Mobile genetic elements of Staphylococcus aureus

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Abstract Bacteria such as Staphylococcus aureus are successful as commensal organisms or pathogens in part because they adapt rapidly to selective pressures imparted by the human host. Mobile genetic elements (MGEs) play a central role in this adaptation process and are a means to transfer genetic information (DNA) among and within bacterial species. Importantly, MGEs encode putative virulence factors and molecules that confer resistance to antibiotics, including the gene that confers resistance to beta-lactam antibiotics in methicillin-resistant S. aureus (MRSA). Inasmuch as MRSA infections are a significant problem worldwide and continue to emerge in epidemic waves, there has been significant effort to improve diagnostic assays and to develop new antimicrobial agents for treatment of disease. Our understanding of S. aureus MGEs and the molecules they encode has played an important role toward these ends and has provided detailed insight into the evolution of antimicrobial resistance mechanisms and virulence.

Keywords Mobile genetic elements · Staphylococcus aureus · Virulence · Antibiotic resistance · Horizontal gene transfer

Introduction

Mobile genetic elements (MGEs) were first described in the maize genome in the late 1940s [1, 2] and are an important means for transfer of genetic information among prokaryotes and eukaryotes. MGEs are typically identified as fragments of DNA that encode a variety of virulence and resistance determinants as well as the enzymes that mediate their own transfer and integration into new host DNA [3]. MGEs demonstrate intracellular and intercellular mobility, and those within one particular cell are called a “mobility” [4]. Transfer of MGEs between cells is known as lateral or horizontal gene transfer (HGT). HGT occurs as prokaryote-to-prokaryote, prokaryote-to-eukaryote, and eukaryote-to-eukaryote transfer of DNA [5, 6] (Fig. 1). MGEs may consist of insertion sequences, transposons, phages, plasmids, pathogenicity islands, and chromosome cassettes. These segments of DNA are largely propagated by vertical gene transfer, which is transmission of genetic information from parent to progeny cell (Fig. 1).

The bacterial genome consists of core and accessory genomes. The core genome contains all genes vital to cell survival, such as genes encoding molecules involved in metabolism, DNA and RNA synthesis, and replication. The accessory gene pool represents the diversity within bacterial species by encoding proteins required for adaptation of bacteria in different ecological niches (resistance, virulence factors, etc.). Accessory genes typically have a different G + C content than those in the core genome, often because they are obtained from other species of bacteria [7, 8]. Bacteria obtain genetic information from other cells or the surrounding environment in three ways: (1) uptake of free DNA from the environment (transformation), (2) bacteriophage transduction, and (3) direct contact between bacterial cells (conjugation).
In prokaryotes, transfer of genetic information between cells and among different species or genera is one of the main forces that generate “step change” or quantum leap evolution [7]. Extrachromosomal DNA elements such as MGEs play a crucial role in the plasticity of the genome, allowing bacteria to adjust readily to new environments. Selective pressure from the environment drives enrichment for specific genes that promote fitness and survival. An example of selective pressure is that imparted by use of antibiotics, which promotes development or acquisition of antibiotic resistance in bacteria. Inasmuch as *S. aureus* is notorious for acquiring resistance to antibiotics, which is encoded by MGEs, and also contains many putative virulence molecules on MGEs, it is an ideal model bacterium for the purpose of this review.

**S. aureus** MGEs

The genus *Staphylococcus* consists of Gram-positive bacteria that colonize human or animal skin and mucosal membranes. Although staphylococci are a part of normal human flora and thus commensal microorganisms, they are also opportunistic pathogens and cause a wide range of diseases. Among staphylococci, *S. aureus* is the most invasive species and an etiological agent of diverse human and animal maladies, including skin infections, abscesses, food poisoning, toxic shock syndrome, septicemia, endocarditis, and pneumonia [9–11]. *S. aureus* is one of the most prominent causes of nosocomial- and community-acquired bacterial infections worldwide [12]. Although the basis for this cadre of diseases is multifactorial and largely dependent on host susceptibility, heterogeneity of *S. aureus* strains likely plays a role in this process. Heterogeneity among *S. aureus* strains develops in part as a consequence of its interaction with the mammalian host. Numerous putative and proven virulence factors, genes responsible directly for host adaptation, and toxins, are located on *S. aureus* MGEs [8, 13–22]. *S. aureus* contains many types of MGEs, including plasmids, transposons (Tn), insertion sequences (IS), bacteriophages, pathogenicity islands, and staphylococcal cassette chromosomes (Figs. 2 and 3). It is remarkable that most genes encoded by MGEs remain under the control of global regulators located within the core genome.

**Plasmid-encoded antibiotic resistance**

Plasmids are auto-replicating DNA molecules. Staphylococci typically carry one or more plasmids per cell and these plasmids have varied gene content. Staphylococcal plasmids can be classified into one of the three following groups: (1) small multicopy plasmids that are cryptic or carry a single resistance determinant; (2) larger (15–30 kb) low copy (4–6/cell) plasmids, which usually carry several resistance determinants; and (3) conjugative multiresistance plasmids [23]. Larger plasmids undergo theta replication.
(a DNA replication mechanism that resembles the Greek letter theta), whereas small plasmids usually replicate by the rolling-circle mechanism \[24, 25\]. As a consequence of the limited ability of \textit{S. aureus} to acquire DNA from the environment (low natural competence) compared to bacteria such as \textit{Escherichia coli} or \textit{Bacillus subtilis}, most of the intercellular transfer of staphylococcal plasmids occurs by transduction or conjugation \[26\]. Upon entering the bacterial host, staphylococcal plasmids remain as free circularized DNA or linearize and integrate into the chromosome (Fig. 2).

Penicillin was the first antibiotic mass produced for use in humans. Although initially highly effective for treatment of \textit{S. aureus} infections, today over 90% of human \textit{S. aureus} strains are resistant to this antibiotic \[27\]. Penicillin resistance is conferred by \( \beta \)-lactamase, which hydrolyzes the \( \beta \)-lactam ring of penicillin thereby inactivating the antibiotic, and/or production of a low-affinity penicillin-binding protein (PBPr2a) encoded by the \textit{mecA} gene \[12, 27, 28\]. In \textit{S. aureus}, \( \beta \)-lactamase is encoded by the \textit{blaZ} gene and the closely linked regulatory genes, \textit{blaI} and \textit{blaR} \[28\]. Aside from plasmid encoded \( \beta \)-lactamase, \textit{bla} genes may be located on transposons or within chromosomal DNA \[27, 29\].

More recently, \textit{S. aureus} acquired vancomycin resistance elements from enterococci, resulting in the emergence of vancomycin-resistant \textit{S. aureus} (VRSA) \[30, 31\]. Compared with vancomycin-intermediate \textit{S. aureus} (VISA, MIC: 4–8 \( \mu \)g/ml), in which the mechanism of resistance is incompletely determined \[32\], high-level vancomycin resistance (that in VRSA) or VanA-mediated resistance is better characterized \[33, 34\].

\textit{Tn1546} encodes the vancomycin resistance gene cluster within a conjugative plasmid. This MGE was most likely transferred to methicillin-resistant \textit{S. aureus} (MRSA) from vancomycin-resistant enterococci (VRE) during co-infection \[25, 30, 31, 35\]. There are two predicted fates of the enterococcal plasmid upon entering staphylococci. On one hand, the enterococcal plasmid could simply be maintained, as occurred with strains VRSA-3, 5, and 6 \[31, 36\]. Alternatively, \textit{Tn1546} could be incorporated into a staphylococcal plasmid (VRSA-1, 7, 8, 9, and 10; plasmid \textit{pLW1043}) in which case the original enterococcal plasmid functions as a suicide vector \[31, 36\].

Transposon \textit{Tn1546} encodes the \textit{vanA} operon, which consists of \textit{vanA}, \textit{vanH}, \textit{vanX}, \textit{vanS}, \textit{vanR}, \textit{vanY} and \textit{vanZ} \[30, 38\]. It is interesting that, for the second VRSA isolate reported in the US (VRSA-2), the \textit{van} operon is located within a truncated \textit{Tn1546} on a 120-kbp plasmid, which is an unusually large plasmid for \textit{S. aureus} \[37\]. \textit{vanA} and \textit{vanH} are responsible for synthesis of a D-Ala-D-Lac precursor that has much lower affinity to glycopeptide antibiotics than the original D-Ala-D-Ala. \textit{vanX} encodes a dipeptidase that plays a role in the elimination of wild-type D-Ala-D-Ala targets by hydrolysis \[39\]. Expression of vancomycin resistance genes occurs only in the presence of vancomycin, a process mediated by a two-component signal transduction system encoded by \textit{vanS} and \textit{vanR}, \textit{vanY} and \textit{vanZ} encode an accessory protein that could play a role in teicoplanin resistance \[34, 40\].
In addition to genes encoding antibiotic resistance and molecules involved in metabolism, staphylococcal plasmids encode resistance to a variety of organic and inorganic ions, such as cadmium, mercury, arsenate, etc., which are highly toxic for living cells (Table 1) [41]. Staphylococcal plasmids may also encode toxin genes. For example, a large 37.5-kb S. aureus plasmid, pRW001, contains genes encoding exfoliative toxin B, bacteriocin, and bacteriocin immunity [42]. Staphylococcal exfoliative toxins (ETs) are associated with strains isolated from patients with staphylococcal scaled-skin syndrome (SSSS) or bullous impetigo [43–45]. ET isoforms A, B and D are serine proteases that specifically cleave host desmoglein 1, resulting in loss of cell–cell adhesion in the epidermal layer of skin, thereby causing blister formation and exfoliation [43, 46]. In addition to pRW001, genes encoding exfoliative toxins are located on plages (φETA, φETA2, and φETA3), a genomic island (vSAγ, former etdPI), and at least one other plasmid (pETB) (Table 2) [21, 42, 44, 45].

Bacteriophages and virulence

Bacteriophages (phages) or bacterial viruses seem to have the greatest impact on staphylococcal diversity and evolution. All phages are classified into one of three distinctive groups: lytic, temperate, and chronic. Lytic phages are the greatest impact on staphylococcal diversity and evolution. All phages are classified into one of three distinctive groups: lytic, temperate, and chronic. Lytic phages are members of the Myoviridae family that have been used in phage therapy, because bacteria lyse completely during release of progeny phages. Bacteria infected with chronic phages release progeny into the extracellular environment without killing the host, which allows bacteria to grow and divide. Temperate phages, which are members of the Siphoviridae family, form the most numerous group among all phages. Temperate phages have the ability to lyse bacteria after infection, but they typically form a long-term relationship with the host cell, whereby the phage DNA integrates into the staphylococcal genome as a prophage [47, 48]. Phages can impact expression of virulence determinants by either positive or negative lysogenic conversion. Following positive lysogenic conversion, bacteria express prophage-encoded virulence determinants. Negative lysogenic conversion occurs when there is insertional inactivation of genes (e.g., β-hemolysin of S. aureus) by integration of the phage DNA into the bacterial chromosome [47, 49]. Although there is loss of β-hemolysin during lysogeny, these prophages contain genes encoding immune-modulator proteins, such as staphylokinase (Sak), staphylococcal inhibitor of complement (SCIN), and chemotaxis inhibitory protein of S. aureus (CHIPs) [49, 50]. Other S. aureus prophages encode virulence molecules such as enterotoxins and Panton-Valentine leukocidin (PVL) (Table 2). PVL belongs to a group of bi-component, pore-forming cytolytic toxins that are specific for myeloid cells [51].

Prophages and prophage-encoded molecules also work in concert with other MGEs within staphylococci. For example, prophages create mobility for some staphylococcal pathogenicity islands. The most common example is the ability of helper phage 80z to mediate excision and transfer of SaPI1 to other staphylococci [52, 53]. Some phages also have the ability to transfer antibiotic resistance by transduction of plasmids or plasmid elements previously incorporated into chromosomal DNA. Plasmid pS194 with a chloramphenicol resistance determinant and pI258 containing erythromycin resistance are transduced by phages φ11 and φ11de, respectively [41].

Pathogenicity islands

Staphylococcal pathogenicity islands (SaPIs) are MGEs of 14–17 kb in size (Table 2). To date, at least 16 SaPIs have been sequenced and SaPI1 is considered as the prototype [53, 54]. SaPIs form a coherent family with highly conserved core genes [53, 55]. Core genes include two open reading frames encoding transcriptional regulatory proteins and a region encoding integrase, Rep protein, and terminase. In addition to core genes, almost all SaPIs encode enterotoxins or toxic shock syndrome toxin (TSST) [56]. SaPlbov2 is an exception to this rule, and instead contains Bap adhesion protein, which plays a role in bovine chronic mastitis infections [57, 58].

Staphylococcal pathogenicity islands are integrated in one of six different specific sites on the chromosome (attR) and each is always in the same orientation [53]. SaPIs can be mobilized following infection by certain staphylococcal bacteriophages or by induction of endogenous prophages [59, 60], such as induced excision of SaPI1 by phage 80z [54]. Several hypotheses to explain the origin and evolution of SaPIs exist [56]. For example, Yarwood et al. [56] proposed the existence of a common ancestral genetic element—probably a prophage—for all SaPIs that then generated diversity of islands through modular recombination events.

Genomic islands

Three families of genomic islands exist among the S. aureus strains whose genomes have been sequenced [8, 13, 16, 61]. These genomic islands, named vSAz, vSA/, and vSAγ (Table 2), are flanked by a broken transposase gene upstream and partial restriction-modification system (RM) type I downstream. Given the composition of genomic islands (remnant transposase genes and a G + C content
| MGE       | Resistance determinant | Antibiotic/heavy metal                                      | Mechanism of action                                                                 | Reference |
|-----------|------------------------|-------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------|
| Plasmid   | aadD                   | Neomycin, kanamycin, paromomycin, and tobramycin            | Aminoglycoside adenyltransferase                                                    | [100, 101]|
|           | ant4                   | Tobramycin                                                  | Aminoglycoside nucleotidyltransferase                                              | [102]     |
|           | arsRBC                 | Arsenate, antimonite                                        | Efflux ATPase                                                                      | [21, 103, 104]|
|           | blaZ, blaI, blaR1      | Penicillin ($\beta$-lactam antibiotics)                    | $\beta$-lactamase                                                                  | [105, 106]|
|           | ble                    | Bleomycin                                                   | Bleomycin-binding protein prevents DNA damage by binding bleomycin                  | [107, 108]|
|           | cadA,B                 | Cadmium resistance and probably zinc                        | Cadmium efflux ATPase                                                              | [109, 110]|
|           | cadD,X                 | Cadmium resistance                                          | Efflux                                                                             | [21, 111]|
|           | cat                    | Chloramphenicol                                             | Chloramphenicol acetyltransferase                                                  | [112, 113]|
|           | cfr                    | Chloramphenicol, florfenicol, and clindamycin               | Methylation of 23S subunit of bacterial ribosome                                    | [114, 115]|
|           | dfrA, dfrK              | Trimethoprim                                                | Dihydrofolate reductase                                                            | [101, 116]|
|           | ermB,C                 | MLSB resistance (macrolides: erythromycin, lincosamides: clindamycin, streptogramin B) | Methylation of 23S subunit of bacterial ribosome                                    | [117, 118]|
|           | fusB                   | Fusidic acid                                                | Ribosome protection mechanism                                                      | [119, 120]|
|           | ileS-2                 | High-level resistance to mupirocin (pseudomonic acid A)    | Isoleucyl RNA synthetase                                                           | [121, 122]|
|           | mer operon             | Mercury                                                     | Reduction of mercury ions to elementary Hg                                         | [123]     |
|           | mphBM                  | Macrolide antibiotics                                       | Putative phosphorylase                                                             | [124]     |
|           | msrA                   | Macrolide antibiotics                                       | Active efflux                                                                      | [124]     |
|           | mapA                   | High-level mupirocin resistance                             | Novel isoleucyl RNA synthetase                                                     | [122, 125]|
|           | qacA,B and smr (qacC/D) | Quaternary ammonium compounds, biocides                   | Drug efflux pump                                                                   | [126–128]|
|           | str                    | Streptomycin                                                | Streptomycin adenyltransferase                                                     | [113]     |
|           | tetK, tetL             | Tetracyclines                                               | Active efflux of tetracycline                                                      | [129–131]|
|           | vat                    | Streptogramins type A                                       | Acetylation of the antibiotic                                                      | [132]     |
|           | vga                    | Streptogramins type A, lincosamides, and pleuromutilins     | Efflux                                                                             | [101]     |
|           | vgb                    | Streptogramins type B                                       | Inactivation by virginiamycin B lyase                                              | [133]     |
| Transposon| aacA-aphD              | Gentamycin, kanamycin, tobramycin                           | Antibiotic modification by aminoglycoside acetyltransferase and aminoglycoside phosphotransferase | [82, 86, 90]|
|           | blaZ, blaI, blaR1      | $\beta$-Lactam antibiotics                                 | Hydrolysis of $\beta$-lactam ring                                                 | [134]     |
|           | cadB, cadC             | Cadmium resistance                                          | Efflux                                                                             | [135]     |
|           | ermA,B                 | MLSB resistance (macrolides: erythromycin, lincosamides: clindamycin, streptogramin B) | Methylation of 23S subunit of bacterial ribosome                                    | [118]     |
|           | fexA                   | Florfenicol, chloramphenicol                                | Efflux                                                                             | [114]     |
|           | merA, B                | Respectively, inorganic and organic mercury resistance      | Ion transport                                                                      | [89, 136, 137]|
|           | sat4                   | Streptothricin                                              | Streptothricin acetyltransferase                                                   | [115]     |
|           | spec(ant9)             | Specinomycin                                                | Specinomycin acetyltransferase                                                     | [102]     |
|           | tetM                   | Tetracycline, minocycline                                   | Protection of ribosome binding site for tetracycline                               | [129, 131]|
|           | vanRSHAXYZ             | Vancomycin                                                  | Production of low affinity peptidoglycan precursor with terminal D-Ala-D-Lac       | [30, 31, 34, 35, 40]|
| SCC-476   | far1                   | Fusidic acid                                                | Ion transport                                                                      | [18]      |
| SCCmercury| mer operon             | Mercury                                                     | Ion transport                                                                      | [69]      |

* Vancomycin resistance is encoded on the Tn1546 transposon but transferred by conjugative plasmid
| Toxin/virulence determinant (gene) | MGE | Disease/mechanism of action | Reference |
|----------------------------------|-----|-----------------------------|-----------|
| Adhesion protein Bap (bap)       | SaPIbov2 | Specific adhesion to bovine mammary mucosa | [55] |
| Bacteriocin (bsa)                | rSAβ | Bactericidal activity against other bacteria | [13] |
| Capsular polysaccharide protein | SCCcap1 | Inhibits phagocytosis | [75] |
| Chemotaxis inhibitory protein of *S. aureus* (chip) | φ13, φtp310-3, φN315, φ252B, φNM3, φMu3A, φSa3USA300, φSa3JH1, φSa3mw, φSa3 ms, φSa3JH9, φβC-USA300, TCH1516 | Blocks C5α and fMLP-induced neutrophil activation and chemotaxis; blocks C5α and formylated peptide receptor | [50, 138] |
| Epidermal cell differentiation inhibitor B (edin-B) | rSAγ (etdPI) | ADP-ribosyltransferase; inhibits morphological differentiation of keratinocytes in vitro and modifies eukaryotic Rho GTPase | [44] |
| Epidermal cell differentiation inhibitor C (edin-C) | pETB | ADP-ribosyltransferase, inhibits morphological differentiation of keratinocytes in vitro and modifies eukaryotic Rho GTPase | [45] |
| Exfoliative toxin A (eta)        | φETA, φETA2, φETA3 | Causes staphylococcal scalded skin syndrome (SSSS), Ritter disease, and bulbous impetigo in neonates | [21, 44] |
| Exfoliative toxin B (etb)        | pETB, pRW001 | Causes SSSS, Ritter disease, and bulbous impetigo in neonates | [42, 45] |
| Exfoliative toxin D (etd)        | rSAγ (etdPI) | Causes SSSS, Ritter disease, and bulbous impetigo in neonates | [44, 45] |
| Enterotoxin A (sea)              | φSa3 ms, φSa3, φSa3mw, φ252B, φNM3, φMu50A, φSa3m1, φSa2, φSa2c | Super antigen (SAg), causes food poisoning | [13] |
| Enterotoxin B (seb)              | SaPI1, SaPI3, pZA10 | SAg, causes food poisoning | [13, 139, 140] |
| Enterotoxin C (sec)              | SaPlbov1 | SAg, causes food poisoning | [13, 141] |
| Enterotoxin C1 (sec1)            | SaPl4, pZA10 | SAg, causes food poisoning | [13, 139] |
| Enterotoxin C3 (sec3)            | SaPlm1/m1 | SAg, causes food poisoning | [13] |
| Enterotoxin C4 (sec4)            | SaPlm2, SaPlm3 | SAg, causes food poisoning | [13] |
| Enterotoxin D (sed)              | pIB485 | SAg, causes food poisoning | [142] |
| Enterotoxin G (seg)              | φSa3, rSAβ (SaPln3/m3) | SAg, causes food poisoning | [13] |
| Enterotoxin I (sei)              | rSAβ (SaPln3/m3) | SAg, causes food poisoning | [13] |
| Enterotoxin J (sej)              | pIB485 | SAg, causes food poisoning | [143] |
| Enterotoxin K (sek)              | φSa3 ms, φSa3mw, SaPlbov1, SaPl1, SaPl3, SaPl5 | SAg, causes food poisoning | [56, 144] |
| Enterotoxin K2 (sek2)            | φSa3 | SAg, causes food poisoning | [145] |
| Enterotoxin L (sel)              | SaPI1, SaPlbov1, SaPl3, SaPln1/m1, SaPl4 | SAg, causes food poisoning | [54, 55, 144] |
| Enterotoxin L2 (sel2)            | SaPlm2, SaPlm3, SaPln1/m1, SaPl1 | SAg, causes food poisoning | [13] |
| Enterotoxin M (sem)              | rSAβ (SaPln3/m3) | SAg, causes food poisoning | [13] |
| Enterotoxin N (sen)              | rSAβ (SaPln3/m3) | SAg, causes food poisoning | [13, 146] |
| Enterotoxin O (seo)              | rSAβ (SaPln3/m3) | SAg, causes food poisoning | [13] |
| Enterotoxin P (sep)              | φN315, φMu50A | SAg, causes food poisoning | [146, 147] |
| Enterotoxin Q (seq)              | φSa3 ms, φSa3mw, SaPl1, SaPl3, SaPl5 | SAg, causes food poisoning | [56] |
| Ferrichrome operon (fhuD)        | SaPl3, SaPlm4 | Iron up-take | [148] |
| α-hemolysin (bla)                | rSAγ (etdPI) | Pore-forming cytolytic toxin | [149, 150] |
that differs from the core genome), a current notion is that genomic islands were once mobile elements acquired by HGT [62]. A complete RM type I comprises host specificity determinant genes hsdR, hsdM, and hsdS, but only hsdM and hsdS are found juxtaposed to the S. aureus genomic islands [13, 61, 63]. Both flanking DNA segments contribute to the stability of genomic islands within the S. aureus chromosome. A lipoprotein gene cluster (lpl) and staphylococcal superantigen-like genes (ssl) are located on vSAz [64]. vSAβ (also known as SaPln3/m3) encodes bacteriocin, enterotoxins, hyaluronate lyase, and a serine protease gene cluster [13, 18, 65]. The third staphylococcal
genomic island, vSAc, contains genes encoding β-type phenol-soluble modulins and a cluster of ssl genes similar to that present within vSAz [16].

Staphylococcal cassette chromosome

Staphylococcal cassette chromosomes (SCCs) are relatively large fragments of DNA that always insert into the orfX gene on the S. aureus chromosome. SCC can encode antibiotic resistance and/or virulence determinants. Considering that many SCCs encode the methicillin resistance gene (mecA), SCCs can be classified into staphylococcal cassette chromosome mec (SCC mec) or non-SCC mec groups.

SCCmec

The first MRSA strain was reported in 1961, 2 years after the introduction of methicillin for treatment of penicillin-resistant S. aureus infections [12, 66]. All MRSA strains contain SCCmec, which encodes the mecA gene, thus conferring resistance to methicillin and all β-lactam antibiotics (reviewed in [12]). SCCmec may have been acquired by S. aureus from S. sciuri [67, 68]. Resistance to β-lactam antibiotics is maintained by production of a low-affinity penicillin-binding protein (PBP2a), which fails to bind methicillin and other β-lactam antibiotics. As a result, these antibiotics do not inhibit the ability of PBPs (transpeptidase enzymes) to cross-link peptidoglycan polymers of the bacterial cell wall. In addition to the mecA gene, SCCmec encodes the repressor MecI, transmembrane β-lactam signal transducer MecR1, recombinases CcrAB and CcrC, and joining (formerly junkyard) regions J, which may also encode additional antibiotic resistance (Fig. 4). Integration and excision of SCCmec by the recombinases occurs within a specific attachment site (attBscC) on the S. aureus chromosome at the 3’ end of orfX [61].

Based on the organization of mec and associated genes within the SCCmec complex, five (A–E) different classes of SCCmec have been defined, of which three (A–C) are the most common in S. aureus [69–71]. Only class A

Fig. 4 Comparison of S. aureus SCCmec types. Class A SCCmec contains a complete mecA regulon (mec1-mecR1-mecA). Class B and class C SCCmec contain regulatory genes that are disrupted by IS, IS1272-ΔmecR1-mecA and IS431-ΔmecR1-mecA, respectively. Tn554 encodes erythromycin (ermA) and streptomycin/spectinomycin resistance (aad9 or spc); copA encodes a putative copper-transport ATPase; hsdR, hsdM, and hsdS encode a partial restriction-modification system (RM) type I; Tn4001 encodes an aminoglycoside resistance operon (aacA-aphD); plasmid pT181 encodes tetracycline resistance (tet); ΨTn554 encodes cadmium resistance (cadB, cadC); and plasmid pUB110 encodes bleomycin (ble) and tobramycin resistance (ant4). pls Plasmin-sensitive surface protein
SCCmec consists of the complete mecA regulon (mecI-mecR1-mecA), as the regulatory genes are disrupted by insertional sequences in class B and C. SCCmec–IS1272-DmecR1-mecA in class B and IS431-DmecR1-mecA in class C SCCmec elements [61, 70]. Three classes of the mec complex and four different ccr allotypes define at present eight SCCmec types (I–VIII) (Fig. 4). However, SCCmec types can be further differentiated into subtypes depending on variations in the J regions. Interestingly, community-associated MRSA (CA-MRSA) strains typically carry SCCmecIV, V, or VII elements [72], whereas HA-MRSA typically contain the larger SCCmecI, II, III, VI, or VIII elements that may encode resistance determinants in addition to mecA [12, 13, 69, 72]. These additional resistance determinants are often encoded by plasmids, transposons, or insertion sequences incorporated into the J regions of SCCmec [61]. For example, the J1 region of SCCmecVIII encodes a putative copper-transport ATPase (copA) and the J2 region has a Tn554 transposon encoding erythromycin (ermA) and streptomycin/spectinomycin resistance (aad9) genes (for more details, see Table 1; Fig. 4) [73, 74].

Non-mec SCC

Staphylococcal cassette chromosomes can be complex and are thus not limited to encoding methicillin resistance. Non-mec SCC and ψ/SCC (without or no functional recombinase) contain virulence or fitness/survival determinants. A methicillin-susceptible S. aureus strain, MSSA476, contains a mec-like element (SCC476) that encodes fusidic acid resistance [18]. SCCmercury encodes resistance to mercury chloride that was probably obtained from coagulase-negative staphylococci (CoNS) by integration of a plasmid that carried the resistance determinant or by direct transfer of the SCCmercury element [69]. Some S. aureus strains produce capsular polysaccharide 1, which has been reported to confer resistance to phagocytosis [75]. The genes encoding synthesis of capsular polysaccharide 1 are located on a special SCC element named SCCcapI [75]. Although SCCcapI resembles type III of SCCmec, it is immobile because it lacks an active ccrA homologue and the ccrB homologue contains a nonsense mutation [75, 76].

Arginine catabolic mobile element

The arginine catabolic mobile element (ACME) was discovered by sequencing the complete genome of USA300, the most prominent CA-MRSA strain of North America [15]. ACME encodes a complete arginine deiminase pathway that converts L-arginine to carbon dioxide, ATP, and ammonia. A cluster of six genes, arcRADBC (arc locus) and opp3 (oligopeptide permease system), constitute type I ACME present in the USA300 strain [15]. Type I ACME is associated with specific SCCmec subtypes (Fig. 3). It is present in clinical isolates belonging to multilocus sequence type (MLST or ST) 8 containing SCCmecIVa, but not in SCCmecIVb, IVc, or IVmisc [77]. An ACME variant that lacks the opp3 operon and varies in DNA sequence has also been found in ST8 MSSA, ST5 (USA100, SCCmecII), and ST59 (USA1000) strains [77–79]. An ACME variant has also been detected in MRSA ST97 strains carrying SCCmecV [77].

The arc cluster contained within ACME is distinct from the other S. aureus arc cluster encoded within the core genome [15]. ACME is adjacent to SCCmec and integrated at the same attB site within orfX [15]. Therefore, it is likely that the recombinases that mediate excision of SCCmec also mobilize ACME [15, 80].

The role played by ACME in the success of USA300 remains unknown. Diep et al. suggest it enhances fitness of S. aureus, possibly by facilitating colonization and/or hematogenous dissemination to target organs [15, 80]. On the other hand, Montgomery et al. [81] found no significant difference between ACME-positive and ACME-negative USA300 strains in a rat model of necrotizing pneumonia and a mouse model of skin infection. Further studies are needed to better understand the importance of this interesting MGE.

Other transposable elements

Both insertion sequences (IS) and transposons (Tn) are widely distributed among the S. aureus genome. They may be present in a single copy or multiple copies on the chromosome or in association with other MGEs.

Insertion sequences

Although insertion sequences (IS) can exist independently in the S. aureus genome, they often present as pairs constituting a composite transposon [82]. IS insert into various loci and may cause changes in the expression of genes in the core chromosome. In addition, IS inactivate genes by direct insertion or by having a polar effect on the transcription of nearby genes [83, 84]. Activation of genes within the vicinity of an IS is usually mediated by promoters carried by IS elements or by forming a hybrid promoter with the native promoter of particular gene [85]. IS256 and IS257, in addition to constituting composite transposons Tn4001 and Tn4003, form a hybrid promoter for the aminoglycoside resistance operon (aacA-aphD) and the gene encoding resistance to trimethoprim (dfrA), respectively [82, 86, 87].
Transposons

Transposons (Tn) predominantly encode antibiotic resistance genes in *S. aureus* (Table 1). The smaller transposons are usually presented in multiple copies in the staphylococcal genome, either inserted into the chromosome or into MGEs, such as SCC or plasmids. This group includes Tn554 and Tn552, which encode resistance to MLSB antibiotics and spectinomycin or penicillinase, respectively [41, 61, 88]. By comparison, larger transposons (>18 kbp) are present in single copies and encode resistance to antibiotics such as tetracycline [89], trimethoprim [87], aminoglycosides [82, 90], or vancomycin [30, 31, 35].

**Concluding remarks**

A wide range of environmental conditions, including interspecies competition within particular ecological niche and antibiotic selective pressure, select for organisms that have acquired MGEs—those that are presumably advantageous for survival—by HGT. Production of antibiotics by microorganisms is mirrored (countered) by development of resistance to these molecules and is a naturally occurring phenomenon. Antibiotics are toxins produced by bacteria and fungi to compete with other microorganisms for a specific ecological niche. Unfortunately, the level of antibiotic resistance among bacteria continues to increase, consistent with the high use of antibiotics by humans. Sub-inhibitory concentrations of antibiotics also create an environment conducive to acquisition of resistance [91]. Antibiotics that interfere with bacterial DNA replication and induce an SOS response also induce excision and transduction of prophages and staphylococcal pathogenicity islands in the bacterial genome, resulting in high frequency of horizontal gene transfer [60, 92, 93]. Consequently, this process promotes dissemination of determinants encoding antibiotic resistance molecules and virulence factors. MGEs can be species-specific, and, therefore, differences exist in MGEs of *S. aureus* strains that have a tropism for humans or animals [94]. Nevertheless, some *S. aureus* strains transmit from animals to humans or vice versa [95–98]. Transfer of staphylococci from one host species to another provides an additional means to acquire new genetic material, often encoded by MGEs [99].

In summary, although MGEs constitute only ~25% of the staphylococcal genome [8], they encode many putative virulence factors and antibiotic determinants and thus play an important role in bacterial adaptability and survival.

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