Pathogenicity of Methicillin Resistant *Staphylococcus aureus* (MRSA) Strains: Molecular and Genetic Perspectives: A Review

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Abstract: Methicillin resistant *Staphylococcus aureus* (MRSA) is a pathogenic bacterium of significant importance that causes most of the hospital and community acquired infections associated with *S. aureus*. Methicillin resistance in strains of *S. aureus* is due to possession of the *mecA* gene or *mecC* gene found on a mobile genetic element (SCC*mec*). The virulence of MRSA is multifactorial because of the combined action of numerous virulence factors that facilitate tissue adhesion, immune evasion, and host cell injury. These virulence determinants involve both structural factors, such as surface adhesins that mediate adherence to host tissues, and secreted factors, such as enzymes, which convert host tissue into nutrients. The virulence factors of MRSA include PVL, TSST-1, *Staphylococcus* protein A (spa). The quorum sensing together with the global accessory regulator of *Staphylococcus aureus* helps control the expression of virulence gene as some are up-regulated during exponential phase of growth and down-regulated during stationary phase and vice-versa. MRSA is versatile and unpredictable. Its capacity for genetic adaptation and the serial emergence of successful epidemic strains cause it to remain a major threat to human health, further understanding of its pathogenicity trends and epidemiology will give an insight on how to tackle it's spread.

Keywords: Pathogenicity, MRSA, *S. aureus*, SCCmec, virulence, genes

INTRODUCTION

Staphylococcus aureus is Gram-positive bacterium that belongs to the family of Micrococcaceae. *S. aureus* are about 0.8 µm- 1.0 µm in diameter, non-motile and non-spore forming bacteria (Arora and Arora, 2008). *S. aureus* is capable of growing in the presence of oxygen (aerobes) and also capable of growing in the absence of oxygen (facultative anaerobes), they are also neutrophiles i.e. capable of growing at neutral pH. *S. aureus* grows at an optimum temperature of 37 ℃ and capable of growing in a high salt condition (Arora and Arora, 2008). *S. aureus* are found to be associated with the human body as part of its normal flora. *S. aureus* are commonly found on the skin and mucous membranes in the human body. However, *S. aureus* is an opportunistic pathogen capable of causing infections in human such as skin infection, pneumonia, sinusitis, Ritter's disease, septicemia, furuncles and also food poisoning (Wendlant *et al.,* 2013).

Methicillin resistant *S. aureus* (MRSA) is a major cause of hospital and community associated infections due to its ability to withstand different antibiotic concentrations (Enright *et al.,* 2002 and Kong *et al.,* 2016). The evolutionary origin of MRSA is not well understood as there is no evolutionary link between MRSA clones isolated from different countries, resistance was due to mecA gene that is transfer through horizontal gene transfer from *S. aureus* ancestral strains that has the mecA gene to other *S. aureus* strains that do not have the mecA gene (Enright *et al.,* 2002). Gordon and Lowy (2008), suggested that the *mec*A gene is found in a coagulase-negative Staphylococcus spp. and is transmitted through horizontal gene transfer to *S. aureus*. However, Enright *et al.* (2002) were able to draw an evolutionary relationship between the MRSA strains using MLST and BURST algorithm and they identified 11 major clones from the five major groups of related genotype of the 912 MRSA and MSSA samples collected worldwide.

Methicillin-resistant *Staphylococcus aureus* (MRSA), or multidrug-resistant *S. aureus*, first reported in the early 1960s in the United Kingdom, are strains of *S. aureus* that through the process of natural selection developed resistance to all available penicillins and other β-lactam antimicrobial drugs (Enright *et al.,* 2002; Kong *et al.,* 2016). Methicillin is a semi synthetic antibiotic produce in 1961 in order to inhibit strains of S. aureus that are resistant to penicillin.

Not long after its introduction, resistant to methicillin was reported (Chambers and DeLeo, 2009). Methicillin resistance in strains of S. aureus is due to possession of the *mec*A gene or *mec*C gene. The *mec*A gene encodes transpeptidase, also known as penicillin binding protein 2A (PBP2A), that has reduced affinity to beta-lactam antibiotics enabling the *S. aureus* strain to withstand high concentration of beta-lactams antibiotics (Lowy, 2003; Chambers and DeLeo, 2009). *Mec*A is part of the Staphylococcal cassette chromosome *mec* (SCCmec), which is a mobile genetic element, found in *Staphylococcus* spp. (Lowy, 2003; Ryan and Ray, 2014).

Although the evolution of such resistance does not cause the organism to be more virulent basically, but it does make MRSA infections more difficult to treat and therefore more dangerous, particularly in hospitalized patients and those with weakened immune systems (Kong *et al.,* 2016). Resistance of *S. aureus* strains to methicillin was developed within a year after its introduction. Methicillin resistance of *S. aureus* was first reported in UK in 19961 was later reported in other European countries, Japan, Australia and United States of America (Enright *et al.,* 2002). The first MRSA outbreaks lead to an epidemic outbreak on a global level, including the first MRSA outbreak in the USA (Otto, 2010; Enright *et al*., 2002). MRSA account for 16.8 % of the antibiotic resistance hospital acquired infections in Europe (Campanile *et al*., 2015).

The ability of *S. aureus* to cause infection and also escape host immune defenses is due to the possession of virulence factors. These factors include, extracellular toxins, extracellular enzymes and cell wall associated factors. These characteristics help *S. aureus* escapes host defenses and causes disease in the host (Arora and Arora, 2008; Kong *et al.,* 2016). Most *S. aureus* strains are capable of producing toxins (Enterotoxin) that help in penetrating the host cell or tissue and causing disease. Some of these toxins are cytolytic and help the bacteria to acquire nutrient from lysed cells. Toxins produced by *S. aureus* include, hemolysin, leucocidin, exfoliative toxin, toxic-shock syndrome toxin 1 (TSST-1) and enterotoxins (Kong *et al.,* 2016). Extracellular enzymes are enzymes produced by the strains of *S. aureus* that are capable of destroying the host cells and tissue and preventing the bacteria against the host defenses and also allowing the growth of the bacteria in the host. There are three types of extracellular enzymes produce by strains of *S. aureus* that help in the pathogenicity of the bacteria. They are hyaluronidase, collagenase coagulase, nucleases, proteases, lipases and staphylokinase or fibrinolysin (Arora and Arora, 2008; Kong *et al.,* 2016). The cell wall-associated factors that increase the virulence of MRSA include the surface proteins, capsular polysaccharide, teichoic acid, peptidoglycan, clumping factor and protein A. These factors facilitate the adherence of bacteria to the host tissue and play an important role in pathogenicity of *Staphylococcus* specie (Gordon and Lowy, 2008).

Similarly *S aureus* contains ample number of virulent determinant that promotes tissue colonization, damage and distant disease. The bacteria are capable of surviving inside host cell by invading variety of nonprofessional phagocytes, thereby escaping host defenses and antibacterial agents due to possession of global regulators. These regulators senses environmental modification such as bacterial density and thus trigger the secretion of proteins that lyse the host cell and allow the proliferation of the bacteria (Bien *et al.,* 2011). However, production of *S. aureus* virulence determinants are controlled by several global regulatory loci e.g. accessory gene regulator (agr), *Staphylococcus* accessory regulator (SarA), sae, sigB, arl and number of SarA homologues that are important in virulence gene expression in *S. aureus* (Bien *et al.,* 2011).

Pathogenicity of MRSA

The virulence of *S. aureus* is multifactorial because of the combined action of numerous virulence factors that facilitate tissue

adhesion, immune evasion, and host cell injury. The virulence of MRSA are not just unique to MRSA, nonetheless certain MRSA strains appear to contain particular factors or genetic background that enhance their virulence or enable them to cause particular disease (Gordon and Lowy, 2008). However, the most essential virulence determinant of MRSA is the ability to secrete different kinds of pyrogenic toxins known as superantigens; such as the Panton–Valentine leucocidin (PVL) and toxic shock syndrome toxin-1 (TSST1) which are found to be associated with MRSA virulence (Kong *et al.,* 2016).

S. aureus has numerous mechanisms to cause disease and to evade host defenses. However, Due to the variation found within strains of S. aureus, some stains are found to have the ability to resist phagocytosis, produce biofilms while others might not and also the type of toxins and adhesins produce by each strain may vary. The type of virulence factors associated with each strain may be related to genetic background and in some instances presence of these factors is unrelated to genetic makeup (Gordon and Lowy, 2008). In this regard, it is important to note that there is limited information on the expression of these genes during infection.

The pathogenicity of *S. aureus* is a multifaceted process involving different types of extracellular and cell wall components that are coordinately expressed during different stages of infection (i.e., colonization, avoidance of host defense, growth and cell division, and bacterial spread) (Bien *et al.,* 2011). The coordinated expression of various virulence factors in response to environmental condition during infections (e.g., expression of adhesins early during colonization or the production of toxins late in infection to facilitate tissue spread) shows that there is a regulatory element that controls the expression of these virulent factors. These regulators help bacteria to adapt to a hostile environment by producing factors enabling the bacteria to survive and cause infection at the appropriate time. The expression of these virulence factors is greatly affected by change in environmental condition such as the pH, nutrient availability, temperature, oxygen tension and osmolarity. (Bien *et al.,* 2011).

Adhesive Factors

S. aureus has several surface proteins referred to as the Microbial surface components recognizing adhesive matrix molecules (MSCRAMMs) that play an important role in facilitating the attachment of the bacteria to the host tissue (Gordon and Lowy, 2008). These MSCRAMMs are produce at the logarithmic growth phase and adhere to molecules such as collagen and fibrinogen and plays an important role in endovascular infections and none infections. MSCRAMMs also adhere to prosthetic devices, causing prosthetic device infections. Biofilm production of *S. aureus* is one of the factors that make *S. aureus* escape host defenses (Gordon and Lowy, 2008). Protein A, which is also part of the MSCRAMMs, is found in almost 90% of strains of *S. aureus* cell wall initiate platelet injury and hypersensitivity reaction, and also prevent opsonization (Gordon and Lowy, 2008; Arora and Arora, 2008). Cell wall associated factors associated with adherence and virulence of *S. aureus* include the following

i. Capsular polysaccharide: Strains of *S. aureus* that have capsule are more virulent than those without the capsule layer. The capsule contains an antigenic polysaccharide that prevents the bacteria from being phagocytized by polymorphonuclear white blood cells. Capsule also aid in adherence of *S. aureus* strains to host cells and prosthetic device (Arora and Arora, 2008).
ii. Teichoic acid: This is found in all strains of *S. aureus* and is an antigenic determinant, it promotes adherence of bacteria to host tissue and also prevent opsonization (Arora and Arora, 2008).
iii. Peptidoglycan: This is an essential part of the bacterial cell wall that provides rigidity and also elicits the production of immune response. It is also involved in several biological activities that promote

S. aureus virulence (Arora and Arora, 2008).

iv. Clumping factor: This is found on the surface of the bacterial cell wall and is associated with the clumping of bacteria when it comes in contact with plasma. It reacts with fibrinogen found in plasma, thereby causing agglutination (Arora and Arora, 2008).

Exoproteins

Exproteins are usually secreted by almost all strains of *S. aureus*, such as exotoxins and enzymes, including nucleases, proteases, lipases, hyaluronidase, and collagenase. The main function of these proteins may be to convert local host tissue into nutrients required for bacterial growth (Bien *et al.,* 2011).

a) Extracellular toxins: Most *S. aureus* strains are capable of producing toxins that help in penetrating the host cell or tissue and causing disease. Some of these toxins are cytolytic and help the bacteria to acquire nutrient from lysed cells. Toxins produced by *S. aureus* include, hemolysin, leucocidin, exfoliative toxin, toxic-shock syndrome toxin 1 (TSST-1) and enterotoxins (Kong *et al*., 2016).

i. Hemolysin: This type of toxin has the ability to destroy red blood cells. There are four types of hemolysin toxin they are alpha, beta, gamma and delta. These toxins differ from each other antigenically, their ability to destroy red blood cells of different animals and their leucocidal activity. Alpha toxin is found to be associated with most pathogenicity of *S. aureus* (Arora and Arora, 2008; Kong *et al.,* 2016).

ii. Leucocidin: Leucocidin is mostly associated with the destruction of leucocytes, i.e. lyses of the red blood cells. The leucocidins are found to have two components based on their ability to migrate on carboxymethylcellulose column, these components are referred to as the fast (F) and slow (S) components that acts together to destroy the red blood cells as well as the macrophages which leads to tumor necrosis. The leucocidins include the Panton-Valentine leucocidin (PVL) that is associated with community acquired methicillin resistant S. aureus (CA-MRSA) (Arora and Arora, 2008; Kong *et al.,* 2016).

iii. Exfoliatin Toxins: These are toxins that are capable of destroying the epidermal layer of the skin i.e. epidermolysis. There are two types of exfoliatin toxin or epidermolytic toxin, epidermolytic toxin type A and epidermolytic toxin type B. Epidermolytic toxin A, is produce due to the presence of the gene in the bacterial chromosome and is capable of withstanding heat. While epidermolytic toxin B is produce due to the acquisition of the gene on the bacterial plasmid and is easy destroy in high temperature i.e. does not withstand high temperature (Arora and Arora, 2008).

iv. TSST-1: Toxic-shock syndrome toxin-1 (TSST-1) is usually associated with *S. aureus* strain found in the vagina. TSST-1 initiates the production of cytokines such as the interleukins (IL-8 and IL-2) and tumor necrosis factor (TNF). The activation of these cytokines causes the inflammation and destruction of the mucosal cell membrane thereby enhancing the interaction of the T-cells with the TSST-1 which give rise to toxic shock (Kong *et al.,* 2016).

v. Enterotoxins: There are about eleven types produced by different strains of *S. aureus*. About 40-45 % of clinical isolates of *S. aureus* are found to produce enterotoxins that cause food poisoning. Enterotoxins are capable of withstanding high temperatures. Enterotoxins and TSST-1 are referred to as super antigens due to their ability to elicit the production of cytokines (Arora and Arora, 2008; Kong *et al.,* 2016).

S. aureus has also other specific proteins that can have profound impact on the innate and adaptive immune system. Examples of such kind of proteins are the Staphylococcal complement inhibitor (SCIN), Chemotaxis inhibitory protein of *S. aureus* (CHIPS), Staphylokinase (SAK), Extracellular fibrinogen binding protein (Efb),

Extracellular adherence protein (Eap), and Formyl peptide receptor-like-1 inhibitory protein (FLIPr). SCIN is a C3 convertase inhibitor, which blocks the formation of C3b on the surface of the bacterium and, thereby, the ability of human neutrophils to phagocytize *S. aureus*. CHIPS and FLIPr block neutrophil receptors for chemoattractants, Epa blocks migration of neutrophils from blood vessels into the tissue, SAK binds to α-defensins and eliminate their bactericidal properties, while Efb inhibits both classical and alternative pathways of complement activation (Bien *et al.,* 2011).

b) Extracellular enzymes: These are enzymes produced by the strains of *S. aureus* that are capable of destroying the host cells and tissue and preventing the bacteria against the host defenses and also allowing the growth of the bacteria in the host. There are three types of extracellular enzymes produce by strains of *S. aureus* that help in the pathogenicity of the bacteria. They are hyaluronidase, coagulase and staphylokinase or fibrinolysin (Arora and Arora, 2008; Kong *et al.,* 2016).

i. Hyaluronidase: This enzyme is found in about 90 % of *S. aureus* strains and is associated with the spread and proliferation of *S. aureus* from one position to another in its host. Hyaluronidase is capable of hydrolyzing hyaluronic acid found in the connective tissue of humans and is associated with the clinical manifestation of infection (Arora and Arora, 2008).

ii. Coagulase: This is an enzyme produced by most strains of *S. aureus*, it is secreted to the outside of the bacterial cell and is capable of activating coagulase-reacting factor (CRF) found in blood plasma, thereby causing the plasma to clot due to conversion of fibrinogen to fibrin. The enzyme coagulase is produced at the exponential growth phase of the bacteria. Detection of coagulase in the laboratory is very important in determining the pathogenicity of *S. aureus* (Arora and Arora, 2008).

iii. Staphylokinase (Fibrinolysin): This enzyme is produced by the strains of *S. aureus* that do not produce beta-lysin. Fibrinolysin has the ability to breakdown fibrin clots thereby promoting the spread of infection into adjacent tissues (Arora and Arora, 2008).

Pathogenicity Genes Of MRSA

Staphylococcus Cassette Chromosome *mec* (SCC*mec*)

Staphylococcal cassette chromosome *mec* (SCC*mec*) is a mobile genetic element found incorporated into the *S. aureus* chromosome. SCC*mec* contains the *mec*A gene that is responsible for methicillin resistance of *S. aureus* strains that contains the SCC*mec* (Chambers and DeLeo, 2009). SCC*mec* is an important genetic element for gene exchange among *Staphylococcus* specie. The SCC*mec* is a site-specific genetic element found integrated at a specific site in the *Staphylococcus* chromosome known as the bacterial chromosome attachment site attBSCC (Hanssen and Ericson Sollid, 2006). SCC*mec* consist of two parts known as the *mec* gene complex and *crr* gene complex. The *mec* gene complex consists of *mecA* gene; insertion sequence and regulatory gene while the *crr* gene complex consist of the *crr* gene and surrounding ORF's (Chongtrakool *et al.,* 2006). SCC*mec* is a variable genetic element with certain conserved features. Among the conserved elements, SCC*mec* contains the mec operon composed of *mecA* and its regulatory genes, as well as the cassette chromosome recombinase complex *ccr* (Plata *et al.,* 2009).

According to the international working committee on staphylococcal cassette chromosome element, there are 11 SCC*mec* types (I-XI) that are found to contain different genetic organization (Castro *et al.,* 2016; Otto, 2012).

SCC*mec* typing by sequencing the internal fragment of the recombinase gene as suggested by Oliveira *et al.* (2006) provides a good SCC*mec* typing as it provides information about the *ccrAB* allelic variation among strains sharing the same SCC*mec* but different genetic background, among SCC*mec* type IV strains and also the nature of the strains that are non- type able based on SCC*mec* (Oliveira *et al.,* 2006).

The first SCC*mec* element was identified in Japanese *S. aureus* strain, N315 in 1999 and shortly after two additional SCC*mec* from different MRSA strains were determined. Based on detailed structural analysis these three SCC*mec* elements were classified as types I to III. In time, both new types of SCC*mec* such as SCC*mec* IV, SCC*mec* V, SCC*mec* VI, SCC*mec* VII, SCC*mec* VIII, SCC*mec* IX, SCC*mec* X, SCC*mec* XI and many new variants of already known SCCmec types have been reported (Turlej *et al.,* 2011; Oliveira *et al.,* 2006).

With growing number of SCC*mec* types and sub-types or variants published in the literature it became obvious that without approved international rules of nomenclature system it would be difficult in the nearest future to keep in order suitable naming of new emerged SCC*mec* elements. To meet the urgent need the International Working Group on Classification of Staphylococcal Cassette Chromosome (SCC) Elements (IWG-SCC) was established in 2009. The main objective of the group was to define consensus rules of a uniform nomenclature system for SCC*mec* elements, determine minimum requirements for the description of the new SCC*mec* elements and establish guidelines for the identification of SCC*mec* elements for epidemiological studies (Turlej *et al.,* 2011). Hospital acquired MRSA (HA-MRSA) stains are usually SCC*mec* type I-III while the community acquired MRSA (CA-MRSA) strains are SCC*mec* type IV-VII (Plata *et al.,* 2009; DeLeo and Chambers, 2009; Kong *et al.,* 2016). The MRSA strains that carry SCC*mec* IV and sometimes SCC*mec* V are more virulent (Gordon and Lowy, 2008). SCC*mec* type IV and IV are smallest of the SCCs that confer methicillin resistance, and are generally susceptible to several non–β-lactam antibiotics. This is in contrast to the multidrug-resistant nosocomial MRSA strains that carry larger SCC*mec* types (Gordon and Lowy, 2008; Kong *et al.,* 2016). CA-MRSA that contains SCC*mec* type IV usually contains *pvl* gene, which makes them more virulent while MSSA and HA-MRSA that do not harbor the *pvl* gene (Gordon and Lowy, 2008; Vasconcelos and Cunha, 2010).

Staphylococcus Protein A (Spa)

Staphylococcus protein A (Spa) is a cell wall component found in *S. aureus* strains, the protein A gene has a polymorphic region designated as the X region located at the upstream of the region that encodes the cell wall binding sequences towards the c-terminal end. The X region has a variable number of repeats ranging from 21-bp to 27-bp (Narukawa *et al.,* 2009). Spa typing is a control measure developed to reduce the spread of infections due to MRSA by rapidly detecting the presence of MRSA in hospital community and outbreak investigations (Harmsen *et al.,* 2003).

The spa typing entails the sequencing of the polymorphic region in other to detect the relationship between MRSA strains and their geographical distribution. The spa typing is accurate, easy, fast and easy to understand and information can be shared from one laboratory to another, unlike the pulse-field gel electrophoresis (PFGE) also used to detect polymorphism and outbreak investigation of MRSA strains which is time-consuming and requires bacterial culture and very complicated (Narukawa *et al.,* 2009).

Panton Valentine Leucocidin (*pvl*) Gene

PVL is a bi-component toxin of the Staphylococcal beta-barrel pore-forming toxin family, which also comprise alpha-toxin, gamma toxin, and similar toxins. It is encoded by the *lukS*-PV and *lukF*-PV genes, which are located on a prophage. Similar to other leucocidins, PVL forms pores in the membranes of the leucocytes, which leads to their lysis (Otto, 2010).

Panton valentine leucocidin gene (*pvl*) is acquired by *S. aureus* through horizontal gene transfer and found mainly in CA-MRSA strains but absent from HA-MRSA strains (Turner *et al.,* 2019). Despite PVL systematic role in neutrophil lysis and an evident association with necrotizing pneumonia and soft tissue infection, subsequent studies in both animals and humans indicate that PVL is neither the sole nor primary determinant of MRSA infection severity (Turner *et al.,* 2019).

This exotoxin functions as a two-component pore-forming protein, encoded by the *lukF*-PV and *lukS*-PV genes, and acts as a leucocidin that can lyse the cell membranes of human neutrophils. Therefore, PVL is hypothesized to be responsible for the enhanced pathogenicity of CA-MRSA strains. The first clinical isolate known to carry the PVL genes in the CA-MRSA era was reported in 2003, and approximately 60% to 100% of CA-MRSA strains have been shown to carry these genes, which can spread from strain to strain by bacteriophages. However, although PVL has been closely linked to infections caused by CA-MRSA strains and shown to be instrumental in producing necrotic skin lesions and necrotizing pneumonia, it is not known with certainty how this toxin contributes to their fitness and or virulence (Kong *et al.,* 2016).

Although it has been speculated that determinants such as PVL encoded on mobile genetic elements (MGEs) have a predominant impact on virulence, recent reports seem to imply that the contribution of these MGEs to CA-MRSA virulence may be comparatively minor. In fact, based on genome comparisons and epidemiological data, findings from one study indicated that high expression of core genome-encoded virulence determinants such as the global virulence and quorum-sensing regulator (*agr*) rather than the acquisition of additional virulence genes, may have a more profound impact on the evolution of virulence. However, PVL was proposed to have an important role in defining the virulence gene expression pattern, which results in the increased virulence potential (Kong *et al.,* 2016).

Toxic Shock Syndrome Toxin-1 (tst) Gene

The toxic shock syndrome toxin-1 (TSST-1), encoded by *tst* gene, has been proposed to cause staphylococcal toxic shock syndrome (TSS) in a susceptible host (Zhao *et al.,* 2019). In a research conducted by Zhao *et al.* (2019), the results indicated that the *tst* gene was prevalent in MRSA this is in line with the study conducted by Mehrotra *et al.* (2000) which stated that *tst* gene is also found in 24.3 % of healthy individual and that *tst* gene can be present in healthy individual and is not always associated with virulence of MRSA, also *tst* gene is found more common than *pvl* gene among MRSA strains It has been repeatedly documented that 30 to 40% of the population is asymptomatically colonized by *S. aureus* strains at one or more of their body sites and approximate 20% of this organism is TSST-1 producer indicating a large disease potential (Zhao *et al.,* 2019).

Various environmental factors including glucose, oxygen, magnesium ions, α and β chains of hemoglobin, a range of antibiotics (e.g. nafcillin and clindamycin) and TSST-1 itself have been proved to influence the expression of TSST-1 (Zhao *et al.,* 2019). These environmental triggers affect TSST-1 expression via a large number of virulence regulators forming a complicated network in *S. aureus* (Andrey *et al.,* 2015).

The accessory gene regulator (*agr*) system and staphylococcal accessory regulator A (*SarA*) are the prominent factors that control TSST-1 production. *Sar*A affects *tst* expression through binding to a certain element in *tst* gene promoter. Other regulators controlling *tst* expression include sigma factor B (SigB), Staphylococcal respiratory response AB (*Srr*AB), Carbon catabolite protein A (*Ccp*A), *Sar*T, and repressor of toxin (*Rot*) (Andrey *et al.,* 2015). However, these regulators are only studied in several type strains, whether they take effects in clinical isolates remains unclear (Zhao *et al.,* 2019).

Accessory Gene Regulator (*agr*) Gene

The accessory gene regulator (*agr*) is a quorum-sensing system that plays a critical role in the regulation of staphylococcal virulence. It has been studied extensively and has been reviewed by Yarwood and Schlievert and Novick among others (Kong *et al.,* 2016). The *agr* mutants appear to have diminished virulence, and certain *agr* types are associated with particular clinical syndromes. Other important regulators include the staphylococcal accessory regulator, ArlR and ArlS, SaeRS, Rot, and mgr (Kong *et al.,* 2016). The agr system plays a central role in the pathogenesis of *S. aureus*, and its effector termed RNAIII has been shown to upregulate TSST-1 production (Zhao *et al.,* 2019).

Regulation Of Expression Of Virulence Factors Of MRSA

Regulation of expression of staphylococcal virulence factors plays a central role in pathogenesis. To reduce undue metabolic demands, expression occurs in a coordinated style only when required by the bacterium. The genes coding for virulence factors are regulated in a tightly coordinated manner that is synchronized with the biological cycle of *S. aureus*. The production of factors involved in virulence is controlled by quorum sensing mechanism. In *S. aureus*, genes coding for surface proteins are down regulated during early stages of the growth whereas genes that encode secreted proteins are up regulated in late exponential phase (Gordon and Lowy, 2008; Plata *et al.,* 2009). This pattern of gene expression in which surface proteins involved in adhesion and defense against host's immune system (protein A, coagulase, fibronectin binding proteins, among many others) are synthesized before production of secreted hemolysins, cytotoxins, proteases and other degradative enzymes seems to reflect a strategy of *S. aureus* in which the pathogen first establishes itself in the host and only then attacks it (Plata *et al.,* 2009; Zhao *et al.,* 2019).

This regulation is, in large part, due to the accessory gene regulator (*agr*) two-component system. The *agr* locus consists of two divergent transcription units RNAII and RNAIII driven by two promoters, P2 and P3, respectively. The P2 transcript, RNAII, contains four cistrons: *agr*A, *agr*B, *agr*C and *agr*D. The sensor, *agr*C, and the response regulator, *agr*A, comprise the two-component system that responds to auto-inducing peptide (AIP). This peptide is present in the extracellular environment and drives transcription from both P2 and P3 promoters. *agr*D encodes the auto-inducing peptide, which is post-translationally modified and secreted by *agr*B. The effector molecule of the agr system is a 514-nt transcript, derived from the P3 promoter, called RNAIII, which also carries the *hld* cistron that codes for delta hemolysin. RNAIII stimulates the expression of post-exponentially synthesized extracellular toxins and enzymes and represses synthesis of exponential-phase surface proteins. RNAIII acts primarily as an antisense RNA for translational activation of certain mRNAs or binds to the ribosome binding site in the case of repressed mRNAs, preventing ribosome binding and inducing fast mRNA degradation by endoribonuclease III (Plata *et al.,* 2009; Kong *et al.,* 2016; Zhao *et al.,* 2019).

CONCLUSION

The virulence of MRSA is due to actions of multiple virulent factors, and involves different processes that are coordinately expressed during infection. Possession of these virulent factors makes MRSA more virulent causing high morbidity and mortality rate in both Hospital and Community associated infections. Future efforts to understand MRSA should therefore focus on better insights into the complex interplay between host and pathogen and research that evaluate genomics, epigenetics, transcription, proteomics and metabolomics in carefully selected animal models, and finally in clinically well-characterized patients with diverse forms of MRSA, this will likely to provide insights into the drastically different forms of MRSA infections and their pathogenicity trends.

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