Review on Molecular Cross-talk of Biofilm Producing
Mechanisms of Staphylococcus aureus

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Abstract: Here the review converses the "molecular cross-talk" of biofuel production mechanisms for Staphylococcus aureus. Staphylococcus aureus is a leading cause of bacterial infections globally in both healthcare and community settings. The success of this bacterium is the of an expansive repertoire of virulence factors in combination with acquired antibiotic resistance and propensity for biofilm formation. S. aureus leverages these factors to adapt to and subvert the host immune response. With the burgeoning fields of immunometabolism, it has become clear that the metabolic program of leukocytes dictates their inflammatory status and overall effectiveness is clearing an infection. The treatment of S. aureus infections become complicated due to the capacity of S. aureus “multidrug-resistant” occurs because of biofilm formationon the surfaces depending on biotic and abiotic factors, genetic factors, and numerous environmental, which vary from species to species. A broad range of molecular phenomenon contributes a high range of recalcitrance that is insisting on the biofilm formation. The previous published literature illustrated that all strains of Staphylococcal sp. contain the “ica locus” and several can form biofilms in vitro condition. Absences of “ica locus” results diminish of capability to produce biofuels, along with "PIA gene", or mediate "N-acetyl glucosaminyl transferase activity" in vitro condition.

Keywords: biofilm formation, ica locus, molecular cross-talk, MSCRAMMs, PIA, PNAG, S. aureus

Introduction

Earlier in 1880 and 1882, Ogston confers for staphylococcal disease and its role in sepsis and abscess formation [1]. Beyond 100 years, Staphylococcus aureus still relics as a versatile organism causing nosocomial infection and as hazardous pathogen for humans. The staphylococcal infections amplified progressively in community and hospital, thus responsible for mortality [2]. Staphylococci tolerate dry condition and high salt concentrations. The staphylococci are divided into two categories, i.e. coagulase-negative and coagulase-positive depending on the production of coagulate enzyme. MSCRAMMs (Microbial surface components recognizing adhesive matrix molecules) may utilize by the bacteria to get attached to human’s cell-membrane and thereby escape from immunoglobulin, discovered by the human immune defense. MSCRAMMs can also mediate adhesion to human membrane plastics and other medical devices.

Bap gene has also been isolated from S. aureus strain and has found to participate in adhering to any surfaces as well as biofilm development phenomenon [3]. The first step of S. aureus pathogenesis is attachment and colonization (Figure 1). The Biofilm make bacteria to get resist organized high antimicrobial agents, concentration, environmental conditions and the host immune responses [4].
Updated research on bacterial biofilm formation and the mechanisms

Valle et al told that SarA stimulate biofilm formed by both enhancing the ica operon transcription (Figure 2) and suppressing the transcription of proteins implicated in the proceeds of PIA/PNAG or repressing its synthesis, whose expression would be B-dependent [5] (Figure 3).

O’ Gara [6] demonstrated that the role of icaADBC-encoded PIA or PNAG in Staphylococcal biofilm development, that had open to understand the pathogenicity of device-related bacterial infections. The Teichoic acid is a copolymers component of Gram-positive bacteria such as S. epidermidis biofilm matrix and therefore the major cyto-membrane autolysin plays a vital role within the primary attachment section of biofilm production, whereas the cell surface biofilm-associated macromolecule and accumulation-associated macromolecule square measure capable of mediating alive obsession accumulation. These findings raised, the exciting prospect that alternative surface proteins and performance is as matter determinants or binding to living thing matrix proteins, might also act as biofilm adhesions.
**Figure 3.** Genomic representation of the ica operon and surrounding sequence in *S. aureus*

**icaADBC dependent biofilm forming pathway in recombinant strains of *S. aureus***

Arana et al. evaluated that Hussain-Hastings-White modified [HHWm] medium determined the factors that reduce the formation of biofilm process by mutagenesis and *S. aureus* biofilm strain systematic disruption. The arlRS mutant showed the PNAG participated in primary attachment and gathering process in biofilm formation. Biofilm formation is done with the help of arlRS mutant that unable to show any changes [7].

*Bap* surface protein occupied, while biofilm development in *S. aureus* strain, that is isolated from chronic mastitis infections. In this study, *Bap* orthologue genes were isolated from many coccus species, i.e., *S. chromogenes*, *S. simulans*, *S. xylosus*, *S. epidermidis*, and *S. hyicus*. However, flanking region sequence analyses discovered that the *Bap* factor of those species wasn’t contained within the SaAPI bov2 pathogenicity island. Even though they didn't contain *icaADBC* deoxyribonucleic acid, all the coagulase-negative coccus isolates harboring *Bap*, were robust biofilm producers. Annoyance of the *Bap* factor in *S. epidermidis* eradicated its ability to provide biofilm, while the heterologous complementation’s of biofilm-negative strain belongs to *S. aureus* with the *Bap* super-molecule from *S. epidermidis* bestowed the capability to make a biofilm on a phenyl ethylene surface. In general, the outcomes reveal that *Bap* orthologues from “coagulase-negative” Staphylococci trigger a different mechanism for the formation of biofilm, independent of “PIA/PNAG exopolysaccharide” [8].

*SarA* mutants unable to synthesize *Bap*-dependent biofilm due to an *agr*-independent mechanism. However, *Bap* promoter characterized, through applying rapid amplification of c-DNA ends technique the transcriptional start point was mapped. Trotonda et al demonstrated that *SarA* signified the regulation of the biofilm formation process within *S. aureus* strain. This study proved that in present of *SarA* clone biofilm development was decreased in presence of *SarA* mutation [9].

Sambanthamoorthy et al. explored the *S. aureus* as an important nosocomial bacterium that have competence for biofilm formation because of *SarA* gene. *SarA* gene plays vital part in the formation of biofilms process and further known as msa gene. It was necessary for controlled the virulence factors and showed *SarA* expression. Here msa gene decreased the expression of *SarA* gene for biofilm development and mutant of msa formed a weak and unstable biofilm whereas, also analysed that bacterial biofilm formation mechanism at the molecular level is complex process and environmental factors and some independent regulators played significant part in the development of assembly of *S. aureus* strain on nature. Sambanthamoorthy also concluded that msa gene is a necessary protein in biofilm formation process like *SarA* gene [10].

Tsang et al. shown that a mutant of *SarA* decreased the biofilm forming capacity, however on the basis of mechanism, the functions are not known yet and also reported that identical genes had participated in biofilm formation [11]. The *SarA* gene engaged in synthesis of nucleolytic and proteolytic exoenzymes, acid tolerance. The inability of mutant repeatedly expresses independent production of extracellular nuclease and multiple proteases, however, gathered effects contributes in the biofilm -deficient phenotype of *SarA* mutated *S. aureus*. This study suggests that the reduced capability of *SarA* mutant creates a biofilm, involves proteases that are serine, amino acid and metalloproteases. Inclusion of enzyme inhibitors conjointly increased biofilm formation in a very *SarA/muc* mutant, with the
combined result of mutating *nuc* and adding enzyme inhibitors leading to the formation of biofilm by means of *SarA* mutant, approached that of UAMS-1 parent strain.

Memmi et al. considered that lysis plays a necessary role in the microorganism biological process and lactam antibiotics. *arlRS* gene, by two part restrictive systems that showed the negatively regulated lysis in MSSA strains that is masculine-sensitive. The study evidenced that the inactivation of "*arlRS*" does not lysis the MRSA strains that were methicillin-resistant. In contrast with MSSA strains, Newman, SH1000, RN6390, and 8325-4, lysis was plagued by *arlRS* gene. Memmi again determined that the hanging characteristic function of *arlRS* gene between MSSA and MRSA strains are not because of the penicillin resistance determinant *mecA* gene.

| Table 1. Comparison between MRSA and MSSA strains regarding biofilm formation |
| S. No | MRSA strain | MSSA strain |
|-------|-------------|-------------|
| 1     | Biofilm formation in the main factor controlling MRSA is surface adherence. which repressed under *agr* expression [15] | In MSSA, the creation of biofilms is more reliant on cell-to-cell adhesion by icaADBC-encoded PIA/PNAG or slime [15] |
| 2     | Multilocus sequence typing using five key genes (MLST) clonal complexes (CCs), i.e. CC5, CC8, CC22, CC30 and CC45 contributes to the biofilm formation under physiologic glucose concentration [16] | (MLST) clonal complexes (CCs), i.e. CC1 contribute to the biofilm formation [17] |
| 3     | MRSA strain shows dry crystalline s(rough) morphology (slime producing positive), near about 0% [15] | MSSA strains show a deviant, dry crystalline (rough) morphology (slime producing positive), near about 14% [15] |
| 4     | MRSA strain was tested positive (*mecA*) for the MRSA-specific *mecA* gene, by real-time multiplex PCR [18] | MSSA strain was tested negative (*mecA*–) for the *mecA* gene |
| 5     | MRSA biofilm growth involves protein adhesions controlled by SarA and Agr and is ica independent [15] | *SarA*-regulated PIA/PNAG plays major in MSSA biofilm development [15] |
| 6     | NaCl activated biofilm development shows the minor biofilm matrix in MRSA isolates responded to NaCl [15] | NaCl activated biofilm development show the major biofilm matrix in MSSA isolates responded to NaCl [15] |
| 7     | 1 percent glucose supplement was added to BHI medium, the biofilm matrix is minor on MRSA clinical isolates [15] | 1 percent glucose supplement was added to BHI medium, the biofilm matrix is major on MSSA clinical isolates [15] |

*icaADBC* independent biofilm forming pathway in recombinant strains of *S. aureus*

Fitzpatrick et al. investigated that clinical isolates of staphylococcal species, *icaADBC*-encoded PIA or PNAG enzymes play a vital role in biofilm formation mechanism [17]. By clinical isolates of MRSA strain, environmental factors don't continually contribute for the increment of the biofilm formation method, but in clinical isolates of MRSA due to addition of aldohexose thus shows *icaADBC* freelance pathway. According to Fitzpatrick, *ica* operon are not necessary for the formation of biofilm on BHI media, however it revealed that the *ica* locus was necessary for biofilm formation in clinical isolates of *S. aureus*. In this study, Fitzpatrick concluded the control of biofilm phenotype phenomenon for clinical isolates staphylococci species by regulatory mechanisms.

Boles and Horswill [18] revealed that the *agr* protein was the essential factor of *Staphylococcus aureus* that participated in quorum-sensing system and *icaADBC* mediated biofilm formation pathways. Recent study discusses about the role of *agr* mutants in *agr* system of *S. aureus* biofilm formation, cells dispersing from biofilm have been showing an active *agr* system. Boles and Horswill discussed the involvement of *S. aureus* bacterium in the formation of biofilms via both mechanisms that was *ica* dependent and/or *ica*-independent.

O’Neill et al. evaluated the biofilm development in MRSA follows the *icaADBC* independent pathway [19]. In MRSA, biofilm development is encouraged by acidic growth medium condition and
triggered by adding glucose into the growth medium. If mutations incorporated in fnbA and fnbB proteins of MRSA, they reduced the biofilm formation process; however, these mutants have no effect on the MSSA biofilm formation. FnBP had not confirmed any relationship in the primary attachment of biofilm, however, encouraged at intercellular accumulation level. FnBP furthermore encouraged the biofilm formation that’s completely dependent on SarA besides this does not show any effect on fnbA or fnbB transcription. S. aureus biofilm formation gets optimized with fnbA and fnbB proteins, showed their independent pathway for known ligand binding activities of the multifunctional surface proteins. The study illustrated that extracellular matrix binding proteins fnbA and fnbB of S. aureus participated in intracellular accumulation and biofilm formation. The implanted surgical and medical biomaterials are coated through a film. These films contain extracellular matrix proteins like- fibronectin. In MRSA virulence factors are cell wall- anchored proteins.

Houston et al. determined the atl protein role in the formation of ica-independent biofilm pathway within S. aureus [20]. The studies evidenced the role of actual protein for biofuel production on hydrophilic polystyrene substance and therefore provided an excellent surface for cell attachment and growth. In this study, they determined the role of sigma factor sigB that decreased the extracellular protease production and RNAIII expression with the help of FnBP. A sigma factor didn't play any role in PIA-dependent biofilm development. The Mutant agr locus macromolecule participated to increase the FnBP-dependent biofilm formation, whether the SarA mutation, that encourage the production of proteinase and closed to their biofilm development function that was mediated by FnBP. For a second time Houston analyzed the regulation of atl gene, every time atlR enhanced the autolysin process and atlR::Tcr mutation in BH1CC increased biofilm-forming capacity. Throughout the study, Houston accomplished that atl macromolecule is essential for the early stage of "FnBP-dependent" S. aureus biofilm phenotype for autolysin. Here Houston accomplished the role of atlR protein, agr protein, SarA protein and sigB proteins for biofilm formation in S. aureus and involvement of atl protein in initial attachment and release of eDNA at initial stages of biofilm development via ica-independent and FnBP-mediated process. The atl act as primary attachment for substance along with the assistance of macromolecule lysis through the cell lysis, eDNA release, and initial cell accumulation during the development of a biofilm and while maturation, "FnBP's" played an essential role.

Lei et al. determined that the biofilm formation method in S. aureus MW2 strain behaved as a virulence factor [21]. The development of Biofilms may be a complex process that includes polysaccharide, protein, and elements of DNA that was maintained by various control factors. In S. aureus MW2 strain, Rsp repress the steps involve in biofilm formation, thus reveal attachment and biofilm formation process through the gene fnbA. The conclusion of the study illustrated that S. aureus formation of biofilms and their regulations, both were very complicated method because of association of multiple elements throughout development that was enclosed to the sugar, proteins, and extracellular DNA. All through this work, Lei accomplished that the family regulators involved AraC/XylS factors, whereas Rsp sequence inhibits the biofilm formation in S. aureus MW2 strain.

Bose et al. said that the most specific murrain hydrolase of S. aureus encoded by AtlA gene and by proteolytic cleavage of bifunctional enzyme, two catalytically active proteins were obtained, i.e. amidase (AM) and glucosaminidase (GL) [22]. Most studies summarize the combined functions of the proteins for metabolic activity of cell wall and biofilm formation. Through this study, Bose discovered derivatives of mutant for clinical isolate of S. aureus strain and UAMS-1, where single or even both AM and GL domains of AtlA gene have been deleted. After these strains were studied, it was discovered that each mutant had growth rates similar to those of the parental strain. However, express clumping phenotypes and lysis profiles distinct from the parents and offspring strain thus suggesting the distinct roles in cell wall metabolism. Bose analyzed the activity of the mutants for biofilm assays and found that both proteins were dominant for biofilm development, together with the function of analysis that release genomic DNA for synthesizing biofilm matrix molecules. Moreover, the application of enzymatically inactive point mutations uncovered the catalyst activity of both the proteins in biofilm formation in S.
The study makes insight relative contributions of the above studied both proteins in *S. aureus* and determine the development of biofilm via Atl-mediated lysis.

Pozzil et al. illustrated that the biofilm phenotypes were supported by autolysin of cell wall and a binding protein called fibronectin as well as the *icaADBC*-encoded PIA/PNAG were also illustrated from clinical isolated of *S. aureus* [23]. The process of Biofilm formation in MSSA strain was dependent on PIA/PNAG however, in isolates that were MRSA express an *atl/FnBP*-mediated biofilm phenotype revealed correlation between process of biofilm synthesis and susceptibility for β-lactam antibiotics. The *S. aureus* causes nosocomial infections that reported universally and express function i.e. resistance organized antibiotics, production of enzymes and toxin, biofilm forming and capacity of immune evasion. Puzzle explained that MSSA was more preferred to form PNAG-dependent biofilm rather than MRSA isolates that produce biofuels, which was *atl/FnBP*-dependent and thus explained the roles of the methicillin susceptibility affects the expression of biofilm.

**Interactions between *icaADBC*-dependent and -independent proteins biofilm forming pathways in recombinant strains of *S. aureus***

Cramton et al. evaluated that the nosocomial infections due to hospitalization because of the formation biofilm on the biomedical implant surfaces, causing sepsis by colonization of *Staphylococcus* species [24]. Biofilm process involves 2 steps: first is cell-cell adhesion and second is the multiple layer formation. Through this work, *icaADBC* locus, which is involved in the formation of extracellular polysaccharide adhesion termed PIA or PNA enzymes and that having a linkage UDP-N-acetylglucosamine *in vitro* condition had been analyzed. The researchers placed an interesting about all the *Staphylococcus* species have *icaADBC* locus, able to developed biofilm *in vitro* condition (Figure 4). *S. aureus* and *S. epidermidis* are gram-positive cocci and able attach with biomedical surfaces for developing biofilm and thus concluded that both the species formed biofilm in 2 steps, i.e. cell to cell adhesion because of *ica* operon and capable of PIA production and development of biofilm *in vitro* condition. The Cramton also accomplished that *S. aureus* bacteria caused nosocomial infections in the human being and shows the high death and morbidity rates as well as spread high frequency of infection by both *S. aureus* and *S. epidermidis* strains by means of *ica* gene.

![Figure 4. *icaADBC*-dependent and -independent pathway-associated proteins](image-url)

Cramton et al. determined that *S. aureus* and *S. epidermidis* strains formed the biofilm via operon "intercellular adhesion" (*ica*) and formed a linear β-1,6-linked glucosaminylglycan [24]. For assembling biofilm steps, cell to cell adhesions are needed in order so that biofilm method will increase the resistance and virulence nature in both strains. Through the work, Cramton additionally concluded that *icaADBC*-encoded PIA/PNAG enzymes contributed the necessary role in the biofilm formation under anaerobic conditions. Cramton accomplished the development of the biofilm technique's molecular cross-talk, which acts as a virulence factor in an anaerobic environment *in vivo* conditions, was facilitated by
icaADBC-encoded (PIA/PNAG) enzymes. Throughout this manuscript, Cramton said that anaerobic surroundings, conditions affected the involvement of new genes in biofilm development [25]. All staphylococcus stains having bap proteins are capable to form a high adhesion power for biofilm development. In mouse, determined chronic infection was caused due to bap protein. In S. aureus strain, ica locus formed the PIA-PNSG for biofilm development. In this result, Cucarella concluded the correlation between BAP-PIA-PNSG and found that both strains bap\(^+\) and bap\(^-\) produced the PIA-PNSG enzyme. Cucarella discovered the new specific types of proteins from S. aureus that is known to us as bap, which was involved in biofilm formation and grow on artificial medium. These proteins participated in attachment of both types of species.

Gross et al. determined the role of clinical isolates of S. aureus played for attachment to artificial surface, i.e. implanted biomedical devices [26]. However, the mechanism for primary attachment to biomedical devices is unknown. Gross accomplished that electrostatic forces reduce the process of biofilm development in clinical isolates of staphylococcal species and teichoic acids involve pre-dominantly in the initial step of biofilm synthesis and/or colonization on medical devices.

Cucarella et al. carried out a study over a period of 3 months at Cardenal Herrera-CEU University, Spain and accomplished that S. aureus is a frequent reason of nosocomial infectious and intramammary infectious diseases in human-being and bovine animals that often become chronic and allied with the capacity to produce biofilm by bacteria [25]. Here, cucarella illustrate a correlation to produce chronic bovine mastitis and the formation of biofilm. Cucarella divided the bacteria “S. aureus (bovine mastitis)” into 3 groups, based on their genetic elements. The group 1 includes ica\(^+\) bap\(^+\), group 2 includes ica\(^-\), bap\(^-\), and group 3 includes ica\(_-\), bap\(_-\) respectively. Cucarella discovered that bap gene were identified on the basis of structure. Cucarella accomplished that intramammary gland presents in a bovine body that occupied a significant role in the biofilm development in S. aureus. The study concluded that bovine mastitis disease emerged due to biofilm formation in S. aureus strains and bap is the most imperative gene for that phenomenon.

Resch et al. screened that the bacteria synthesize biofilm confirmed the extreme resistivity against compared to their planktonic counterparts, antibiotics and the immune system and elucidate that biofilm cells showed different metabolic activity [27]. Resch implicated that staphylococci species bacteria protected themselves from pigmentation formation on exposing to UV- radiation and radical’s in vivo condition. According to Resch, SsaA is a staphylococcal secretory antigen that contributes in disease related to biofilm and anti-SsaA immunoglobulin G antibody are often present in human serum of S. epidermidis strain, which was endocarditis. Research explained that S. aureus stain gene is essential for detoxification procedure of reactive oxygen species (ROS) and thus illustrated expression at higher levels in biofilm cells.

O’Neill et al. determined that the pathway of staphylococci species was formed i.e. dependent or independent, and form via icaADBC-encoded PIA/PNAG [19]. Here, O’Neill illustrates that methicillin is essential for the phenotype of biofilm in S. aureus strain. O’Neill again described the roles of icaADBC-encoded PIA/PNAG in MRSA and MSSA stains for the process of biofilm formation. O’Neill concluded that biofilm formation in MRSA strain is due to the ica independent pathway and the pathway is governed by SarA and agr proteins but in MSSA strain biofilm formation is governed by SarA.

Tu Quoc et al. investigated that S. aureus produces the biofilm and the colonization using this mode facilitates infections, is very complicated to treat and confirm high morbidity and mortality [28]. To create an international mutant library, they exploited bacteriophage Mu transposition methods for highly biofilm-forming S. aureus clinical isolate. In S. aureus and S. epidermidis both strains have the capacity to form biofilm due to PIA and produced by icaADBC operon having insertions. The S. aureus S30 strain of clinical isolates are collected from a Geneva hospital that caused various serious diseases due to the formation of biofilm in human-being. Disruption of Em-Mu in icaADBC demonstrated the utility
of PIA by obtaining a high proportion of independent, for biofilm development in this clinical isolates of S. aureus strain and express the strong validation for procedure of screening, which concomitantly uncovered additional mutants. The strain was explored as a model for identification of genes, which involved in major role in biofilm production. In this study, Tu Quoc concluded that Em-Mu insertions were presented in only 2 factors i.e. fmtA and atpF. These factors didn't show any relationship among WTA staining technique and mutants of the above factors for production of Teichoic acid wall.

Schroeder et al. demonstrated that Staphylococci species are leading causes of implant-associated infections universally, as its colonies formed on implanted medical devices [29]. Bacteria attach to the surface of a medical device to multiply and build up into multilayered cell clusters known as biofilms. The biofilm formations were also mediated by carbohydrate and macromolecule. It was accomplished that S. aureus have "specific surface protein factor (SasC)" that participated in aggregation of cell, same colonization-related biofilm formation and facilitate the accumulation in infected bacterium. Through this study, Schroeder accomplished that nosocomial isolated organisms are associated with biofilm forming process with artificial surfaces, owing S. aureus and "coagulase-negative" staphylococci illustrating the high rates of morbidity and mortality.

Gruszka et al. observed the both S. aureus and S. epidermidis are capable to formed an assembly like structure, called biofilms artificial surfaces and thus cause the infections that affect worldwide peoples and cause morbidity as well as mortality [30]. Because of resistance against antibiotics and device removal, biofilms are commonly needed to resolve the infection. Thus, they were needed to grow new therapies and molecular information, to assist. Accumulation-associated supermolecule (Aap) and Surface proteins (SasG) promote the biofilm formation of S. epidermidis through "B" regions. “B” regions contain tandem array of “G5 domains” about fifty residue sequences (referred to as E here) are dotted throughout, and it has been suggested that these sequences may act as a mediator of intercellular accumulation via Zinc$^{2+}$-mediated homodimerization. Although unstructured E areas are predicted, SasG and Aap form extensive fibrils on the surface of the bacterium.

**Conclusions**

The Gram-positive S. aureus nosocomial pathogen that is connected to infection related to medical implants. The stage of cell to cell adhesion is mediated by the bacterial species in biofilm development process and considered as a complicated phenomenon. Around 80% diseases had cause due to biofilm formation on medical devices. The review article established that some mutant i.e. SarA, ica, agr, fnbA, fnbB, arlRS, sigB, and sarZ etc participating in adhesion to any surfaces and biofilm forming Staphylococcus bacterial species. The ica locus is a crucial target of potential therapy for the avoidance of persistent infections linked to prosthetic medical devices because due to the substantial morbidity and mortality brought on by S. aureus infections in addition to the rate of infection via both species. A more complete understanding in molecular cross-talk of biofilm producing mechanisms will lead the development of novel therapies to understand biofilm formation.

Future prospects: Biofilms are understood as bacterial communities that adhere to surfaces by encasing into a self-produced extracellular polymeric matrix. The staphylococcal biofilm matrix may contain exopolysaccharides and proteins as well as extracellular (e)DNA. A more complete understanding in molecular cross-talk of biofilm producing mechanisms will lead the development of novel therapies to understand biofilm formation.

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