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Review

# Molecular Characteristics and Exotoxins of Methicillin-Resistant *Staphylococcus aureus*

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Methicillin-resistant *Staphylococcus aureus* (MRSA) is a bacterial pathogen capable of causing human diseases, such as soft tissue infection, bacteremia, endocarditis, toxic shock syndrome, pneumonia, and sepsis. Although the incidence rate of diseases caused by MRSA has declined in recent years, these diseases still pose a clinical threat due to their consistently high morbidity and mortality rates. However, the role of virulence factors in staphylococcal infections remains incompletely understood. Methicillin resistance, which confers resistance to all β-lactam antibiotics in cellular islets, is mediated by the *mec*A gene in the staphylococcal cassette chromosome *mec* (SCC*mec*). Differences in SCC*mec* types and differences in their sizes and structures serve epidemiological purposes and are used to differentiate between hospital-associated (HA)-MRSA and community-associated (CA)-MRSA. Some virulence factors of *S. aureus* are also providing a distinction between HA-MRSA and CA-MRSA. These factors vary depending on the presence of toxins, adhesion, immune evasion, and other virulence determinants. In this review, we summarized an overview of MRSA such as resistance mechanisms, SCC*mec* types, HA- and CA-MRSA, and virulence factors that enhance pathogenicity or MRSA epidemiology, transmission, and genetic diversity.

**Key Words:** Methicillin-resistant *Staphylococcus aureus* (MRSA), Staphylococcal cassette chromosome *mec*, Hospital-associated-MRSA, Community-associated MRSA, Exotoxins

## INTRODUCTION

*Staphylococcus aureus* is a major bacterial pathogen that causes a range of infectious diseases in humans, including skin infections, bacteremia, endocarditis, toxic shock syndrome (TSS), pneumonia, and sepsis (Tong et al., 2015). Although *S. aureus* is usually a commensal bacterium, it can cause infection in immunocompromised patients or during surgery with invasive medical devices (Anderson et al.,

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2012; Moran et al., 2012; Nimmo, 2012; Tong et al., 2012).

There are many kinds of antibiotics that target key bacterial processes, such as cell wall synthesis, translation, transcription, and DNA synthesis, and that can be used to treat staphylococcal infections (Samanta and Elasri, 2014; Assis et al., 2017; G et al., 2019). Methicillin-resistant *S. aureus* (MRSA) attracted global attention in the 1960s (Benner and Kayser, 1968; Chambers and Deleo, 2009; Melo et al., 2017; Fri et al., 2020), and its antibiotic resistance occurs via several mechanisms. Currently, MRSA has spread globally, and its prevalence has increased both in hospital-associated MRSA (HA-MRSA) and community-associated MRSA (CA-MRSA) (Saiman et al., 2003; Bratu et al., 2005; Gregory et al., 2009; Sassi et al., 2017).

Infectious diseases caused by MRSA include superficial skin and soft tissue infections, endocarditis, bacteremia, necrotizing pneumonia, fasciitis, and osteomyelitis, all of which are life-threatening conditions. The emergence of MRSA strains has resulted in severe mortality and morbidity because of the spread of these strains in hospitals and communities (Bratu et al., 2005). MRSA tends to occur during population infections, often characterized by a series of predominant strains. MRSA infection without a single predominant strain also occurs worldwide, and it is more difficult to treat. In order to address the problem caused by MRSA, guidelines have been published in several countries. There are recommendations for the identification of MRSA, as well as protocols and procedures for the diagnosis of MRSA. These guidelines include the Clinical and Laboratory Standards Institute (CLSI; formerly the National Clinical Laboratory Standards, NCCLS) in the USA, the European Antimicrobial Resistance Surveillance System (EARSS) in Europe, and the Sociedad Española de Infectologia y Microbiologia Clinica (SEIMC) in Spain.

MRSA has a copy of the *mec* gene, which is located in the staphylococcal cassette chromosome *mec* (SCC*mec*), which encodes the penicillin-binding proteins (PBPs) with reduced affinity for β-lactam antibiotics. These PBPs include *mec*A, *mec*B, *mec*C, and *mec*D (Harrison et al., 2013; Gomez-Sanz et al., 2015; Schwendener and Perreten, 2018). The resistance of MRSA infections to all types of β-lactam antibiotics, such as penicillin and methicillin, makes its treatment challenging. Other antibiotics, such as mupirocin, bind to the enzyme leucine-specific tRNA aminoacyl synthetase and inhibit protein synthesis. However, long-term and widespread use of mupirocin for decolonization has been associated with mutations in the *Mup*A gene and chromosomal point mutations, conferring mupirocin resistance (Hayden et al., 2016; Dadashi et al., 2020). The macrolide antibiotic fusidic acid is commonly used to treat skin infections caused by *S. aureus* (Liu et al., 2017; Chen et al., 2020; Liu et al., 2020). In *S. aureus*, the main resistance mechanism to various types of antibiotics is the pump-mediated efflux mechanism (da Cruz et al., 2020). The multidrug efflux pumps found in *S. aureus* are grouped into five families of membrane proteins: the ATP-binding cassette, small multidrug resistance family, major stimulator superfamily (MFS), resistant nodular division superfamily, and multidrug and toxin extrusion family (Jang, 2016). Furthermore, MRSA strains have additional virulence factors, such as toxins and adhesion proteins (Alvaro-Afonso et al., 2018; Smart et al., 2019).

Recently, studies have focused on various virulence factors that play important roles in the pathogenesis of MRSA, which are encoded by multiple genes (Boulton et al., 2005; Shettigar and Murali, 2020). Exotoxins, which are virulence factors of *S. aureus*, secrete different staphylococcal enterotoxins (SEs), such as staphylococcal enterotoxins from types A to U and TSS toxin-1 (TSST-1) (Wang et al., 2008; Krakauer and Stiles, 2013). Exotoxins are superantigens (SAgs) because they combine with the major histocompatibility complex class II molecules in antigenic cells and variable beta region of T-cell receptors to activate T cells more strongly than during normal Ag reactions and cause strong inflammatory reactions (Proft and Fraser, 2003; Loncarevic et al., 2005). SE, an exotoxin of *S. aureus*, is prevalent worldwide, causes gastrointestinal syndrome in humans, which presents with food poisoning, vomiting, and diarrhea (Lovseth et al., 2004; Oliveira et al., 2018).

Other virulence factors include Panton-Valentine leucocidin (PVL), encoded by the *lukS/F-PV* and *lukE/D* genes, exfoliative toxins (ETs) (Ladhani, 2001; Rasheed and Hussein, 2020), arginine catabolic mobile element (ACME, arcA), β-hemolysin (hlb), TSST-1, accessory gene regulator

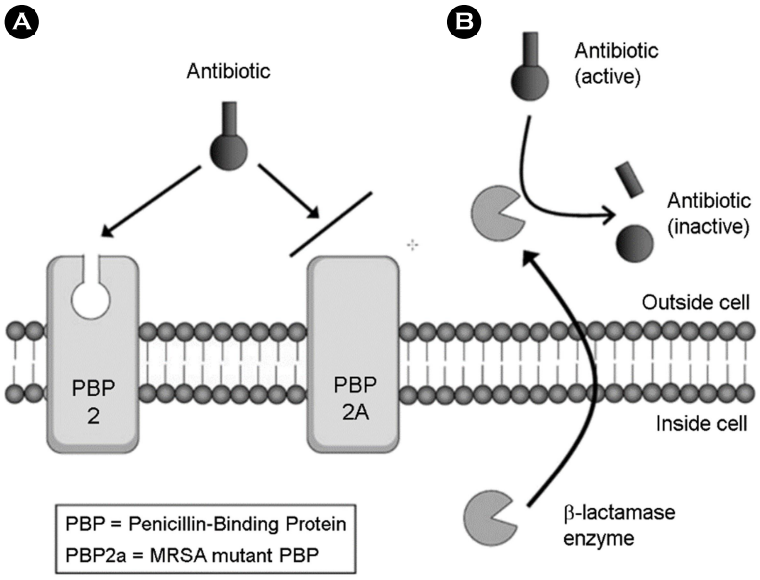


**Fig. 1. Diagram of the two principal antibiotic resistance mechanisms observed in MRSA bacteria.** (A) Expression of an alternate form of penicillin-binding protein (PBP2), PBP2a, with reduced binding affinity for antibiotics. (B) Production and release of the β-lactamase enzyme, which cleaves antibiotic molecules and renders them inactive. The illustration is adapted from Murphy et al. (Murphy et al., 2011).

(agr), and α-hemolysin (hla) (Yarwood et al., 2004; Scherr et al., 2015). This review aims to provide an understanding of the *mec*hanism of exotoxins and the molecular characteristics of *S. aureus*, focusing on MRSA strains and summarizing the current epidemic and virulence factors of MRSA.

Recent epidemiological studies of *S. aureus* have focused particularly on the distribution of MRSA in healthcare settings and communities. However, in the past century, methicillin-susceptible *S. aureus* (MSSA) was also a major cause of outbreaks and global spread in healthcare settings. Moreover, it remains as one of the leading pathogens of hospital-acquired infections (Monaco et al., 2017).

## 1. Mechanisms of methicillin resistance

MRSA contains *mec*A gene that encodes the peptidoglycan transpeptidase, PBP2a, which reduces the affinity for β-lactam antibiotics (Fishovitz et al., 2014). β-lactam antimicrobial agents target and inhibit bacterial cell wall biosynthesis, particularly the synthesis of the peptidoglycan layer (Sarkar et al., 2017). Peptidoglycan is a major structural component of the cell wall and is made of glycan strands, which are composed of repeating patterns of N-acetylglucosamine and N-acetylmuramic acids that form peptide crosslinks between the N-acetyl muramic acid moieties of adjacent strands (Peacock and Paterson, 2015). For the past 75 years, β-lactams have been known to be the most important class of antibiotics used for the treatment of *S. aureus* infections, but some strains of *S. aureus* were found to have strong resistance *mec*hanisms in the form of β-lactamase even before penicillin was marketed (Fair and Tor, 2014; Vestergaard et al., 2019). In addition to transpeptidase activity, *S. aureus* has several PBPs that regulate peptidoglycan synthesis (Typas et al., 2011) (Fig. 1). The combination of β-lactam antibiotics and PBP slows the formation of the acyl-enzyme complex, essentially blocking the transpeptidase activity of these enzymes (Fisher and Mobashery, 2020). The *mec*A gene encodes PBP2a, an enzyme that crosslinks peptidoglycans in bacterial cell walls (Srisuknimit et al., 2017). PBP2a has a low affinity for β-lactams, making it resistant to antibiotics (Baek et al., 2014). *S. aureus* is resistant to almost all antibiotics as a result of a single genetic element—SCC*mec*—and this has led to an increase in the number of severe MRSA strains (Lakhundi and Zhang, 2018).

## 2. Staphylococcal cassette chromosome *mec* types of MRSA

The methicillin resistance of MRSA is primarily caused by the acquisition of *mec*A that is located on a mobile genomic island known as SCC*mec* (Fig. 2) (Senok et al., 2019). MRSA produces PBP2a, encoded by the *mec*A gene, which induces methicillin resistance in staphylococci

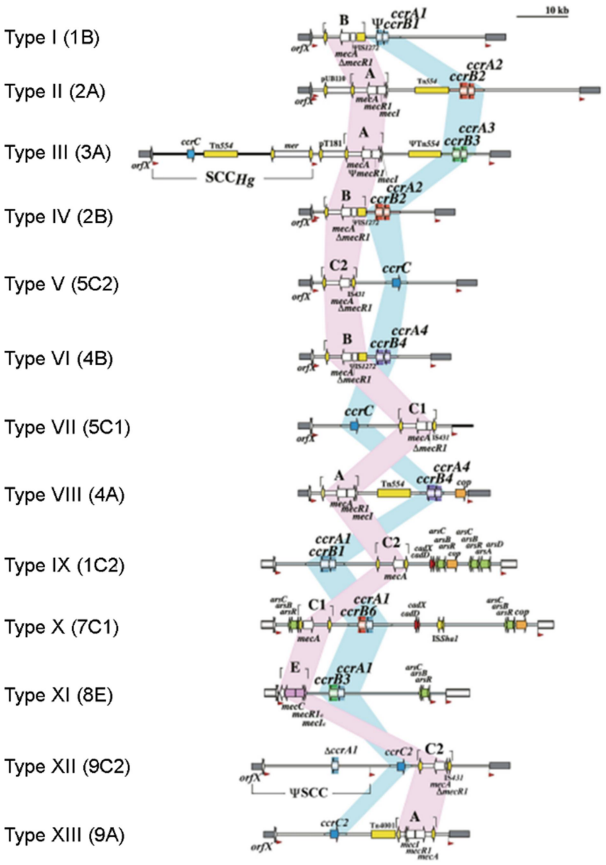


**Fig. 2. Genetic features of SCC*mec* elements I-XIII.** Genetic features of SCC*mec* elements I-XIII. The overall structures of the 13 IWG-SCC-acknowledged SCC*mec* types are illustrated based on the following nucleotide sequences (SCC*mec* type), isolate ID (GenBank accession no.): type I, NCTC10442 (AB033763); type II, N315 (D86934); type III, 85/2082 (AB037671); type IV, CA05 (AB063172); type V, WIS [WBG8318] (AB121219); type VI, HDE288 (AF411935); type VII, JCSC6082 (AB373032); type VIII, C10682 (FJ390057); type IX, JCSC6943 (AB505628); type X, JCSC6945 (AB505630); type XI, LGA251 (FR821779.1); type XII, BA01611 (KR187111); and type XIII, 55-99-44 (MG674089). The illustration is adapted from Hiramatsu et al. (Hiramatsu et al., 2013).

(Cikman et al., 2019). SCC*mec* is a mobile genetic element that ranges from 21 to 67 kbps in size and confers resistance to methicillin in the *S. aureus* species (Hashemizadeh et al., 2019). SCC*mec* elements are classified into 13 types (SCC*mec* I to XIII) based on their structural composition and genetic content (Baig et al., 2018; Singh-Moodley et al., 2019). SCC*mec* types II and III induce resistance to several antibiotics because of the presence of ancillary drug resistance genes in SCC*mec*, whereas other SCC*mec* types (I, IV, V, VI, and VII) are known to confer β-lactam antibiotic resistance (Lim et al., 2019).

## 3. Molecular characteristics of HA- and CA-MRSA

MRSA was first observed in clinical isolates from hospitalized patients in the 1960s. However, it has rapidly spread since the early 1990s (David and Daum, 2010). In many countries, the incidence of HA-MRSA is very high, and the classes of antibiotics that are important for preventing and treating this infection are ineffective (Lindsay, 2013). Numerous CA-MRSA lineages have been found on every continent, and CA-MRSA strains are increasingly involved in nosocomial infections. MRSA is one of the most common causes of hospital- and community-associated infections, most of which have SCC*mec* types I, II, or III, whereas CA-MRSA strains predominantly have SCC*mec* type IV or V (Diep and Otto, 2008; Valsesia et al., 2010; Otto, 2013). It is unclear whether CA-MRSA strains are hospital strains that have spread from hospitals or whether these strains have acquired new SCC*mec* chromosomal DNA (Diederen and Kluytmans, 2006; van Duin and Paterson, 2020).

Monitoring in-hospital outbreaks and identifying worldwide clones are key objectives of the HA-MRSA epidemiologic research. HA-MRSA can spread rapidly in hospitals and replace other *S. aureus* strains (Hart et al., 2014). ST22-MRSA-IV (also known as epidemic MRSA (EMRSA)-15) is the most common HA-MRSA clone found in Europe (Aucken et al., 2002). EMRSA-15 was discovered in the early 1990s in southeast England and the Midlands, whereas EMRSA-16 was discovered a year or two later in a hospital epidemic, and both have since spread widely (Aires de Sousa and de Lencastre, 2004). EMRSA-15 and EMRSA-16 are genetically diverse, with CC22 (ST22) for EMRSA-15 and CC30 (ST36) for EMRSA-16, belonging to different multi-locus sequence type (MLST) clonal complexes (Lindsay, 2010; Silva et al., 2020). EMRSA-15 is the most common clone in the nosocomial and community settings (Johnson et al., 2005).

## 4. Virulence factors of *S. aureus*

Similar to the toxicity of MRSA, the toxicity of *S. aureus* varies depending on the presence of adhesion, toxins, immune evasion, and other virulence determinants (Otto, 2012).

Clumping factors, fibronectin-binding proteins, adhesions, hemolysins, and various SAgs determine toxicity. Among these, surface proteins can evade innate immune responses, interfere with adaptive immune responses, and function as antigens in vaccines (Foster et al., 2014). Therefore, understanding the cell wall structure of *S. aureus* or the genetic *mec*hanism for expressing proteins is important for its treatment.

**4-1. Adhesion genes (*clf*A, *clf*B, *fnb*A, and *fnb*B)**

Clumping factor A (*Clf*A), which is involved in a variety of infections, is a representative virulence factor of *S. aureus* (Munoz-Planillo et al., 2009). *Clf*A is responsible for the accumulation of bacteria in the plasma and can lead to arthritis and endocarditis (Bonar et al., 2015; Herman-Bausier et al., 2018). In addition, *clf*A promotes invasion of biomaterials coated with plasma proteins and adhesion of bacteria and induces bacterial colonization and biofilm formation (Feuillie et al., 2017). *Clf*B is only 26% identical to *clf*A in the binding domain, but the overall structure is similar (D et al., 1998). Unlike *clf*A, *clf*B binds to fibrinogen by binding to the α-chain (Walsh et al., 2008). Interestingly, *clf*B promotes adhesion to nasal epithelial cells by binding to the keratinized envelope proteins, cytokeratin 10 and loricrin. (Crosby et al., 2016; Foster, 2019). In addition, *clf*B has recently been shown to promote bacterial adhesion to keratinocytes obtained from patients with atopic dermatitis. Some studies have shown that considerably more *clf*B is present in *agr* mutants than in wild-type cells, indicating that the agr system downregulates *clf*B gene expression (Xue et al., 2012).

In addition, *S. aureus* expresses microbial surface components that recognize adhesive matrix molecules, including *fnb*A, *fnb*B, and fib (Josse et al., 2017). Fibronectin-binding proteins, including FnBPA and FnBPB, are involved in tissue invasion in a variety of pathological conditions, such as ocular keratitis, osteomyelitis, and medical device-borne infections (Soltani et al., 2019). Moreover, *fnb*A and *fnb*B are mediators of cell signaling and actin cytoskeleton rearrangements (Hauck and Ohlsen, 2006). The identification of genes related to bacterial colonization has attracted the attention of researchers, and specific primers have been used to determine the frequency of these genes and their mRNA expression levels using polymerase chain reaction (Delgado et al., 2011).

**4-2. Hemolysins**

Hla (α-toxin) and hlb are two types of pore-forming toxins (Munoz-Planillo et al., 2009). Hla is a 33-kDa polypeptide secreted by most strains of *S. aureus*, accounting for 95% of the clinical strains (Oliveira et al., 2018). Although this toxin is not toxic, it confers toxicity by oligomerizing and binding to the heptameric structure of the host cell membrane (Berube and Bubeck Wardenburg, 2013). Once hla binds to the target cell, it oligomerizes to a pre-pore structure and extrudes the β-barrel through the lipid bilayer to attack the cell membrane, thus forming a hydrophilic transmembrane channel (Voskoboinik et al., 2015; Seilie and Bubeck Wardenburg, 2017). This toxin is known to be widely expressed in human cells, including epithelial cells, endothelial cells, T cells, monocytes, and macrophages (Cikman et al., 2019).

Unlike other cytotoxins, β-toxin hydrolyzes the plasma membrane lipid sphingomyelin into ceramide and phosphorylcholine without forming pores in the plasma membrane (Lovseth et al., 2004). β-Toxins also have a DNA biofilm-ligase activity (Herrera et al., 2017). The β-toxin of *S. aureus* is neutral sphingomyelinase, whose ability to lyse red blood cells and kill proliferating human lymphocytes is related to its activity (Linehan et al., 2003). This homology led to the hypothesis that β-toxin could bind and cleave DNA, and the examination of this hypothesis led to the unexpected conclusion that β-toxin plays a key role (Huseby et al., 2010; Luther et al., 2018).

In addition, mutant strains that do not express the *hlb* gene for biofilm formation exhibited reduced pathogenicity for endocarditis and are less likely to cause pneumonia and murine ear and skin infections than the strains that express the *hlb* gene (Typas et al., 2011; Zheng et al., 2019). γ-hemolysin (hlg) is produced in virtually all strains of *S. aureus*, and *hlg* can lyse a variety of mammalian erythrocytes (Yoong and Torres, 2013). The *hlg* gene is transcribed at a single locus on a 4.5-kb ScaI chromosome fragment (Lovseth et al., 2004). Hemolytic and leukemic toxicity was found in

extracts from clones containing this fragment (Diep and Otto, 2008). The hlg and PVL in *S. aureus* make two types of binary toxins called S and F components (for proteins that elute slowly or rapidly in ion exchange columns). The S-class subunit is primarily responsible for cell targeting, first binding to the cell, and then bringing up the F-class subunit (Diederen and Kluytmans, 2006; DuMont and Torres, 2014). δ-hemolysin (hld), composed of a 26-amino acid peptide, can cause membrane damage in a variety of mammalian cells (Otto, 2012). Hld has the ability to lyse erythrocytes and other mammalian cells as well as subcellular structures, such as membrane-bound organelles, spheroids, and protoplasts (Melo et al., 2017).

In the case of the overall hemolysin gene, MRSA appeared slightly more than MSSA. In one study, it was found that the presence of the genes encoding hla and hld significantly affected the antibiotic resistance pattern of MRSA isolates (Motamedi et al., 2018). The prevalence of the hemolysin gene in *S. aureus* is observed in a holistic way, because its diversity is also related to different geographic regions (Mir et al., 2019).

**4-3. Superantigen genes (toxic shock syndrome toxin, enterotoxins)**

SAgs are non-glycosylated, low-molecular-weight exo-proteins. They are secreted depending on cleavable signal peptides, which are secreted by all human pathogenic *S. aureus* and group A streptococci (Spaulding et al., 2013). SAgs are highly effective T cell mitogens that can stimulate T cells. SAg-induced T cell proliferation is followed by a T cell unresponsive state, in which activated T cells fail to proliferate or undergo apoptosis. The SAg system is one of the several ways by which *S. aureus* manipulates the host immune system to prevent the generation of functional adaptive immunity (Tam and Torres, 2019).

TSS is an acute disease that can be potentially fatal. It results in high fever, diffuse erythematous rash, peeling of the skin one to two weeks after onset, and hypotension (Tang et al., 2006; Bonar et al., 2015). This disease attracted considerable attention in 1978 when Todd et al. identified it as a major systemic disease associated with non-invasive *S. aureus* infections in children (Feuillie et al., 2017). TSST is a *S. aureus* SAg that triggers TSS by stimulating the release of interleukin (IL)-1, IL-2, tumor necrosis factor-α, and other cytokines (Khan et al., 2009).

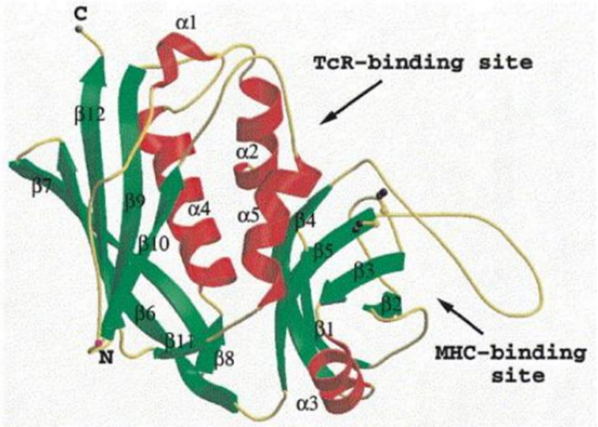


**Fig. 3. 3D structure of Staphylococcus enterotoxin B.** The polypeptide fold for SEB. Helices are coloured in red, β-strands in green and loops in yellow. The illustration is adapted from Papageorgiou et al. (Papageorgiou et al., 1998).

**4-4. Staphylococcal enterotoxins**

Enterotoxins have a common structure consisting of two domain folds, a long central alpha-helix, and specific N-terminal and C-terminal motifs with a beta barrel structure (Fig. 3) (Josse et al., 2017). The exact mechanism of SE is unknown, but it activates the release of cytokines and eventually induces cell death by apoptosis (Soltani et al., 2019). Enterotoxins are the leading cause of food poisoning and can cause severe intestinal peristalsis (Becker et al., 2003). Staphylococcal SAg toxins are a wide range of virulence factors associated with *S. aureus*. In addition to previously known SEs, at present, 29 SEs or enterotoxin-like proteins have been identified (Hu et al., 2021). SEB is a toxin that is highly associated with several outbreaks of food poisoning (Wieneke et al., 1993). SEB is commonly found in humans and mammals, as well as in areas with high levels of environmental pollutants, such as sewage and smoke. SEC from CA-MRSA strains has also been found to cause sepsis, infectious endocarditis, and kidney damage (Diep and Otto, 2008).

**4-5. Other virulence factors (PVL, LukED, ETA, and ETB)**

PVL and LukED are heterologous families in which toxin components are classified as F or S proteins. They are separately secreted and assembled on the cell surface to form heterologous oligomeric pores and lyse blood cells (Yanai et al., 2014). Additionally, they are associated with purulent infections and are encoded by two successive and co-transcribed genes that are passed on to bacteriophages, causing leukocyte destruction and tissue necrosis. However, their exact role in skin infections has not yet been identified (Cocchi et al., 2013). PVL was generally found at the beginning of the CA-MRSA epidemic, and the *luk*S and *luk*F genes were found in almost all CA-MRSA clones. Recently, PVL has been shown to be associated with CA-MRSA in a study on the association between infections that are in progress and strains (Bhatta et al., 2016); however, the association between PVL and CA-MRSA remains controversial. Although PVL can be utilized as a screening marker for CA-MRSA, it is difficult to determine because of the presence of PVL-positive HA-MRSA strains. HA-MRSA may lead to the emergence of multidrug-resistant HA-MRSA isolates with increased toxicity (Rossney et al., 2007; Hu et al., 2015). As PVL phages from existing MRSA are expected to spread to other HA-MRSA strains, HA-MRSA infections need to be further divided into hospital-borne or community-borne infections (Narita et al., 2001; Klevens et al., 2007).

ETs, also known as specific serine proteases, are secreted virulence factors produced by staphylococci (Shopsin et al., 2003; Abimanyu et al., 2013). These proteases have high substrate specificity and recognize and hydrolyze desmosomal proteins in the skin. ETs are involved in the loss of cell-cell adhesion and cleavage of keratinocyte junctions in the epidermis of the host that can cause skin damage. Strains of ETs include ETA, ETB, ETC, and ETD. ETA and ETB are the most important factors in human skin damage. ETC has not yet been associated with human diseases. These ETs are produced in approximately 5% of the *S. aureus* strains. ETA is highly prevalent in Europe, Africa, and the United States, whereas ETB is more common in Japan. The production of ETs in certain strains of *S. aureus* is associated with local epidermal infections, such as bullous impetigo and staphylococcal laceration skin syndrome, which are common diseases (Saiman et al., 2003; Healy et al., 2004; Bratu et al., 2005).

## CONCLUSION

We described the resistance of MRSA to β-lactam antibiotics, with an emphasis on *mec*A, which is carried by a mobile genetic element called SCC*mec*. The *mec*A gene encodes PBP2a that has a low affinity for β-lactam antibiotics. In this review, the classification criteria for *mec*A, new *mec* homologs (*mec*B, *mec*C, and *mec*D), and SCC*mec* types (13 SCC*mec* types that have been found to date) were discussed. SCC*mec* has entered *S. aureus* on multiple occasions with a relatively high frequency, but the origin of the *mec* element remains unclear. MRSA strains possess specific virulence mechanisms controlled by toxins, adhesion proteins, and enzymes. However, the molecular factors underlying the spread of the CA- and HA-MRSA strains remain unknown. Important strains have emerged, such as EMRSA and CA-MRSA, and each strain poses unique challenges to human healthcare and animal husbandry. Therefore, conducting research on the virulence of infectious MRSA strains is important. Further studies are needed to determine the regulation of virulence factors and dynamics of virulence factor transmission in MRSA strains.

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**CONFLICT OF ENTEREST**

Authors declare no competing interests.

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