) (Shore et al. 2016) is identical to pSK73 but very different from pSK41 and pWBG749 (Néron et al. 2009; E. E. Udo et al. 1992).

11.11 Mobilization System of RC-Replicating Plasmids

Small conjugative plasmids of less than 5 kb in size usually replicate by rolling circle (RC) mechanism. These plasmids mostly harbor a single resistance-determinant and exist as multiple copies within each cell (10–60 copies) (Mojumdart and Khan 1988). Initially, there were four identified groups of plasmids in this category based on the resistance genes as follows: plasmid pT181 with *tet(k)* games encoding tetracycline resistance (Mojumdart and Khan 1988), pC194 harboring *cat* gene conferring chloramphenicol resistance (Horinouchit and Weisblum 1982a), pE194 carrying *erm(C)* conferring erythromycin resistance (Horinouchit and Weisblum 1982b), and the cryptic pSN2 plasmids (Novick et al. 1989; Walters and Dyke 2006). Each of these plasmids has a distinct replication protein namely (Rep_trans for pT181, Rep_1 for pC194, Rep_2, and RepL for pE194). Additional RC-replicating plasmids were also described which carry a mosaic of resistance determinants due to the continuous mobilization of various DNA segments in these functional modules (Novick et al. 1989; Projan and Archer 1989). Examples include RC plasmids conferring resistance to streptomycin (*str*) (Projan and Archer 1989) lincomycin [*lnu(A)*] (Brisson-Noel et al. 1988), fosfomycin (*fosB*) (Dionisio et al. 2019), quaternary ammonium compounds (*qacC* and *smr*) (Littlejohn et al. 1991), aminoglycosides *(aadD*), or bleomycin *(ble*) (McKenzie et al. 1986). Non-conjugative plasmids like pC221 are transferred via a *mobCAB* operon and origin of transfer *(oriT*) (Caryl et al. 2004; Projan and Archer 1989).

11.12 Bacteriophages

Bacteriophages are viruses that are capable of infecting bacteria. These elements play a significant role in disseminating MGEs through transduction mainly (Lindsay 2014; Xia and Wolz 2014). Bacteriophages have been demonstrated to be effective tools in biotechnology with diverse applications in therapeutics and research including alternatives to antibiotics in killing bacteria (Ul Haq et al. 2012). Phages have been shown to either act as gene transfer vehicles or carry accessory virulence-conferring genes in bacteria (Quiles-Puchalt et al. 2014b). A classic example is how bacteriophages mediate the transfer of plasmid-encoded virulence-conferring genes in *Staphylococcus aureus* (Dowell and Rosenblum 1962; Novick 1963). The range of virulence genes carried by *Staphylococcus* phages is diverse including enterotoxin A, Exfoliative toxin A, Pantheon-Valentine leucocidins (PVL), and

staphylokinase (Brüssow et al. 2004). Moreover, the *Staphylococcus aureus* pathogenicity island (SaPIs) encoding superantigens utilize the help of bacteriophages to the horizontal gene transfer (Lindsay et al. 1998; Novick et al. 2010). Experimental models have attempted to demonstrate the mobility of SaPI via bacteriophages. It was shown that the SOS induction of SaPI has resulted in the recruitment of replicating phage packaging proteins to be used for their transfer in helper phage φ11(Quiles-Puchalt et al. 2014b). Bacteriophages involved in transferring genes horizontally in staphylococci are members of the order *Caudovirales* which have three families on the basis of the structure of their tails (Hatfull and Hendrix 2011; Tolstoy et al. 2018). Transduction in bacteriophages occurs mainly during the lytic cycle during which a foreign DNA or host plasmid is packaged at low frequency (Chiang et al. 2019). *Caudovirales* are mainly temperate phages that undergo lysogeny during which their genome is integrated into the host genome as prophages. Prophages become established in the bacterial lineages if they harbor advantageous survival machinery to the host, i.e., virulence or resistance-conferring genes.

Helper bacteriophages, however, are much more related to MGE packaging which happens at a very high frequency compared to generalized transduction. This is known as molecular piracy in which the prophage propagation is significantly suppressed after the integration into the host DNA (Christie and Dokland 2012). In addition, phage proteins are almost completely exploited by the MGEs for their own excision and replication, and redirection of capsid size to their own advantage (Christie and Dokland 2012). The pathway for capsid assembly and Packaging of virion DNA for the *Caudovirales* are relatively similar. The basic capsid protein (CP) is alternatively called "phage capsid fold" or "HK97 fold" (Wikoff et al. 2000). The P2/P4 paradigm serves as a classical example by which MGE are molecular piracies. P2 is a myovirus with a very small genome (33 kb) first described in the 1950s (G. Bertani 1951; L. E. Bertani 1980), and has been mainly associated with *Escherichia coli* (Nilsson et al. 2004). P4 is a Satellite bacteriophage that was initially thought to be P2-dependant MGE (Six and Klug 1973), however, later it was found to be an integrative plasmid, also known as a phasmid that is able to replicate autonomously as a plasmid and/or integrate within the genome of the host (Briani et al. 2001; Dehò and Ghisotti 2006). P4 phage does not have the ability to form infectious particles as it lacks the genes encoding structural proteins. Therefore, once a host cell with P4 becomes infected with P2, it will recruit P2 helper phage-encoded genes to package into phage particles (Six 1975).

11.13 *Staphylococcus aureus* Pathogenicity Islands (SaPIs)

Staphylococcus aureus Pathogenicity Islands (SaPIs) are chromosomally located genomic islands which are usually large in size (up to 14 kb). The first SaPIs described were reported to harbor toxic shock syndrome toxin (TSST-1) known as *tst* gene. SaPIs are usually composed of an integrase gene located at one end, a repressor gene, and a replication module each expressed by different promoters in

opposing directions (Novick and Ram 2017; Penadés and Christie 2015; Viana et al. 2010). A "helper exploitation" module is located at the terminal of the genome, there is dedicated to phage interactions. However, in type 2 SaPIs, the helper module is lacking and instead, these are packaged by 80α, such as SaPIbov5, which do not change the capsid size due to the lack of *cpmA* and *cpmB* (Viana et al. 2010; Quiles-Puchalt et al. 2014a).

Moreover, similar Phage-Inducible Chromosomal Islands (PICIs) have been reported in a number of Gram-positive bacteria including *Enterococcus, Streptococcus, and Lactococcus* (Martínez-Rubio et al. 2017). It was demonstrated in *Enterococcus faecalis* strain (V583), that mitomycin C induction resulted in the formation of small capsids (Martínez-Rubio et al. 2017). PICIs were also described in Gram-negative bacteria which were similar in function, but different in the genetic composition in *Escherichia coli* and *Pasteurella multocida* (Fillol-Salom et al. 2018, 2019).

The assembly pathways of phages have evolved along the way with the evolution of MGEs. Although the phages and PICIs share a similar proto-phage ancestor, the PICIS still depend for their mobilization on the helper phages, as these lack the structural genes modules, which were either lost early in evolution or were never acquired (Dokland 2019). The mechanisms by which the capsid redirection occurs are diverse, suggesting that these structural genes encoding capsid and scaffolding proteins have been acquired horizontally at different time points. Some MGEs like P4-like elements have distinct evolutionary branches as these are more closely related to plasmids rather than phages or PICIs, however, retained their ability to redirect helper capsid assembly by a different mechanism (Briani et al. 2001).

11.14 Insertion Sequences (IS) and Composite Transposons (Tn)

Insertion sequences are a vital entity of MGEs that have long been involved in revolution of the bacterial genomes by their unique ability to transpose or alter the expression of surrounding genes (Siguier et al. 2014, 2015). These IS facilitated the recombination of transposons in plasmids as well as chromosomes (Mahillon and Chandler 1998). IS are about 2.5 kb long transposable elements (TE) composed mainly of the enzyme transposase (*tnp*) catalyzing DNA excision and transfer from the donor site to another recipient or target site. IS are diverse TEs containing short imperfect terminal inverted repeat sequences (IR) and upon insertion, short flanking directly repeated target DNA sequences (DR) are generated. Traditionally, IS can only mobilize resistance genes through composite transposons. To date, there are at least 27 different families of IS (Siguier et al. 2006, 2015) assigned in groups based on the following criteria: similarities in the sequence of the transposition enzyme (*tnp*) using Markov cluster (MCL) algorithm (Enright et al. 2002; Siguier et al. 2009), their transposition mechanism and similarities in the sequences of the ends. A complete list of families can be found in the ISfinder database (ISfinder, https://www-is.biotoul.fr/). The full description of the IS can be found in the TnCentral database (https://tncentral.proteininformationresource.org/) under Tn encyclopedia. The significance of IS in transposition of resistance-conferring genes has soon been

recognized after the discovery of these elements in the 1970s (Barth et al. 1976; Hedges and Jacob 1974).

Important examples of IS are IS256 and IS257 families which play a key role in spreading resistance genes in staphylococci through various transposons (Partridge et al. 2018; Varani et al. 2021). Unit transposons are a sub-class of transposons that are flanked by IR instead of IS, a *tnp* gene (s) (which includes a transposase regulator) in addition to internal passenger genes that encode for antibiotic resistance. The latter can be exemplified by Tn*552* in Staphyloccoci which has a different transposition pathway targeting particular site(s). It is believed that Tn*552*-like elements are responsible for the dissemination of β-lactamases in staphylococci (Gregory et al. 1997). Tn*552* transposons can be found in chromosomes, however, these are mostly associated with multiresistant plasmids inserted within the *res* site of the plasmid resolution system (Berg et al. 1998; Ito et al. 2003; Paulsen et al. 1994; Rowland et al. 2002).

Most of the published literature addressing the role of MGEs in antimicrobial resistance focused on the antibiotic's efflux or inactivation, and target site modification. However, recent work has shed light on the overlooked role of heterodiploidy of metabolic genes in reducing the fitness cost in Staphylococci (Andersson 2006; Ciusa et al. 2012). For example, the dihydrofolate reductase (*dhfr*) conferring resistance to trimethoprim, is present in plasmids and conjugative elements that are located in the Tn*4003* transposon which enable the *dfrA* gene to be mobilized by IS*257* in *S. aureus* (Needham et al. 1995). Other examples include *dfrA* gene transposed by Tn*7* in *E. coli* (Barth et al. 1976), and the TE Tn*5801* harboring *dfrG* and IS*256* in various Gram-positive species (León-Sampedro et al. 2016).

Furthermore, mupirocin resistance in staphylococci has recently been attributed to an additional copy of plasmid-encoded *mupA* gene (also known as *ileS2*), which is also mobilized by IS256 (Gilbart et al. 1993; Woodford et al. 1998). Mupirocin is an antibiotic and a disinfectant that acts as a potent inhibitor of the isoleucyl tRNA synthetase and has long been used for decolonization of MRSA. However, global use of mupirocin has resulted in increased resistance by MRSA, which led to changes in the decolonization protocols (Deeny et al. 2015; Hetem and Bonten 2013). The wide use of triclosan as a disinfectant has been concerning, as it targets FabI, the NADH-dependent trans-2-enoyl-acyl carrier protein (ACP) reductase, which is involved in the bacterial fatty acid biosynthesis (Hijazi et al. 2016; Schweizer 2001). Due to absence of the eukaryotic orthologue of FabI, the selective toxicity of the drugs against the prokaryotic protein is ideal, however, there might be a reciprocal resistance to antimicrobials as well (Coelho et al. 2013; Maillard et al. 2013; Morrissey et al. 2014; Oggioni et al. 2013, 2015). In the latter case of triclosan resistance, it was demonstrated that it was due to mutations in the promoter region or the chromosomal sequence of *fabI* gene (Ciusa et al. 2012; Grandgirard et al. 2015; Heath et al. 1999; McBain et al. 2012; Oggioni et al. 2013; Slater-Radosti et al. 2001). Moreover, more than half of *S. aureus*-resistant isolates carryan additional copy of *fabI* that originated from *Staphylococcus haemolyticus*, and therefore named as *(sh-fabI*) (Ciusa et al. 2012). It was found that *sh-fabI* gene was part of a TE and mobilized by IS*1272* that belongs to the IS*1182* family and present as a truncated IS

in the *mec* element in *Staphylococcus haemolyticus,* however, it is absent in *S. aureus* (Archer et al. 1994; Archer et al. 1996; Siguier et al. 2015; Tonouchi et al. 1994). Furi et al. reported the presence of two composite transposons (Tn*Sha*1 and Tn*Sha*2) facilitating the dissemination of *sh-fabI* gene, with Tn*Sha*1 mostly found in *S. aureus* and Tn*Sha*2 carried in plasmids of *S. epidermidis* and *S. haemolyticus* (Furi et al. 2016). As in the case of *iles2* and *dfrA* and *dfrG* genes, *sh-fabI* is similarly mobilized by insertion sequence and duplication of drug-target metabolic genes consequently (Furi et al. 2016). The integration mechanism of *sh-fabI* involves targeting of DNA secondary structures and generation of blunt-end deletions in these hairpin structures.

11.15 Integrative and Conjugative Elements

Integrative and Conjugative Elements (ICEs) are a group of MGEs found in a diverse range of bacteria. These elements were originally called conjugative transposons that are capable of self-transposition via conjugation. Moreover, ICEs have the ability to integrate into the host chromosome and replicate either as part of the host or self-replicating after excision (Carraro and Burrus 2015). This group can be exemplified by Tn*916*-like elements encoding for tetracycline/minocycline resistance via *tet(M)*; as well as MLS [*erm(B)*] and kanamycin/neomycin (*aphA-3*) in Tn*1545* (Cochetti et al. 2008). ICEs can mobilize resistance genes by recombination mechanisms as in transposons and phages, and conjugation mechanisms similar to plasmids. Most ICEs in literature have tyrosine recombinases to facilitate excision and integration, with much fewer examples of serine recombinases and DDE transposes (Cury et al. 2017). ICEs elements are arranged in the form of modules, with similar genetic composition shared among a number of important Tn*916*-like elements for example, Tn*5397,* Tn*6000*, and Tn*5801*, conferring tetracycline resistance via *tet(M)/tet(S)* and each have different genes for excision and integration and structure due to the various recombination events (Brouwer et al. 2010; Kuroda et al. 2001; Roberts and Mullany 2011; Tsvetkova et al. 2010). In addition, Tn*1549* harbors *vanB* that resulted in the global dissemination of resistance to vancomycin in staphylococci and enterococci (Launay et al. 2006). The mechanism of integration in these elements utilizes a tyrosine integrase that targets AT-rich regions (Sansevere and Robinson 2017).

ICE6013 is another type of ICE, however, not related to Tn*916* which was first described in ST239 strains of *S. aureus* carrying Tn*552* insertions (Smyth and Robinson 2009). A number of sub-families were subsequently identified in other staphylococcal species (Sansevere et al. 2017). ICE6013 utilizes a transposase-like enzyme for its transposition (Smyth and Robinson 2009).

11.16 Others

The occurrence of class I integrons in staphylococci has only been identified by a few studies using conventional PCR detection methods of *intI1*, with no significant evidence that integrons are associated with larger segments of mobile elements or plasmids. Apart from fragments, GenBank search of Whole genome sequences and shotgun sequences failed to identify any integrons as entities in staphylococci (accessed May 2022).

11.17 Conclusion Remarks

As staphylococci continue to evolve, our knowledge of mobile genetic elements in Gram-positive bacteria is rapidly expanding. The accessory genome of Staphylococci carries most of the antimicrobial, as well as virulence-conferring determinants. Despite the intraspecies and interspecies exchange of the mobile elements among staphylococci, there are significant variations among species and strains. For example, the successful lineages of *S. aureus* vary in their composition of MGEs of insertion sequences, genomic and pathogenicity islands, transposons, and bacteriophages. The most common example is the various evolutionary trends observed in SCC*mec* in *S. aurous* that is continuously changing practically in related ACME and COMER elements. This observation strongly supports the ability of the MGEs to evolve independently from their microbial hosts as seen in phylogenies constructed for these elements in many studies to facilitate our understanding of their emergence.

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