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REVIEW

# 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

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## 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 "mobilome" [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).

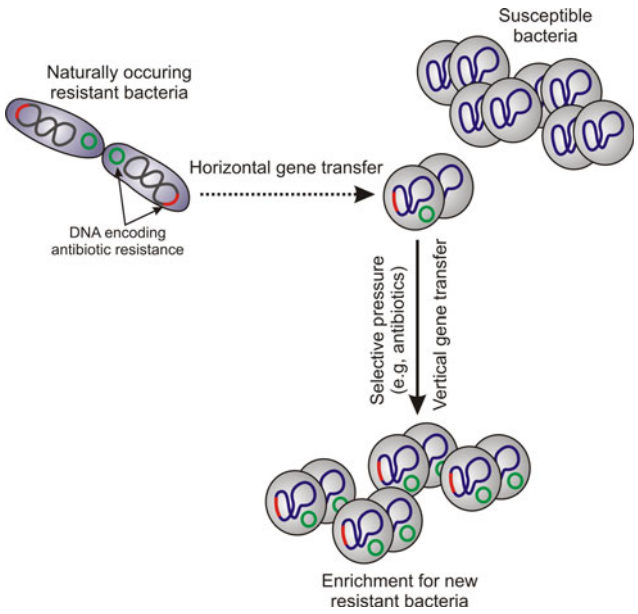


**Fig. 1** Horizontal and vertical gene transfer

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, some of 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

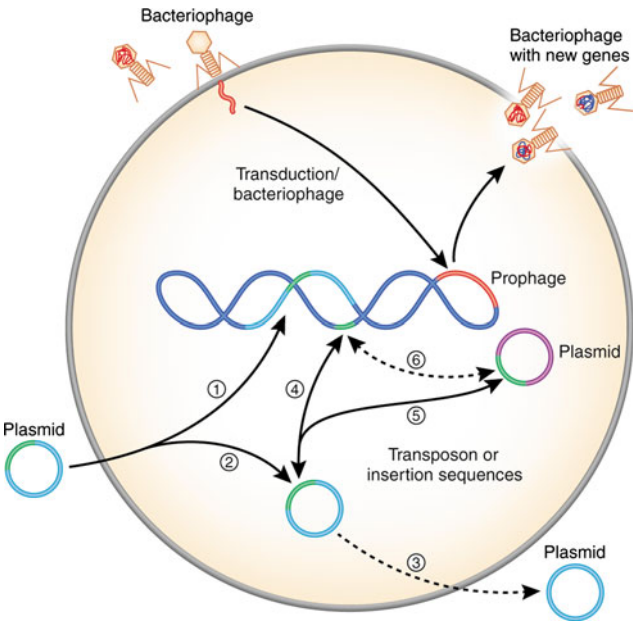


**Fig. 2** Acquisition of MGEs by *S. aureus*. *1* Incorporation of plasmids or plasmid elements into genomic DNA. *2* Plasmids can be maintained as free circular DNA. *3* Suicide plasmid. *4* Transfer of a transposon or an insertion sequence between plasmid and genomic DNA. *5* Transfer of a transposon or an insertion sequence between plasmids within the cell. *6* Transfer of a transposon or an insertion sequence from genomic DNA to another plasmid

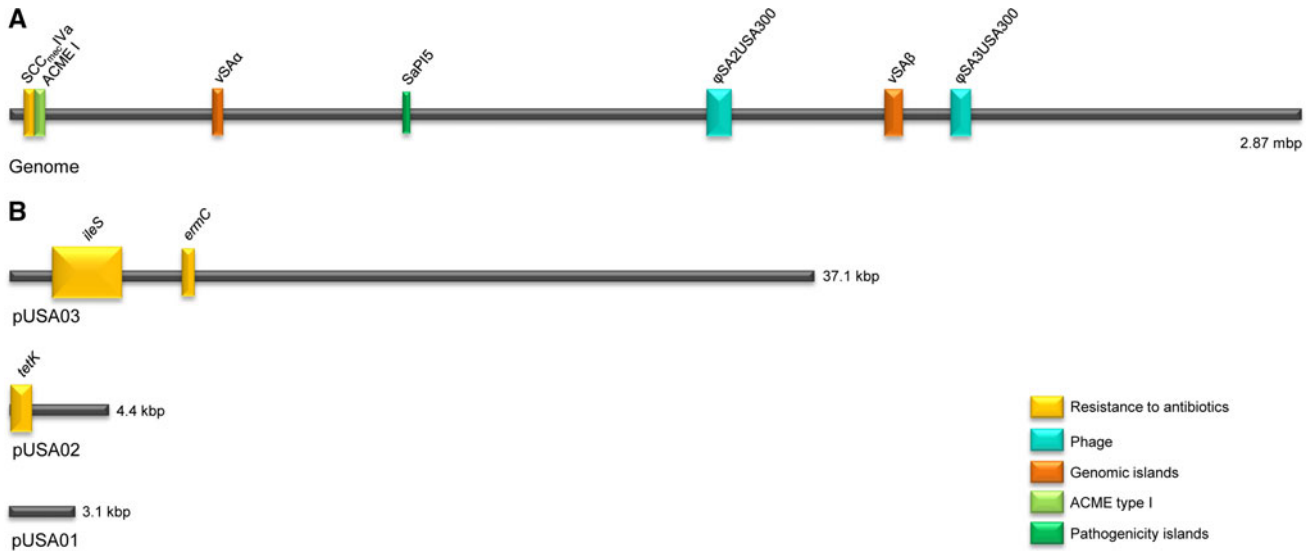


**Fig. 3** Linear schematic of the USA300 genome (strain FPR3757) and its major MGEs. **a** Genome. $SCC_{mec}$IVa encodes methicillin resistance. *v*SA*α* encodes *lpl*, *ssl* and *v*SA*β* encodes *lukDE*, *spl*, *bsa*. SaPI5 encodes *seq2* and *sek2*, *φ*SA2USA300 encodes *lukS/F-PV*, and *φ*SA3USA300 encodes *sak* and *chip*. **b** Plasmids of FPR3757. pUSA03 contains genes encoding resistance to mupirocin (*ileS*) and $MLS_B$ (*ermC*). pUSA02 encodes resistance to tetracycline (*tetK*). pUSA01 is a cryptic plasmid

(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 *S. aureus* to acquire DNA from the environment (low natural competence) compared to bacteria such as *Escherichia coli* or *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 *S. aureus* infections, today over 90% of human *S. aureus* strains are resistant to this antibiotic [27]. Penicillin resistance is conferred by *β*-lactamase, which hydrolyzes the *β*-lactam ring of penicillin thereby inactivating the antibiotic, and/or production of a low-affinity penicillin-binding protein (PBP2a) encoded by the *mecA* gene [12, 27, 28]. In *S. aureus*, *β*-lactamase is encoded by the *blaZ* gene and the closely linked regulatory genes, *blaI* and *blaR* [28]. Aside from plasmid encoded *β*-lactamase, *bla* genes may be located on transposons or within chromosomal DNA [27, 29].

More recently, *S. aureus* acquired vancomycin resistance elements from enterococci, resulting in the emergence of vancomycin-resistant *S. aureus* (VRSA) [30, 31]. Compared with vancomycin-intermediate *S. aureus* (VISA, MIC: 4–8 μg/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 [30, 33, 34].

Tn*1546* encodes the vancomycin resistance gene cluster within a conjugative plasmid. This MGE was most likely transferred to methicillin-resistant *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, Tn*1546* could be incorporated into a staphylococcal plasmid (VRSA-1, 7, 8, 9, and 10; plasmid pLW1043) in which case the original enterococcal plasmid functions as a suicide vector [31, 36]. Transposon Tn*1546* encodes the *vanA* operon, which consists of *vanA*, *vanH*, *vanX*, *vanS*, *vanR*, *vanY* and *vanZ* [30, 38]. It is interesting that, for the second VRSA isolate reported in the US (VRSA-2), the *van* operon is located within a truncated Tn*1546* on a 120-kbp plasmid, which is an unusually large plasmid for *S. aureus* [37]. *vanA* and *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. *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 *vanS* and *vanR*. *vanY* and *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 phages ($\varphi$ETA, $\varphi$ETA2, and $\varphi$ETA3), a genomic island ($\nu$SA$\gamma$, former *etd*PI), 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 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., $\beta$-hemolysin of *S. aureus*) by integration of the phage DNA into the bacterial chromosome [47, 49]. Although there is loss of $\beta$-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 80$\alpha$ 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 $\varphi$11 and $\varphi$11de, 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 intergrase, Rep protein, and terminase. In addition to core genes, almost all SaPIs encode enterotoxins or toxic shock syndrome toxin (TSST) [56]. SaPIbov2 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 ($att_s$) 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 80$\alpha$ [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 $\nu$SA$\alpha$, $\nu$SA$\beta$, and $\nu$SA$\gamma$ (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

**Table 1** Resistance determinants encoded on non-SCC*mec* staphylococcal MGEs

| 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 (*β*-lactam antibiotics) | *β*-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] |
| | *mupA* | 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* | *β*-Lactam antibiotics | Hydrolysis of *β*-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] |
| | *spc(ant9)* | Spectinomycin | Spectinomycin adenyltransferase | [102] |
| | *tetM* | Tetracycline, minocycline | Protection of ribosome binding site for tetracycline | [129, 131] |
| | *vanRSHAXYZ*[a] | Vancomycin | Production of low affinity pepdydoglican precursor with terminal D-Ala-D-Lac | [30, 31, 34, 35, 40] |
| $SCC_{476}$ | *far1* | Fusidic acid resistance | | [18] |
| $SCC_{mercury}$ | *mer* operon | Mercury | Ion transport | [69] |

[a] Vancomycin resistance is encoded on the Tn*1546* transposon but transferred by conjugative plasmid

**Table 2** *S. aureus* virulence determinant encoded on MGEs

| Toxin/virulence determinant (gene) | MGE | Disease/mechanism of action | Reference |
|---|---|---|---|
| Adhesion protein Bap (*bap*) | SaPIbov2 | Specific adhesion to bovine mammary mucosa | [55] |
| Bacteriocin (*bsa*) | *v*SA*β* | Bactericidal activity against other bacteria | [13] |
| Capsular polysaccharide protein | SCC*cap1* | Inhibits phagocytosis | [75] |
| Chemotaxis inhibitory protein of *S. aureus* (*chip*) | *φ*13, *φ*tp310-3, *φ*N315, *φ*252B, *φ*NM3, *φ*Mu3A, *φ*Sa3USA300, *φ*Sa3JH1, *φ*Sa3mw, *φ*Sa3 ms, *φ*Sa3JH9, *φβ*C-USA300_TCH1516 | Blocks C5a and fMLP-induced neutrophil activation and chemotaxis; blocks C5a and formylated peptide receptor | [50, 138] |
| Epidermal cell differentiation inhibitor B (*edin-B*) | *v*SA*γ* (*etd*PI) | 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*) | *φ*ETA, *φ*ETA2, *φ*ETA3 | 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*) | *v*SA*γ* (*etd*PI) | Causes SSSS, Ritter disease, and bulbous impetigo in neonates | [44, 45] |
| Enterotoxin A (*sea*) | *φ*Sa3 ms, *φ*Sa3, *φ*Sa3mw, *φ*252B,*φ*NM3, *φ*Mu50A, | Super antigen (SAg), causes food poisoning | [13] |
| Enterotoxin B (*seb*) | SaPI1, SaPI3,pZA10 | SAg, causes food poisoning | [13, 139, 140] |
| Enterotoxin C (*sec*) | SaPIbov1 | SAg, causes food poisoning | [13, 141] |
| Enterotoxin C1 (*sec1*) | SaPI4, pZA10 | SAg, causes food poisoning | [13, 139] |
| Enterotoxin C3 (*sec3*) | SaPIn1/m1 | SAg, causes food poisoning | [13] |
| Enterotoxin C4 (*sec4*) | SaPImw2, SaPIm3 | SAg, causes food poisoning | [13] |
| Enterotoxin D (*sed*) | pIB485 | SAg, causes food poisoning | [142] |
| Enterotoxin G (*seg*) | *φ*Sa3, *v*SA*β* (SaPIn3/m3) | SAg, causes food poisoning | [13] |
| Enterotoxin I (*sei*) | *v*SA*β* (SaPIn3/m3) | SAg, causes food poisoning | [13] |
| Enterotoxin J (*sej*) | pIB485 | SAg, causes food poisoning | [143] |
| Enterotoxin K (*sek*) | *φ*Sa3 ms, *φ*Sa3mw, SaPIbov1, SaPI1, SaPI3, SaPI5 | SAg, causes food poisoning | [56, 144] |
| Enterotoxin K2 (*sek2*) | *φ*Sa3 | SAg, causes food poisoning | [145] |
| Enterotoxin L (*sel*) | SaPI1, SaPIbov1, SaPI3, SaPIn1/m1, SaPI4 | SAg, causes food poisoning | [54, 55, 144] |
| Enterotoxin L2 (*sel2*) | SaPImw2, SaPIm3, | SAg, causes food poisoning | [13] |
| Enterotoxin M (*sem*) | *v*SA*β* (SaPIn3/m3) | SAg, causes food poisoning | [13] |
| Enterotoxin N (*sen*) | *v*SA*β* (SaPIn3/m3) | SAg, causes food poisoning | [13, 146] |
| Enterotoxin O (*seo*) | *v*SA*β* (SaPIn3/m3) | SAg, causes food poisoning | [13] |
| Enterotoxin P (*sep*) | *φ*N315, *φ*Mu50A | SAg, causes food poisoning | [146, 147] |
| Enterotoxin Q (*seq*) | *φ*Sa3 ms, *φ*Sa3mw, SaPI1, SaPI3, SaPI5 | SAg, causes food poisoning | [56] |
| Ferrichrome operon (*fhuD*) | SaPI3, SaPIm4 | Iron up-take | [148] |
| α-hemolysin (*hla*) | *v*SA*γ* (*etd*PI) | Pore-forming cytolytic toxin | [149, 150] |

**Table 2** continued

| Toxin/virulence determinant (gene) | MGE | Disease/mechanism of action | Reference |
|---|---|---|---|
| Hyaluronate lyase (*hysA*) | *v*SA*β* | Degradation of mucopolysaccharide hyaluronic acid | [13, 151] |
| Leukocidin (*lukM, lukF*) | *φ*PV83 | Pore-forming leukocyte toxin | [152] |
| Leukotoxin D, E (*lukD, lukE*) | *v*SA*β* | Pore-forming leukocyte toxin | [13, 153] |
| Lipoprotein-like (*lpl*) | *v*SA*α* | Induce inflammatory response of host immune system | [13, 65] |
| Lysophospholipase | pAvX (poultry strains) | Hypothetical role in virulence | [99] |
| Pantone-Valentine leukocidin (*lukF-PV, lukS-PV*) | *φ*Sa2mw, *φ*PVL108, *φ*Sa2, *φ*Sa2USA300, *φ*SLT, *φ*PVL, *φ*SLT-USA300_TCH1516, *φ*tp310-1, *φ*2958PVL | Pore-forming leukocyte toxin, linked by epidemiology to necrotic infections | [154–158] |
| Pathogenicity island protein (*ear*) | SaPImw2; SaPI1, SaPI3, SaPI4, SaPI5 | Unknown | [54] |
| Phenol-soluble modulin located within SCC*mec* (*psm-mec*) | SCC*mec* | Pro-inflammatory and cytolytic activity | [159] |
| Phenol-soluble modulins (*psmβ*) | *v*SA*γ* (*etd*PI) | Possible pro-inflammatory activity | [16, 160, 161] |
| Plasmin-sensitive surface protein (*pls*) | SCC*mec* I | Decreases the invasiveness of MRSA strains, acts as an adhesin | [162] |
| Serine protease-like protein (*spl*) | *v*SA*β* (SaPIn3/m3) | Hypothetical role in virulence | [13, 163] |
| Staphopain A (*scpA*) | pAvX | Edematous and necrotic dermatitis in chickens | [99, 164] |
| Staphylococcal inhibitor of complement (*scn*) | *φ*13, *φ*tp310-3, *φ*N315, *φ*Sa3mw, *φ*252B, *φ*NM3, *φ*Mu50A, *φ*Sa3JH1, *φ*Sa3 ms, *φ*Sa3JH9, *φ*Mu3A, *φ*Sa3USA300, *φβ*C-USA300_TCH1516 | Inhibits phagocytosis of *S. aureus* by human neutrophils; blocks formation of C3b | [50, 165] |
| Staphylococcal superantigen-like, SSL (former, staphylococcal enterotoxin-like, *set*) | *v*SA*α* (SaPIn2/m2) | Targeting elements of innate immune response | [13, 166] |
| Staphylokinase (*sak*) | *φ*N315, *φ*Mu50A, *φ*Sa2, *φ*Sa3mw, *φ*6390, *φ*13, *φ*252B, *φ*NM3, *φ*Mu3A, *φ*Sa3 ms, *φ*tp310-3, *φβ*C-USA300_TCH1516, *φ*Sa3USA300 *φ*Sa3JH1, *φ*Sa3JH9, | Proteolytic destruction of host tissue; activates conversion of plasminogen to plasmin; inhibits opsonization by degradation of IgG and C3b, promotes resistance to defensins | [147, 167–169] |
| TSST-1 (*tst*) | SaPI1, SaPI2, SaPIbov1, SaPI3, SaPIn1/m1 | Causes toxic shock syndrome (TSS) | [46, 55, 170, 171] |

Genomic islands: *v*SA*α*, *v*SA*β*, and *v*SA*γ* (etdPI)

Pathogenicity islands: SaPIbov1 and SaPIbov2, SaPI1- SaPI5, SaPIn1/m1, SaPIn3/m3, SaPImw2, SaPIm3, and SaPIm4

Phages: *φ*13, *φ*tp310-3, *φ*N315, *φ*Sa3, *φ*Sa3mw, *φ*252B, *φ*NM3, *φ*Mu50A, *φ*Sa3JH1, *φ*Sa3 ms, *φ*Sa3JH9, *φ*Mu3A, *φ*Sa3USA300, *φβ*C-USA300_TCH1516, *φ*ETA, *φ*ETA2, *φ*ETA3, *φ*PV83, *φ*PVL108, *φ*SLT, *φ*PVL, *φ*SLT-USA300_TCH1516, *φ*tp310-1, and *φ*2958PVL

Plasmids: pAvX, pIB485, pZA10, pETB, and pRW001

*SCC* Staphylococcal cassette chromosome

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 *v*SA*α* [64]. *v*SA*β* (also known as SaPIn3/m3) encodes bacteriocin, enterotoxins, hyaluronate lyase, and a serine protease gene cluster [13, 18, 65]. The third staphylococcal

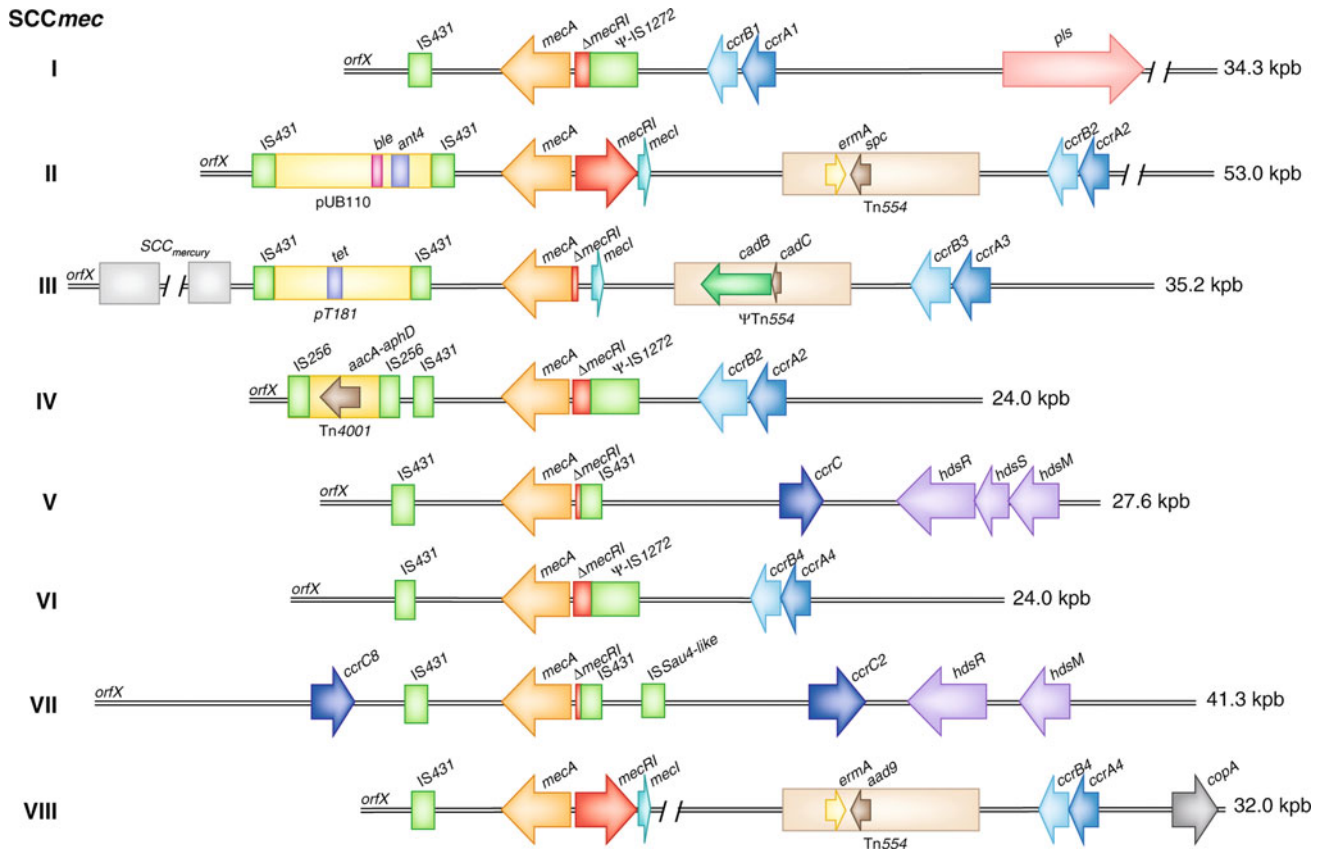


**Fig. 4** Comparison of *S. aureus* SCC*mec* types. Class A SCC*mec* contains a complete *mecA* regulon (*mec1-mecR1-mecA*). Class B and class C SCC*mec* contain regulatory genes that are disrupted by IS, IS*1272*-Δ*mecR1-mecA* and IS*431*-Δ*mecR1-mecA*, respectively. Tn*554* encodes erythromycin (*ermA*) 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; Tn*4001* encodes an aminoglycoside resistance operon (*aacA-aphD*); plasmid pT181 encodes tetracycline resistance (*tet*); ΨTn*554* encodes cadmium resistance (*cadB, cadC*); and plasmid pUB110 encodes bleomycin (*ble*) and tobramycin resistance (*ant4′*). *pls* Plasmin-sensitive surface protein

genomic island, *v*SA*γ*, contains genes encoding *β*-type phenol-soluble modulins and a cluster of *ssl* genes similar to that present within *v*SA*α* [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.

### SCC*mec*

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 SCC*mec*, which encodes the *mecA* gene, thus conferring resistance to methicillin and all *β*-lactam antibiotics (reviewed in [12]). SCC*mec* 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, SCC*mec* 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 SCC*mec* 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 SCC*mec* complex, five (A–E) different classes of SCC*mec* have been defined, of which three (A–C) are the most common in *S. aureus* [69–71]. Only class A

SCC*mec* consists of the complete *mecA* regulon (*mec1-mecR1-mecA*), as the regulatory genes are disrupted by insertional sequences in class B and C, SCC*mec*–IS*1272*-Δ*mecR1-mecA* in class B and IS*431*-Δ*mecR1-mecA* in class C SCC*mec* elements [61, 70]. Three classes of the *mec* complex and four different *ccr* allotypes define at present eight SCC*mec* types (I–VIII) (Fig. 4). However, SCC*mec* types can be further differentiated into subtypes depending on variations in the J regions. Interestingly, community-associated MRSA (CA-MRSA) strains typically carry SCC*mec*IV, V, or VII elements [72], whereas HA-MRSA typically contain the larger SCC*mec*I, 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 SCC*mec* [61]. For example, the J1 region of SCC*mec*VIII encodes a putative copper-transport ATPase (*copA*) and the J2 region has a Tn*554* 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 ψSCC (without or no functional recombinase) contain virulence or fitness/survival determinants. A methicillin-susceptible *S. aureus* strain, MSSA476, contains a *mec*-like element ($SCC_{476}$) that encodes fusidic acid resistance [18]. SCC*mercury* 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 SCC*mercury* 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 SCC*cap1* [75]. Although SCC*capI* resembles type III of SCC*mec*, 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 SCC*mec* subtypes (Fig. 3). It is present in clinical isolates belonging to multilocus sequence type (MLST or ST) 8 containing SCC*mec*IVa, but not in SCC*mec*IVb, 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, SCC*mec*II), and ST59 (USA1000) strains [77–79]. An ACME variant has also been detected in MRSA ST97 strains carrying SCC*mec*V [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 SCC*mec* and integrated at the same *attB* site within *orfX* [15]. Therefore, it is likely that the recombinases that mediate excision of SCC*mec* 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]. IS*256* and IS*257*, in addition to constituting composite transposons Tn*4001* and Tn*4003*, 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 Tn*554* and Tn*552*, which encode resistance to $MLS_B$ 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]. Consequentially, 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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## References

1. McClintock B (1950) The origin and behavior of mutable loci in maize. Proc Natl Acad Sci USA 36:344–355
2. McClintock B (1951) Chromosome organization and genetic expression. Cold Spring Harb Symp Quant Biol 16:13–47
3. Frost LS, Leplae R, Summers AO, Toussaint A (2005) Mobile genetic elements: the agents of open source evolution. Nat Rev Microbiol 3:722–732
4. Siefert JL (2009) Defining the mobilome. Methods Mol Biol 532:13–27
5. Jain R, Rivera MC, Lake JA (1999) Horizontal gene transfer among genomes: the complexity hypothesis. Proc Natl Acad Sci USA 96:3801–3806
6. Keeling PJ, Palmer JD (2008) Horizontal gene transfer in eukaryotic evolution. Nat Rev Genet 9:605–618
7. Hacker J, Kaper JB (2000) Pathogenicity islands and the evolution of microbes. Annu Rev Microbiol 54:641–679
8. Lindsay J, Holden M (2004) *Staphylococcus aureus:* superbug, super genome? Trends Microbiol 12:378–385
9. DeLeo FR, Chambers HF (2009) Reemergence of antibiotic-resistant *Staphylococcus aureus* in the genomics era. J Clin Invest 119:2464–2474
10. van Belkum A (2006) Staphylococcal colonization and infection: homeostasis versus disbalance of human (innate) immunity and bacterial virulence. Curr Opin Infect Dis 19:339–344
11. Weems JJ (2001) The many faces of *Staphylococcus aureus* infection. Recognizing and managing its life-threatening manifestations. Postgrad Med 110:24–26, 29–31, 35–36
12. Chambers HF, DeLeo FR (2009) Waves of resistance: *Staphylococcus aureus* in the antibiotic era. Nat Rev Microbiol 7:629–641
13. Baba T, Takeuchi F, Kuroda M, Yuzawa H, Aoki K-I, Oguchi A, Nagai Y, Iwama N, Asano K, Naimi T, Kuroda H, Cui L, Yamamoto K, Hiramatsu K (2002) Genome and virulence determinants of high virulence community-acquired MRSA. Lancet 359:1819–1827
14. Baba T, Bae T, Schneewind O, Takeuchi F, Hiramatsu K (2008) Genome sequence of *Staphylococcus aureus* strain Newman and comparative analysis of staphylococcal genomes: polymorphism and evolution of two major pathogenicity islands. J Bacteriol 190:300–310
15. Diep B, Gill S, Chang R, Phan T, Chen J, Davidson M, Lin F, Lin J, Carleton H, Mongodin E, Sensabaugh G, Perdreau-Remington F (2006) Complete genome sequence of USA300, an epidemic clone of community-acquired meticillin-resistant *Staphylococcus aureus*. Lancet 367:731–739
16. Gill SR, Fouts DE, Archer GL, Mongodin EF, DeBoy RT, Ravel J, Paulsen IT, Kolonay JF, Brinkac L, Beanan M, Dodson RJ, Daugherty SC, Madupu R, Angiuoli SV, Durkin AS, Haft DH, Vamathevan J, Khouri H, Utterback T, Lee C, Dimitrov G, Jiang L, Qin H, Weidman J, Tran K, Kang K, Hance IR, Nelson KE,

Fraser CM (2005) Insights on evolution of virulence and resistance from the complete genome analysis of an early methicillin-resistant *Staphylococcus aureus* strain and a biofilm-producing methicillin-resistant *Staphylococcus epidermidis* strain. J Bacteriol 187:2426–2438
17. Herron-Olson L, Fitzgerald JR, Musser JM, Kapur V (2007) Molecular correlates of host specialization in *Staphylococcus aureus*. PLoS One 2:e1120
18. Holden MTG, Feil EJ, Lindsay JA, Peacock SJ, Day NPJ, Enright MC, Foster TJ, Moore CE, Hurst L, Atkin R, Barron A, Bason N, Bentley SD, Chillingworth C, Chillingworth T, Churcher C, Clark L, Corton C, Cronin A, Doggett J, Dowd L, Feltwell T, Hance Z, Harris B, Hauser H, Holroyd S, Jagels K, James KD, Lennard N, Line A, Mayes R, Moule S, Mungall K, Ormond D, Quail MA, Rabbinowitsch E, Rutherford K, Sanders M, Sharp S, Simmonds M, Stevens K, Whitehead S, Barrell BG, Spratt BG, Parkhill J (2004) Complete genomes of two clinical *Staphylococcus aureus* strains: evidence for the rapid evolution of virulence and drug resistance. Proc Natl Acad Sci USA 101:9786–9791
19. Holden MT, Lindsay JA, Corton C, Quail MA, Cockfield JD, Pathak S, Batra R, Parkhill J, Bentley SD, Edgeworth JD (2010) Genome sequence of a recently emerged, highly transmissible, multi-antibiotic- and antiseptic-resistant variant of methicillin-resistant *Staphylococcus aureus*, sequence type 239 (TW). J Bacteriol 192:888–892
20. Kennedy AD, Otto M, Braughton KR, Whitney AR, Chen L, Mathema B, Mediavilla JR, Byrne KA, Parkins LD, Tenover FC, Kreiswirth BN, Musser JM, DeLeo FR (2008) Epidemic community-associated methicillin-resistant *Staphylococcus aureus*: recent clonal expansion and diversification. Proc Natl Acad Sci USA 105:1327–1332
21. Kuroda M, Ohta T, Uchiyama I, Baba T, Yuzawa H, Kobayashi I, Cui L, Oguchi A, Aoki K-I, Nagai Y, Lian J, Ito T, Kanamori M, Matsumaru H, Maruyama A, Murakami H, Hosoyama A, Mizutani-Ui Y, Takahashi NK, Sawano T, Inoue R-I, Kaito C, Sekimizu K, Hirakawa H, Kuhara S, Goto S, Yabuzaki J, Kanehisa M, Yamashita A, Oshima K, Furuya K, Yoshino C, Shiba T, Hattori M, Ogasawara N, Hayashi H, Hiramatsu K (2001) Whole genome sequencing of meticillin-resistant *Staphylococcus aureus*. Lancet 357:1225–1240
22. Musser JM, Kapur V (1992) Clonal analysis of methicillin-resistant *Staphylococcus aureus* strains from intercontinental sources: association of the *mec* gene with divergent phylogenetic lineages implies dissemination by horizontal transfer and recombination. J Clin Microbiol 30:2058–2063
23. Berg T, Firth N, Apisiridej S, Hettiaratchi A, Leelaporn A, Skurray RA (1998) Complete nucleotide sequence of pSK41: evolution of staphylococcal conjugative multiresistance plasmids. J Bacteriol 180:4350–4359
24. Khan SA (2005) Plasmid rolling-circle replication: highlights of two decades of research. Plasmid 53:126–136
25. Lindsay JA (2010) Genomic variation and evolution of *Staphylococcus aureus*. Int J Med Microbiol 300:98–103
26. Morikawa K, Inose Y, Okamura H, Maruyama A, Hayashi H, Takeyasu K, Ohta TA (2003) New staphylococcal sigma factor in the conserved gene cassette: functional significance and implication for the evolutionary processes. Gen Cell 8:699–712
27. Olsen JE, Christensen H, Aarestrup FM (2006) Diversity and evolution of *blaZ* from *Staphylococcus aureus* and coagulase-negative staphylococci. J Antimicrob Chemother 57:450–460
28. Hackbarth CJ, Chambers HF (1993) blaI and blaR1 regulate beta-lactamase and PBP 2a production in methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother 37:1144–1149
29. Sidhu MS, Heir E, Leegaard T, Wiger K, Holck A (2002) Frequency of disinfectant resistance genes and genetic ginkage with ß-lactamase transposon Tn*552* among clinical staphylococci. Antimicrob Agents Chemother 46:2797–2803
30. Weigel LM, Clewell DB, Gill SR, Clark NC, McDougal LK, Flannagan SE, Kolonay JF, Shetty J, Killgore GE, Tenover FC (2003) Genetic analysis of a high-level vancomycin-resistant isolate of *Staphylococcus aureus*. Science 302:1569–1571
31. Zhu W, Clark NC, McDougal LK, Hageman J, McDonald LC, Patel JB (2008) Vancomycin-resistant *Staphylococcus aureus* isolates associated with inc18-like vanA plasmids in Michigan. Antimicrob Agents Chemother 52:452–457
32. Mwangi MM, Wu SW, Zhou Y, Sieradzki K, de Lencastre H, Richardson P, Bruce D, Rubin E, Myers E, Siggia ED, Tomasz A (2007) Tracking the in vivo evolution of multidrug resistance in *Staphylococcus aureus* by whole-genome sequencing. Proc Natl Acad Sci USA 104:9451–9456
33. Hiramatsu K (2001) Vancomycin-resistant *Staphylococcus aureus*: a new model of antibiotic resistance. Lancet Infect Dis 1:147–155
34. Pantosti A, Sanchini A, Monaco M (2007) Mechanisms of antibiotic resistance in *Staphylococcus aureus*. Future Microbiol 2:323–334
35. Ballard SA, Pertile KK, Lim M, Johnson PDR, Grayson ML (2005) Molecular characterization of vanB elements in naturally occurring gut anaerobes. Antimicrob Agents Chemother 49:1688–1694
36. Perichon B, Courvalin P (2009) VanA-type vancomycin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother 53:4580–4587
37. Tenover FC, Weigel LM, Appelbaum PC, McDougal LK, Chaitram J, McAllister S, Clark N, Killgore G, O'Hara CM, Jevitt L, Patel JB, Bozdogan B (2004) Vancomycin-resistant *Staphylococcus aureus* isolate from a patient in Pennsylvania. Antimicrob Agents Chemother 48:275–280
38. Saha B, Singh AK, Ghosh A, Bal M (2008) Identification and characterization of a vancomycin-resistant *Staphylococcus aureus* isolated from Kolkata (South Asia). J Med Microbiol 57:72–79
39. Lessard IA, Walsh CT (1999) Mutational analysis of active-site residues of the enterococcal D-ala-D-Ala dipeptidase VanX and comparison with *Escherichia coli* D-ala-D-Ala ligase and D-ala-D-Ala carboxypeptidase VanY. Chem Biol 6:177–187
40. Courvalin P (2006) Vancomycin resistance in Gram-positive cocci. Clin Infect Dis 42:S25–S34
41. Jensen SO, Lyon BR (2009) Genetics of antimicrobial resistance in *Staphylococcus aureus*. Future Microbiol 4:565–582
42. Jackson MP, Iandolo JJ (1986) Cloning and expression of the exfoliative toxin B gene from *Staphylococcus aureus*. J Bacteriol 166:574–580
43. Nishifuji K, Sugai M, Amagai M (2008) Staphylococcal exfoliative toxins: "Molecular scissors" of bacteria that attack the cutaneous defense barrier in mammals. J Dermatol Sci 49:21–31
44. Yamaguchi T, Nishifuji K, Sasaki M, Fudaba Y, Aepfelbacher M, Takata T, Ohara M, Komatsuzawa H, Amagai M, Sugai M (2002) Identification of the *Staphylococcus aureus* etd pathogenicity island which encodes a novel exfoliative toxin, ETD, and EDIN-B. Infect Immun 70:5835–5845
45. Yamaguchi T, Hayashi T, Takami H, Ohnishi M, Murata T, Nakayama K, Asakawa K, Ohara M, Komatsuzawa H, Sugai M (2001) Complete nucleotide sequence of a *Staphylococcus aureus* exfoliative toxin B plasmid and identification of a novel ADP-ribosyltransferase, EDIN-C. Infect Immun 69:7760–7771
46. Plano LR (2004) *Staphylococcus aureus* exfoliative toxins: how they cause disease. J Invest Dermatol 122:1070–1077

47. Goerke C, Pantucek R, Holtfreter S, Schulte B, Zink M, Grumann D, Broker BM, Doskar J, Wolz C (2009) Diversity of prophages in dominant *Staphylococcus aureus* clonal lineages. J Bacteriol 191:3462–3468
48. Mann NH (2008) The potential of phages to prevent MRSA infections. Res Microbiol 159:400–405
49. Coleman DC, Sullivan DJ, Russell RJ, Arbuthnott JP, Carey BF, Pomeroy HM (1989) *Staphylococcus aureus* bacteriophages mediating the simultaneous lysogenic conversion of beta-lysin, staphylokinase and enterotoxin A: molecular mechanism of triple conversion. J Gen Microbiol 135:1679–1697
50. van Wamel W, Rooijakkers S, Ruyken M, van Kessel K, van Strijp J (2006) The innate immune modulators staphylococcal complement inhibitor and chemotaxis inhibitory protein of *Staphylococcus aureus* are located on beta-hemolysin-converting bacteriophages. J Bacteriol 188:1310–1315
51. Szmigielski S, Prevost G, Monteil H, Colin DA, Jeljaszewicz J (1999) Leukocidal toxins of staphylococci. Zentralbl Bakteriol 289:185–201
52. Fitzgerald JR, Monday SR, Foster TJ, Bohach GA, Hartigan PJ, Meaney WJ, Smyth CJ (2001) Characterization of a putative pathogenicity island from bovine *Staphylococcus aureus* encoding multiple superantigens. J Bacteriol 183:63–70
53. Novick R, Subedi A (2007) The SaPIs: mobile pathogenicity islands of staphylococcus. Chem Immunol Allergy 93:42–57
54. Novick RP (2003) Mobile genetic elements and bacterial toxinoses: the superantigen-encoding pathogenicity islands of *Staphylococcus aureus*. Plasmid 49:93–105
55. Ubeda C, Tormo MA, Cucarella C, Trotonda P, Foster TJ, Lasa I, Penades JR (2003) Sip, an integrase protein with excision, circularization and integration activities, defines a new family of mobile *Staphylococcus aureus* pathogenicity islands. Mol Microbiol 49:193–210
56. Yarwood JM, McCormick JK, Paustian ML, Orwin PM, Kapur V, Schlievert PM (2002) Characterization and expression analysis of *Staphylococcus aureus* pathogenicity island 3. J Biol Chem 277:13138–13147
57. Carles U, Ma Angeles T, Carme C, Pilar T, Timothy JF, Inigo L, Jose RP (2003) Sip, an integrase protein with excision, circularization and integration activities, defines a new family of mobile *Staphylococcus aureus* pathogenicity islands. Mol Microbiol 49:93–210
58. Tormo MA, Knecht E, Gotz F, Lasa I, Penades JR (2005) Bap-dependent biofilm formation by pathogenic species of *Staphylococcus*: evidence of horizontal gene transfer? Microbiology 151:2465–2475
59. Tormo MA, Ferrer MD, Maiques E, Ubeda C, Selva L, Lasa I, Calvete JJ, Novick RP, Penades JR (2008) *Staphylococcus aureus* pathogenicity island DNA is packaged in particles composed of phage proteins. J Bacteriol 190:2434–2440
60. Ubeda C (2005) Antibiotic-induced SOS response promotes horizontal dissemination of pathogenicity island-encoded virulence factors in staphylococci. Mol Microbiol 56:836–844
61. Ito T, Okuma K, Ma XX, Yuzawa H, Hiramatsu K (2003) Insights on antibiotic resistance of *Staphylococcus aureus* from its whole genome: Genomic island SCC. Drug Resist Update 6:41–52
62. Dobrindt U, Hochhut B, Hentschel U, Hacker J (2004) Genomic islands in pathogenic and environmental microorganisms. Nat Rev Micro 2:414–424
63. Waldron D, Lindsay J (2006) Sau1: a novel lineage-specific type I restriction-modification system that blocks horizontal gene transfer into *Staphylococcus aureus* and between *S. aureus* isolates of different lineages. J Bacteriol 188:5578–5585
64. Lina G, Bohach Gregory A, Nair Sean P, Hiramatsu K, Jouvin-Marche E, Mariuzza R (2004) Standard nomenclature for the superantigens expressed by Staphylococcus. J Infect Dis 189:2334–2336
65. Tsuru T, Kobayashi I (2008) Multiple genome comparison within a bacterial species reveals a unit of evolution spanning two adjacent genes in a tandem paralog cluster. Mol Biol Evol 25:2457–2473
66. Jevons MP, Rolinson GN, Knox R (1961) "Celbenin"-resistant staphylococci. BMJ 1:124–126
67. Severin A, Wu SW, Tabei K, Tomasz A (2005) High-level $\beta$-lactam resistance and cell wall synthesis catalyzed by the mecA homologue of *Staphylococcus sciuri* introduced into *Staphylococcus aureus*. J Bacteriol 187:6651–6658
68. Wu S, Piscitelli C, De Lencastre H, Tomasz A (1996) Tracking the evolutionary origin of the methicillin resistance gene: cloning and sequencing of a homologue of mecA from a methicillin susceptible strain of *Staphylococcus sciuri*. Microb Drug Resist 2:435–441
69. Chongtrakool P, Ito T, Ma XX, Kondo Y, Trakulsomboon S, Tiensasitorn C, Jamklang M, Chavalit T, Song J-H, Hiramatsu K (2006) Staphylococcal cassette chromosome *mec* (SCC*mec*) typing of methicillin-resistant *Staphylococcus aureus* strains isolated in 11 Asian countries: a proposal for a new nomenclature for SCC*mec* elements. Antimicrob Agents Chemother 50:1001–1012
70. de Lencastre H, Oliveira D, Tomasz A (2007) Antibiotic resistant *Staphylococcus aureus*: a paradigm of adaptive power. Curr Opin Microbiol 10:428–435
71. International Working Group on the Classification of Staphylococcal Cassette Chromosome Elements (IWG-SCC) (2009) Classification of staphylococcal cassette chromosome mec (SCCmec): guidelines for reporting novel SCCmec elements. Antimicrob Agents Chemother 53:4961–4967
72. Ma XX, Ito T, Tiensasitorn C, Jamklang M, Chongtrakool P, Boyle-Vavra S, Daum RS, Hiramatsu K (2002) Novel type of staphylococcal cassette chromosome mec identified in community-acquired methicillin-resistant *Staphylococcus aureus* strains. Antimicrob Agents Chemother 46:1147–1152
73. Sitthisak S, Knutsson L, Webb JW, Jayaswal RK (2007) Molecular characterization of the copper transport system in *Staphylococcus aureus*. Microbiol 153:4274–4283
74. Zhang K, McClure J-A, Elsayed S, Conly JM (2009) Novel staphylococcal cassette chromosome mec type, tentatively designated type VIII, harboring class a mec and type 4 ccr gene complexes in a Canadian epidemic strain of methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother 53: 531–540
75. Luong TT, Ouyang S, Bush K, Lee CY (2002) Type 1 capsule genes of *Staphylococcus aureus* are carried in a staphylococcal cassette chromosome genetic element. J Bacteriol 184: 3623–3629
76. Hanssen AM, Sollid JUE (2006) SCCmec in staphylococci: genes on the move. FEMS Immunol Med Microbiol 46:8–20
77. Ellington MJ, Yearwood L, Ganner M, East C, Kearns AM (2008) Distribution of the ACME-arcA gene among methicillin-resistant *Staphylococcus aureus* from England and Wales. J Antimicrob Chemother 61:73–77
78. Goering RV, McDougal LK, Fosheim GE, Bonnstetter KK, Wolter DJ, Tenover FC (2007) Epidemiologic distribution of the arginine catabolic mobile element among selected methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* isolates. J Clin Microbiol 45:1981–1984
79. Miragaia M, de Lencastre H, Perdreau-Remington F, Chambers HF, Higashi J, Sullam PM, Lin J, Wong KI, King KA, Otto M, Sensabaugh GF, Diep BA (2009) Genetic diversity of arginine catabolic mobile element in *Staphylococcus epidermidis*. PLoS One 4:e7722

80. Diep BA, Stone GG, Basuino L, Graber CJ, Miller A, des Etages S-A, Jones A, Palazzolo-Ballance AM, Perdreau-Remington F, Sensabaugh GF, DeLeo FR, Chambers HF (2008) The arginine catabolic mobile element and staphylococcal chromosomal cassette mec linkage: convergence of virulence and resistance in the USA300 clone of methicillin-resistant *Staphylococcus aureus.* J Infect Dis 197:1523–1530
81. Montgomery CP, Boyle-Vavra S, Daum RS (2009) The arginine catabolic mobile element is not associated with enhanced virulence in experimental invasive disease caused by the community-associated methicillin-resistant *Staphylococcus aureus* USA300 genetic background. Infect Immun 77: 2650–2656
82. Byrne ME, Rouch DA, Skurray RA (1989) Nucleotide sequence analysis of IS256 from the *Staphylococcus aureus* gentamicin-tobramycin-kanamycin-resistance transposon Tn4001. Gene 81:361–367
83. Fiandt M, Szybalski W, Malamy MH (1972) Polar mutations in lac, gal and phage lambda consist of a few IS-DNA sequences inserted with either orientation. Mol Gen Genet 119:223–231
84. Jansen A, Türck M, Szekat C, Nagel M, Clever I, Bierbaum G (2007) Role of insertion elements and yycfg in the development of decreased susceptibility to vancomycin in *Staphylococcus aureus*. Int J Med Microbiol 297:205–215
85. Jaurin B, Normark S (1983) Insertion of IS2 creates a novel ampC promoter in *Escherichia coli*. Cell 32:809–816
86. Rouch DA, Byrne ME, Kong YC, Skurray RA (1987) The aacA-aphD gentamicin and kanamycin resistance determinant of Tn4001 from *Staphylococcus aureus:* expression and nucleotide sequence analysis. J Gen Microbiol 133:3039–3052
87. Rouch DA, Messerotti LJ, Loo LSL, Jackson CA, Skurray RA (1989) Trimethoprim resistance transposon Tn*4003* from *Staphylococcus aureus* encodes genes for a dihydrofolate reductase and thymidylate synthetase flanked by three copies of IS*257*. Mol Microbiol 3:161–175
88. Phillips S, Novick RP (1979) Tn554—a site-specific repressor-controlled transposon in *Staphylococcus aureus*. Nature 278:476–478
89. Soge OO, Beck NK, White TM, No DB, Roberts MC (2008) A novel transposon, Tn6009, composed of a Tn916 element linked with a *Staphylococcus aureus* mer operon. J Antimicrob Chemother 62:674–680
90. Lange CC, Werckenthin C, Schwarz S (2003) Molecular analysis of the plasmid-borne aacA/aphD resistance gene region of coagulase-negative staphylococci from chickens. J Antimicrob Chemother 51:1397–1401
91. Palumbi SR (2001) Humans as the world's greatest evolutionary force. Science 293:1786–1790
92. Carles U, Elisa M, Erwin K, Inigo L, Richard PN, José RP (2005) Antibiotic-induced SOS response promotes horizontal dissemination of pathogenicity island-encoded virulence factors in staphylococci. Mol Microbiol 56:836–844
93. Maiques E, Ubeda C, Campoy S, Salvador N, Lasa I, Novick RP, Barbe J, Penades JR (2006) $\beta$-Lactam antibiotics induce the SOS response and horizontal transfer of virulence factors in *Staphylococcus aureus*. J Bacteriol 188:2726–2729
94. Sung JM-L, Lloyd DH, Lindsay JA (2008) *Staphylococcus aureus* host specificity: comparative genomics of human versus animal isolates by multi-strain microarray. Microbiology 154:1949–1959
95. van Belkum A, Melles DC, Peeters JK, van Leeuwen WB, van Duijkeren E, Huijsdens XW, Spalburg E, de Neeling AJ, Verbrugh HA, Dutch Working Party on Surveillance and Research of MRSA-SOM (2008) Methicillin-resistant and -susceptible *Staphylococcus aureus* sequence type 398 in pigs and humans. Emerg Infect Dis 14:479–483
96. van Loo I, Huijsdens X, Tiemersma E, de Neeling A, van de Sande-Bruinsma N, Beaujean D, Voss A, Kluytmans J (2007) Emergence of methicillin-resistant *Staphylococcus aureus* of animal origin in humans. Emerg Infect Dis 13:1834–1839
97. Vitale CB, Gross TL, Weese JS (2006) Methicillin-resistant *Staphylococcus aureus* in cat and owner. Emerg Infect Dis 12:1998–2000
98. Weese JS, Archambault M, Willey BM, Hearn P, Kreiswirth BN, Said-Salim B, McGeer A, Likhoshvay Y, Prescott JF, Low DE (2005) Methicillin-resistant *Staphylococcus aureus* in horses and horse personnel, 2000–2002. Emerg Infect Dis 11:430–435
99. Lowder BV, Guinane CM, Ben Zakour NL, Weinert LA, Conway-Morris A, Cartwright RA, Simpson AJ, Rambaut A, Nübel U, Fitzgerald JR (2009) Recent human-to-poultry host jump, adaptation, and pandemic spread of *Staphylococcus aureus*. Proc Natl Acad Sci USA 106:19545–19550
100. Byrne ME, Gillespie MT, Skurray RA (1991) 4′, 4″ adenyltransferase activity on conjugative plasmids isolated from *Staphylococcus aureus* is encoded on an integrated copy of pUB110. Plasmid 25:70–75
101. Kadlec K, Schwarz S (2009) Novel ABC transporter gene, vga(C), located on a multiresistance plasmid from a porcine methicillin-resistant *Staphylococcus aureus* ST398 strain. Antimicrob Agents Chemother 53:3589–3591
102. Lelievre H, Lina G, Jones ME, Olive C, Forey F, Roussel-Delvallez M, Nicolas-Chanoine M-H, Bebear CM, Jarlier V, Andremont A, Vandenesch F, Etienne J (1999) Emergence and spread in French hospitals of methicillin-resistant *Staphylococcus aureus* with increasing susceptibility to gentamicin and other antibiotics. J Clin Microbiol 37:3452–3457
103. Broer S, Ji G, Broer A, Silver S (1993) Arsenic efflux governed by the arsenic resistance determinant of *Staphylococcus aureus* plasmid pI258. J Bacteriol 175:3480–3485
104. Ji G, Silver S (1992) Regulation and expression of the arsenic resistance operon from *Staphylococcus aureus* plasmid pI258. J Bacteriol 174:3684–3694
105. Kaase M, Lenga S, Friedrich S, Szabados F, Sakinc T, Kleine B, Gatermann SG (2008) Comparison of phenotypic methods for penicillinase detection in *Staphylococcus aureus*. Clin Microbiol Infect 14:614–616
106. Hou Z, Meng J-R, Zhao J-R, Hu B-Q, Liu J, Yan X-J, Jia M, Luo X-X (2007) Inhibition of beta-lactamase-mediated oxacillin resistance in *Staphylococcus aureus* by a deoxyribozyme. Acta Pharmacol Sin 28:1775–1782
107. Gennimata D, Davies J, Tsiftsoglour S (1996) Bleomycin resistance in *Staphylococcus aureus* clinical isolates. J Antimicrob Chemother 37:65–75
108. McElgunn CJ, Zahurul M, Bhuyian A, Sugiyama M (2002) Integration analysis of pSK41 in the chromosome of a methicillin-resistant *Staphylococcus aureus* K-1. J Basic Microbiol 42:190–200
109. Crupper SS, Worrell V, Stewart GC, Iandolo JJ (1999) Cloning and expression of cadD, a new cadmium resistance gene of *Staphylococcus aureus*. J Bacteriol 181:4071–4075
110. Nies DH (1992) Resistance to cadmium, cobalt, zinc, and nickel in microbes. Plasmid 27:17–28
111. Massidda O, Mingoia M, Fadda D, Whalen MB, Montanari MP, Varaldo PE (2006) Analysis of the beta-lactamase plasmid of borderline methicillin-susceptible *Staphylococcus aureus:* focus on bla complex genes and cadmium resistance determinants cadD and cadX. Plasmid 55:114–127
112. Projan SJ, Novick R (1988) Comparative analysis of five related staphylococcal plasmids. Plasmid 19:203–221
113. Projan SJ, Moghazeh S, Novick RP (1988) Nucleotide sequence of pS194, a streptomycin-resistance plasmid from *Staphylococcus aureus*. Nucl Acids Res 16:2179–2188

114. Kehrenberg C, Schwarz S (2006) Distribution of florfenicol resistance genes *fexA* and *cfr* among chloramphenicol-resistant staphylococcus isolates. Antimicrob Agents Chemother 50:1156–1163
115. Schwarz S, Kehrenberg C, Doublet B, Cloeckaert A (2004) Molecular basis of bacterial resistance to chloramphenicol and florfenicol. FEMS Microbiol Rev 28:519–542
116. Tennent JM, Young H-K, Lyon BR, Amyes SGB, Skurray RA (1988) Trimethoprim resistance determinants encoding a dihydrofolate reductase in clinical isolates of *Staphylococcus aureus* and coagulase-negative staphylococci. J Med Microbiol 26:67–73
117. Otsuka T, Zaraket H, Takano T, Saito K, Dohmae S, Higuchi W, Yamamoto T (2007) Macrolide-lincosamide-streptogramin B resistance phenotypes and genotypes among *Staphylococcus aureus* clinical isolates in Japan. Clin Microbiol Infect 13:325–327
118. Westh H, Hougaard D, Vuust J, Rosdahl V (1995) Prevalence of erm gene classes in erythromycin-resistant *Staphylococcus aureus* strains isolated between 1959 and 1988. Antimicrob Agents Chemother 39:369–373
119. Jappe U, Heuck D, Strommenger B, Wendt C, Werner G, Altmann D, Witte W (2008) *Staphylococcus aureus* in dermatology outpatients with special emphasis on community-associated methicillin-resistant strains. J Invest Dermatol 128:2655–2664
120. O'Brien FG, Price C, Grubb WB, Gustafson JE (2002) Genetic characterization of the fusidic acid and cadmium resistance determinants of *Staphylococcus aureus* plasmid pUB101. J Antimicrob Chemother 50:313–321
121. de Oliveira NEM, Cavalcanti EDAC, Laport MS, Bastos MDCDF, Giambiagi-deMarval M (2009) Constitutive expression of the ileS-2 gene responsible for high-level mupirocin resistance in *Staphylococcus aureus*. J Med Microbiol 58:1582–1584
122. Patel JB, Gorwitz RJ, Jernigan JA (2009) Antimicrobial resistance: mupirocin resistance. Clin Infect Dis 49:935–941
123. Laddaga RA, Chu L, Misra TK, Silver S (1987) Nucleotide sequence and expression of the mercurial-resistance operon from *Staphylococcus aureus* plasmid pI258. Proc Natl Acad Sci USA 84:5106–5110
124. Matsuoka M, Endou K, Kobayashi H, Inoue M, Nakajima Y (1998) A plasmid that encodes three genes for resistance to macrolide antibiotics in *Staphylococcus aureus*. FEMS Microbiol Lett 167:221–227
125. Antonio M, McFerran N, Pallen MJ (2002) Mutations affecting the Rossman fold of isoleucyl-tRNA synthetase are correlated with low-level mupirocin resistance in *Staphylococcus aureus*. Antimicrob Agents Chemother 46:438–442
126. Littlejohn TG, DiBerardino D, Messerotti LJ, Spiers SJ, Skurray RA (1991) Structure and evolution of a family of genes encoding antiseptic and disinfectant resistance in *Staphylococcus aureus*. Gene 101:59–66
127. Liu Q, Liu M, Wu Q, Li C, Zhou T, Ni Y (2009) Sensitivities to biocides and distribution of biocide resistance genes in quaternary ammonium compound tolerant *Staphylococcus aureus* isolated in a teaching hospital. Scan J Infect Dis 41:403–409
128. Nakaminami H, Noguchi N, Nishijima S, Kurokawa I, Sasatsu M (2008) Characterization of the pTZ2162 encoding multidrug efflux gene qacB from *Staphylococcus aureus*. Plasmid 60:108–117
129. Bismuth R, Zilhao R, Sakamoto H, Guesdon JL, Courvalin P (1990) Gene heterogeneity for tetracycline resistance in *Staphylococcus* spp. Antimicrob Agents Chemother 34:1611–1614
130. Guay GG, Khan SA, Rothstein DM (1993) The tet(K) gene of plasmid pT181 of *Staphylococcus aureus* encodes an efflux protein that contains 14 transmembrane helices. Plasmid 30:163–166
131. Trzcinski K, Cooper BS, Hryniewicz W, Dowson CG (2000) Expression of resistance to tetracyclines in strains of methicillin-resistant *Staphylococcus aureus*. J Antimicrob Chemother 45:763–770
132. Korczynska M, Mukhtar TA, Wright GD, Berghuis AM (2007) Structural basis for streptogramin B resistance in *Staphylococcus aureus* by virginiamycin B lyase. Proc Natl Acad Sci 104:10388–10393
133. Mukhtar TA, Koteva KP, Hughes DW, Wright GD (2001) Vgb from *Staphylococcus aureus* inactivates streptogramin B antibiotics by an elimination mechanism not hydrolysis†. Biochem 40:8877–8886
134. Rowland S-J, Dyke KGH (1990) Tn552, a novel transposable element from *Staphylococcus aureus*. Mol Microbiol 4:961–975
135. Dubin DT, Chikramane SG, Inglis B, Matthews PR, Stewart PR (1992) Physical mapping of the mec region of an Australian methicillin-resistant *Staphylococcus aureus* lineage and a closely related American strain. J Gen Microbiol 138:169–180
136. Babich K, Engle M, Skinner JS, Laddaga RA (1991) Deletion mutant analysis of the *Staphylococcus aureus* plasmid pI258 mercury-resistance determinant. Can J Microbiol 37:624–631
137. Bogdanova E, Minakhin L, Bass I, Volodin A, Hobman JL, Nikiforov V (2001) Class II broad-spectrum mercury resistance transposons in Gram-positive bacteria from natural environments. Res Microbiol 152:503–514
138. Postma B, Poppelier MJ, van Galen JC, Prossnitz ER, van Strijp JAG, de Haas CJC, van Kessel KPM (2004) Chemotaxis inhibitory protein of *Staphylococcus aureus* binds specifically to the c5a and formylated peptide receptor. J Immunol 172: 6994–7001
139. Altboum Z, Hertman I, Sarid S (1985) Penicillinase plasmid-linked genetic determinants for enterotoxins b and c1 production in *Staphylococcus aureus*. Infect Immun 47:514–521
140. Frea JI, McCoy E, Strong FM (1963) Purification of type b staphylococcal enterotoxin. J Bacteriol 86:1308–1313
141. Avena RM, Bergdoll MS (1967) Purification and some physicochemical properties of enterotoxin C, *Staphylococcus aureus* strain 361. Biochem 6:1474–1480
142. Bayles KW, Iandolo JJ (1989) Genetic and molecular analyses of the gene encoding staphylococcal enterotoxin D. J Bacteriol 171:4799–4806
143. Zhang S, Iandolo JJ, Stewart GC (1998) The enterotoxin D plasmid of *Staphylococcus aureus* encodes a second enterotoxin determinant (sej). FEMS Microbiol Lett 168:227–233
144. Chiang Y-C, Chang L-T, Lin C-W, Yang C-Y, Tsen H-Y (2006) PCR primers for the detection of staphylococcal enterotoxins K, L, and M and survey of staphylococcal enterotoxin types in *Staphylococcus aureus* isolates from food poisoning cases in Taiwan. J Food Protect 69:1072–1079
145. Sumby P, Waldor MK (2003) Transcription of the toxin genes present within the staphylococcal phage phiSa3 ms is intimately linked with the phage's life cycle. J Bacteriol 185:6841–6851
146. Chiang Y-C, Liao W-W, Fan C-M, Pai W-Y, Chiou C-S, Tsen H-Y (2008) PCR detection of staphylococcal enterotoxins (SEs) N, O, P, Q, R, U, and survey of SE types in *Staphylococcus aureus* isolates from food-poisoning cases in Taiwan. Int J Food Microbiol 121:66–73
147. Brussow H, Canchaya C, Hardt W-D (2004) Phages and the evolution of bacterial pathogens: from genomic rearrangements to lysogenic conversion. Microbiol Mol Biol Rev 68:560–602
148. Cabrera G, Xiong A, Uebel M, Singh VK, Jayaswal RK (2001) Molecular characterization of the iron-hydroxamate uptake system in *Staphylococcus aureus*. Appl Environ Microbiol 67:1001–1003
149. Essmann F, Bantel H, Totzke G, Engels IH, Sinha B, Schulze-Osthoff K, Janicke RU (2003) *Staphylococcus aureus* alpha-

toxin-induced cell death: predominant necrosis despite apoptotic caspase activation. Cell Death Differ 10:1260–1272
150. Highlander S, Hulten K, Qin X, Jiang H, Yerrapragada S, Mason E, Shang Y, Williams T, Fortunov R, Liu Y, Igboeli O, Petrosino J, Tirumalai M, Uzman A, Fox G, Cardenas A, Muzny D, Hemphill L, Ding Y, Dugan S, Blyth P, Buhay C, Dinh H, Hawes A, Holder M, Kovar C, Lee S, Liu W, Nazareth L, Wang Q, Zhou J, Kaplan S, Weinstock G (2007) Subtle genetic changes enhance virulence of methicillin resistant and sensitive *Staphylococcus aureus*. BMC Microbiol 7:99
151. Makris G, Wright JD, Ingham E, Holland KT (2004) The hyaluronate lyase of *Staphylococcus aureus*—a virulence factor? Microbiol 150:2005–2013
152. Zou D, Kaneko J, Narita S, Kamio Y (2000) Prophage, phiPV83-pro, carrying panton-valentine leukocidin genes, on the *Staphylococcus aureus* P83 chromosome: comparative analysis of the genome structures of phiPV83-pro, phiPVL, phi11, and other phages. Biosci Biotech Biochem 64:2631–2643
153. Barrio MB, Rainard P, Prévost G (2006) LukM/LukF'-PV is the most active *Staphylococcus aureus* leukotoxin on bovine neutrophils. Microb Infect 8:2068–2074
154. Gillet Y, Issartel B, Vanhems P, Fournet JC, Lina G, Bes M, Vandenesch F, Piémont Y, Brousse N, Floret D, Etienne J (2002) Association between *Staphylococcus aureus* strains carrying gene for Panton-Valentine leukocidin and highly lethal necrotising pneumonia in young immunocompetent patients. Lancet 359:753–759
155. Lina G, Piémont Y, Godail-Gamot F, Bes M, Peter MO, Gauduchon V, Vandenesch F, Etienne J (1999) Involvement of Panton-Valentine leukocidin-producing *Staphylococcus aureus* in primary skin infections and pneumonia. Clin Infect Dis 29:1128–1132
156. Panton PN, Valentine FCO (1932) Staphylococcal toxin. Lancet 219:506–508
157. Tristan A, Bes M, Meugnier H, Lina G, Bozdogan B, Courvalin P, Reverdy ME, Enright MC, Vandenesch F, Etienne J (2007) Global distribution of Panton-Valentine leukocidin—positive methicillin-resistant *Staphylococcus aureus*, 2006. Emerg Infect Dis 13:594–600
158. Voyich JM, Otto M, Mathema B, Braughton KR, Whitney AR, Welty D, Long RD, Dorward DW, Gardner DJ, Lina G, Kreiswirth BN, DeLeo FR (2006) Is Panton-Valentine leukocidin the major virulence determinant in community-associated methicillin-resistant *Staphylococcus aureus* disease? J Infect Dis 194:1761–1770
159. Queck SY, Khan BA, Wang R, Bach T-HL, Kretschmer D, Chen L, Kreiswirth BN, Peschel A, DeLeo FR, Otto M (2009) Mobile genetic element-encoded cytolysin connects virulence to methicillin resistance in MRSA. PLoS Pathog 5:e1000533
160. Mehlin C, Headley CM, Klebanoff SJ (1999) An inflammatory polypeptide complex from *Staphylococcus epidermidis*: isolation and characterization. J Exp Med 189:907–918
161. Vuong C, Dürr M, Carmody AB, Peschel A, Klebanoff SJ, Otto M (2004) Regulated expression of pathogen-associated molecular pattern molecules in *Staphylococcus epidermidis*: quorum-sensing determines pro-inflammatory capacity and production of phenol-soluble modulins. Cell Microbiol 6:753–759
162. Werbick C, Becker K, Mellmann A, Juuti KM, von Eiff C, Peters G, Kuusela PI, Friedrich AW, Sinha B (2007) Staphylococcal chromosomal cassette mec type I, spa type, and expression of pls are determinants of reduced cellular invasiveness of methicillin-resistant *Staphylococcus aureus* isolates. J Infect Dis 195:1678–1685
163. Stec-Niemczyk J, Pustelny K, Kisielewska M, Bista M, Boulware KT, Stennicke HR, Thogersen IB, Daugherty PS, Enghild JJ, Baczynski K, Popowicz GM, Dubin A, Potempa J, Dubin G (2009) Structural and functional characterization of splA, an exclusively specific protease of *Staphylococcus aureus*. J Biochem 419:555–564
164. Takeuchi S, Matsunaga K, Inubushi S, Higuchi H, Imaizumi K, Kaidoh T (2002) Structural gene and strain specificity of a novel cysteine protease produced by *Staphylococcus aureus* isolated from a diseased chicken. Vet Microbiol 89:201–210
165. Rooijakkers SHM, Ruyken M, Roos A, Daha MR, Presanis JS, Sim RB, van Wamel WJB, van Kessel KPM, van Strijp JAG (2005) Immune evasion by a staphylococcal complement inhibitor that acts on C3 convertases. Nat Immunol 6:920–927
166. Fraser JD, Proft T (2008) The bacterial superantigen and superantigen-like proteins. Immunol Rev 225:226–243
167. Bokarewa M, Tarkowski A (2004) Human alpha-defensins neutralize fibrinolytic activity exerted by staphylokinase. Thromb Haemost 91:991–999
168. Jin T, Bokarewa M, Foster T, Mitchell J, Higgins J, Tarkowski A (2004) *Staphylococcus aureus* resists human defensins by production of staphylokinase, a novel bacterial evasion mechanism. J Immunol 172:1169–1176
169. Rooijakkers SHM, van Wamel WJB, Ruyken M, van Kessel KPM, van Strijp JAG (2005) Anti-opsonic properties of staphylokinase. Microb Infect 7:476–484
170. Kreiswirth BN, Projan SJ, Schlievert PM, Novick RP (1989) Toxic shock syndrome toxin-1 is encoded by a variable genetic element. Rev Infect Dis 11:S75–S82
171. Lindsay JA, Ruzin A, Ross HF, Kurepina N, Novick RP (1998) The gene for toxic shock toxin is carried by a family of mobile pathogenicity islands in *Staphylococcus aureus*. Mol Microbiol 29:527–543