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A REVIEW ON BACTERIAL BIOFILM FORMATION AND DISASSEMBLY

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ABSTRACT: The *icaADBC* gene was first identified in *Staphylococcus epidermidis*, and is also present in *Staphylococcus aureus* and other *Staphylococcal* species. PIA is produced by the gene products encoded by the *icaADBC* operon. Asymptomatically colonized patients and health care workers are the major sources of MRSA in the hospital environment. MRSA-infected patients in burns units are particularly problematic because the big surface area of denuded skin can produce a large inoculum of organisms that can be easily transmitted to other patients via the hands of health care workers. Extensive skin lesions also result in heavy shedders of MRSA. Clinical isolates of *Staphylococcus aureus* can express the *icaADBC*-encoded polysaccharide intercellular adhesin/poly-N-acetylglucosamine (PIA/ PNAG). The *icaADBC* dependent and independent pathways will be stimulated using different chemicals and level of biofilm formation as well as PIA/PNAG level will be assayed. Besides, proteomics and transcriptomics analysis will be performed to get insights in the interaction of various factors of the pathways involved in the biofilm formation in wild type as well as mutant strains. The biofilm development in MRSA is *ica* independent and involves a protein adhesin(s) regulated by *SarA* and *agr*, whereas *SarA*-regulated PIA/PNAG plays a more important role in MSSA biofilm development in *ica* dependent pathway. This will lead to the establishment of a comprehensive interactome of biofilm formation.

INTRODUCTION: Bacterial biofilms are important topic interest for hospital related infections. Clinical isolates of *Staphylococcus aureus* plays an important role for the attachment on artificial surface i.e. implanted biomedical devices causing bacterial biofilms.

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Bacterial biofilms mostly caused by *Staphylococcal aureus* or *Staphylococcus epidermidis* results in colonization on biomedical implants and subsequent sepsis. However biofilm formation is not restricted to *Staphylococcus* species.

The phenomenon has been observed in different other bacterial species, including *Streptococcus gordonii* [1], *Escherichia coli* [2], *Pseudomonas fluorescens* [3] and *Pseudomonas aeruginosa* etc. Bacterial biofilms can be defined as an assemblage of microorganisms which can attach to any type of surfaces and subsequently get covered by an extracellular polysaccharide matrix.

Henrici was the first to observe bacterial biofilm formation in 1933 as he found that water bacteria doesn't grow in a free floating form but attached to a submerged surface. Bacterial biofilm formation is a two-step process involving attachment of bacteria to substrate surface followed by formation of multiple layers of biofilm due to cell-cell adhesion [4-6] is shown in **Figure 1.**

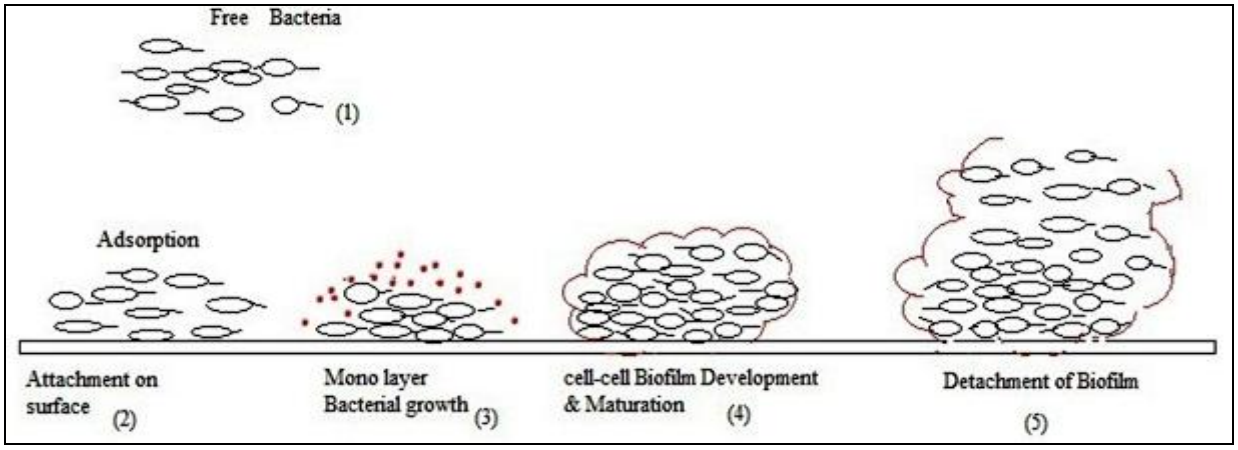

FIGURE 1: MODEL OF BIOFILM FORMATION

Bacterial teichoic acids play important role in initial step of biofilm formation or colonization on medical devices like- Artificial surfaces. Molecular mechanisms underlying the bacterial biofilm formation is complex and variations exist in among different strains. Since the last two decades, various surface proteins, extracellular proteins, capsular polysaccharides, adhesin (PSA) and autolysins are found to be involved in regulation of biofilm development. Different bacterial mutants have been collected for the last two decades and the functions of the genes have been identified as listed in **Table 1.**

TABLE 1: FUNCTION OF THE MUTANT GENES INVOLVED IN BIOFILM FORMATION OF DEPENDENT AND INDEPENDENT PATHWAYS OF *S. AUREUS* STRAINS

S. No.	Mutant involved	Biofilm forming genes present in other species	Function
1	*SarA* mutant (Staphylococcal accessory regulator)	*Homo sapiens* *Drosophila melanogaster* ***Staphylococcus aureus MRSA252*** *Streptococcus gordonii*	Reduced capacity to biofilm formation *in vivo* [13]
2	*ica* mutant (Intracellular adhesion)	*Homo sapiens* *Drosophila melanogaster* ***Staphylococcus aureus MSSA476*** *Mus musculus*	No effect on biofilm formation by MRSA strain & colonized the substrates [13]
3	*agr* mutant (Accessory gene regulator)	*Agrobacterium tumefaciens str. C58* *Bordetella bronchiseptica RB50* *Rhizobium etli CFN 42* *Rhizobium leguminosarum bv. trifolii WSM1325*	1. Increased biofilm [20] 2.Decreased levels of the RNAIII-encoded toxin [17]
4	*fnbA* mutant (Fibronectin binding protein A)	***Staphylococcus aureus subsp. aureus MRSA252*** ***Staphylococcus aureus subsp. aureus MSSA476*** ***Staphylococcus aureus subsp. aureus M013*** ***Staphylococcus aureus subsp. aureus COL***	Reduced biofilm formation by MRSA strains [17]
5	*fnbB* mutant (Fibronectin binding protein B)	***Staphylococcus aureus subsp. aureus MSHR1132*** ***Staphylococcus aureus subsp. aureus MRSA252*** ***Staphylococcus aureus subsp. aureus MW2*** ***Staphylococcus aureus subsp. aureus MSSA476***	Reduced biofilm formation by MRSA strains [17]

6	*arlRS* mutant (Autolysis-related locus)	*Staphylococcus aureus* *Bacillus thuringiensis* *Vibrio cholera* *Pseudomonas putida*	Showed increased initial attachment as well as increased accumulation of poly-*N* acetylglucosamine (PNAG) [10]
7	*sigB* mutant (Alternative transcription factor)	*Listeria monocytogenes* *Staphylococcus aureus* *Ricinus communis* *Glycine max*	Modulating the expression of virulence determinants in *S. aureus* [28]
8	*cidA* mutant	*Staphylococcus aureus subsp. aureus NCTC 8325* *Staphylococcus aureus subsp. aureus M013* *Staphylococcus aureus 04-02981* *Bacillus cereus F837/76*	Reduced capacity for biofilm adherence compared to wild-type [29]
9	*atl* mutant (autolysin)	*Homo sapiens* *Staphylococcus aureus* *Escherichia coli* *Salmonella enteric*	Cell lysis during biofilm development[30]
10	*msa* mutant (Modulator of *sarA*)	*Homo sapiens* *Homo sapiens* *Staphylococcus aureus* *Glycine max*	Formed weak biofilm formation due to a reduction in *SarA* expression [9]

Broadly the mechanisms of bacterial biofilm formation can be classified into two groups i.e. the biofilm formation via *icaADBC* dependent pathway and *icaADBC* independent pathways shown in **Figure 2.**

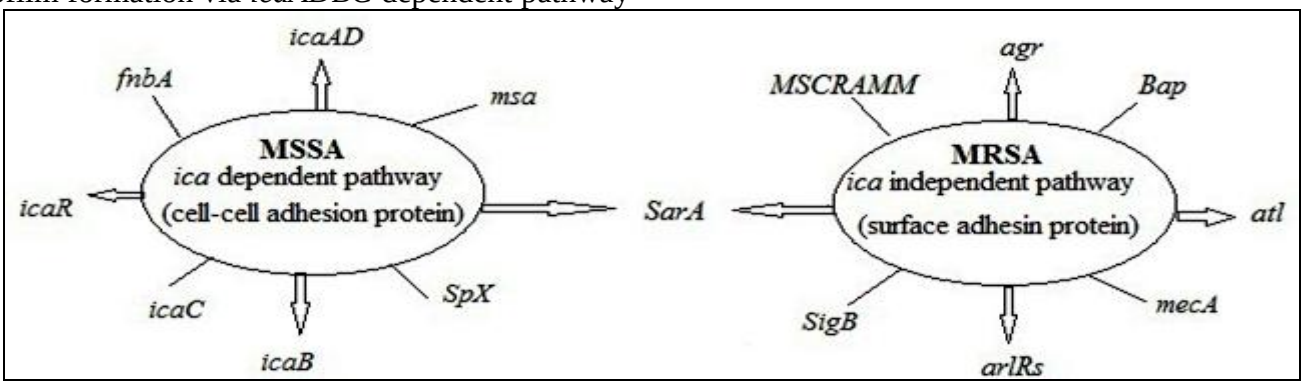

FIGURE 2: REPRESENTATION OF PROTEINS INVOLVED IN *icaADBC* DEPENDENT PATHWAY AND *ICAADBC* INDEPENDENT PATHWAYS

The *icaADBC* locus is found to be the major factor responsible for the bacterial biofilm formation via *icaADBC* independent pathway. The *icaADBC* locus is involved in formation of extracellular polysaccharide adhesion termed polysaccharide intercellular adhesion (PIA) or polymeric N-acetyl glucosamine (PNAG).

Both *S. aureus* and *S. epidermidis* which are gram-positive cocci bacteria have capacity to attach with biomedical surfaces for the development of biofilm phenomenon. Both of the species forms biofilm in 2 steps i.e. cell-cell adhesion due to ica operon and have capacity to produce PIA and develop biofilm in vitro condition enzymes, that having a linkage UDP-N-acetylglucosamine *in vitro* condition [7].

The high level of morbidity and mortality caused by Staphylococcus found in human being is due to the high frequency of infection by both *S. aureus* and *S. epidermidis* strains with the help of *ica* gene locus and it is found that all Staphylococcus species have *icaADBC* locus that have capacity to developed biofilm formation *in vitro* conditions.

icaADBC-encoded polysaccharide intercellular adhesin or poly-*N*-acetylglucosamine (PIA/PNAG) enzymes contributed important role for production of biofilm phenomenon in anaerobic conditions in both *Staphylococcus aureus* and *Staphylococcus epidermidis*, thus *icaADBC*-encoded (PIA/PNAG) enzymes promoted the production of the molecular cross-talk of biofilm process and they as a

virulence factor in an anaerobic environment condition in vivo (natural medium) [8]. The exact role of poly-*N*-acetylglucosamine (PNAG) was identified in *arlRS* mutant who showed that PNAG participated in both process of primary attachment and gathering of biofilm formation. The authors used Hussain-Hastings-White modified medium [HHWm] for determining of those factors that decrease the biofilm formation process in presence of mutagenesis and systematic disruption S. *aureus* biofilm strain. Biofilm formation is done with the help of the *arlRS* mutant then do not shows any changes, if *icaADBC* gene are present in this process, that report shows exopolysaccharide PNAG is not participated in biofilm formation in HHW medium [9].

One of the major factors identified in bacterial biofilm formation is the *SarA* protein. This protein is found to play an important role in biofilm development. *SarA* protein also known as *msa* protein and it is necessary for controlled the virulence factors and showed *SarA* expression. Reduced *msa* gene expression resulted in reduced *SarA* gene expression in biofilm development steps [10]. Also the *msa* mutant is found to form a weak and unstable biofilm. The molecular mechanisms underlying the bacterial biofilm formation is complex and some independent regulators and environmental factors are play important role in development of assembly of *S. aureus* strain in nature. Both *msa* and *SarA* genes are play important role as a regulator of biofilm formation process of *S. aureus* strain [11-13].

Another representative member involved in *icaADBC* independent pathway is the *Bap* protein *bap* protein present in *Staphylococcus aureus* surface contributed in biofilm development process and recognized the new genes that involved in biofilm development. All staphylococcus stains have *Bap* protein, having capacity to formed high adhesion power for formation of biofilm process.

In this result, authors concluded the relationship between BAP–PIA-PNSG and find out Bap^{+} and Bap^{-} proteins by both strains produced the PIA-PNSG enzyme. *Bap* protein is involved in biofilm formation on artificial medium providing a role of attachment [14]. One another interesting is the *agr* protein of *Staphylococcus aureus* which participate in quorum-sensing system and *icaADBC* mediated biofilm forming pathways as well as that protein improved the virulence factors expression power in auto-inducing peptides (AIPs) or glucose depletion triggers detachment [15].

Although *icaADBC* dependent pathway consist of the major mechanisms of bacterial biofilm formation, however parallel mechanisms do exist for bacterial biofilm formation. In clinical isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) strain, environmental factors do not always contributed for the increment of the biofilm formation process, however it is major mechanism of bacterial biofilm formation in clinical isolates and MRSA biofilm formation due to added of glucose in medium then it showed *icaADBC* independent pathway [16].

Thus, although biofilm formation in clinical isolates of the biofilm formation is independent phenomenon of *ica* operon as suggested by the authors however on BHI medium it is not essential. This result concluded that the regulatory mechanisms controlled the biofilm phenotype phenomenon of clinical staphylococcus species. In this study authors concluded that the regulatory mechanisms controlled the biofilm phenotype phenomenon of clinical isolates staphylococci species. Thus there is an inherent difference within the MRSA and MSSA. While the biofilm development in MSSA is *icaADBC* dependent, in MRSA it is independent due to presence of other factors and the environment such as acidic growth medium and glucose. It was interesting to look at the MRSA [17].

Two proteins *fnbA* and *fnbB* proteins were found to reduce the biofilm formation in MRSA strain however these mutants have no effect in MSSA biofilm formation thus these proteins could be having important role in *icaADBC* independent pathway. It was gradually found that the primary attachment of the biofilm is not mediated by *FnBP* but encouraged the level of intracellular communication.

The independent pathway of biofilm formation is encouraged by *FnBP* and is completely dependent on *SarA*. Thus both *fnbA* and *fnbB* proteins have potential role in independent pathway and possibly with the known ligand binding activities of these multi-factorial.

fnbA and *fnbB* are actually the extracellular matrix proteins which participated in intercellular accumulation and biofilm formation in *S. aureus*. Fibronectin protein also has an important role to play in *S. aureus* biofilm formation. The virulence of the extracellular matrix formation is dependent on the extracellular matrix protein like fibronectin. There are also other reports that MRSA strain from clinical samples that have capacity to between a proteineous and an exopolysaccharidic biofilm matrix, depending on environmental conditions [18].

An *FnBP* mutant shows more biofilm production in clinical isolated samples like- implanted catheter than PIA/PNAG-deficient mutant. It is concluded that clinical samples like- colonization in a murine foreign-body infection of catheters naturally formed biofilm by *S. aureus* stain due to *FnBPs* factor than PIA/PNAG. It will be interesting to discover the natural strains of bacteria those have capacity to form biofilm in matrix and interchange between polysaccharide and a protein-based biofilm. Various other protein factors were also reported to be participating in *ica* independent *S. aureus* biofilm formation pathway like *atl* protein [19] *atl* protein important in the early events of the *FnBP*-dependent *S. aureus* biofilm phenotype for autolysin.

Mutant *agr* locus protein participated in the increment of *FnBP*-dependent biofilm formation, whether the *SarA* mutation, which encourage the protease production and closed to their *FnBP*-mediated biofilm development function. Again authors analyzed the *atl* regulation role; whenever *atlR* are enhanced the autolysin process and *atlR*::*Tcr* mutation in BH1CC enhanced biofilm-forming capacity. In this study authors concluded the role of *atlR, agr, SarA,* and *sigB* proteins in *S. aureus* biofilm formation as well as *atl* protein participated in initial attachment and *cDNA* release during the initial stages of *ica*-independent, *FnBP*-mediated biofilm development. *Atl* play primary attachment on substance with the help of protein lysis through the cell lysis, *cDNA* release, and cell accumulation. *FnBPs* played important role in initial biofilm formation and maturation [17, 20].

Another set of interesting gene is *hfq* expression in low fluid shear culture in gram positive organism. In this result authors concluded that presence of *S. aureus* strain in low-fluid-shear environment and it's proved the formation of biofilm/colonization phenotype due to virulence characteristics i.e. *hfq* gene as well as shows the influence key factors between colonization during the initial host-pathogen interaction [21]. In this work, it is concluded that fluid-shear culture environment supports *S. aureus* presentation and showed the independent biofilm formation pathway.

In this work, it is concluded that the persisting nosocomial bacteria are present in liquid fluid of human body and formed the colonization in that due to forming of independent biofilm forming pathway. Biofilms development is a multi-factorial involving polysaccharide, protein, and DNA components, which is maintained by various regulating factors. In *Staphylococcus aureus* MW2 strain, *Rsp* is represent as a repressor in biofilm formation steps and shows attachment and biofilm formation process by *fnbA* factor [22]. Clinical isolates of *Staphylococcus aureus* strain showed the biofilm phenotypes supported by the major cell wall autolysin and the fibronectin-binding proteins or the *icaADBC*-encoded polysaccharide intercellular adhesin/poly-N-acetylglucosamine (PIA/PNAG).

Thus, *S. aureus* biofilm formation and regulation both are very complex process due to contribution of multiple components in this phenomenon, which are included to the polysaccharide, proteins, and extracellular DNA. There are also findings that an *AraC*/*XylS* factors are family regulator as well as *Rsp* gene behave like a repressed biofilm formation in *Staphylococcus aureus* MW2 strain.

Biofilm formation process in methicillin-susceptible *S. aureus* (MSSA) strain is dependent on PIA/PNAG but methicillin-resistant isolate (MRSA) express an *atl/FnBP*-mediated biofilm phenotype showed a relationship between susceptibility to β-lactam antibiotics and biofilm process, whether MRSA changed the biofilm phenotype and attenuates virulence process in *Staphylococcus aureus* device- associated infections.

S. aureus is one of the leading cause of nosocomial infections, reported worldwide which shows many roles like- antibiotic resistance, enzyme and toxin production, biofilm forming and immune evasion capability.

Authors data showed that clinical isolates of MSSA are more likely to form a PNAG-dependent biofilm than MRSA isolates, which produce an *atl/FnBP*-dependent biofilm, explained the methicillin susceptibility influences biofilm expression roles [23].

Staphylococcus aureus strain is a leading cause of nosocomial chronic infection and widely associated in biofilm formation pathway on biotic and abiotic surfaces with the help of *bap*-mediated matrix protein, which stops the cellular internalization through binding to host receptor. Biofilm forming organisms also showed resistance against antibiotics/antiseptics due to formation of biofilm matrix, composed of exopolysaccharides, proteins, nucleic acids and lipids and participated as a defense structure protecting bacteria against the host immune system and antimicrobial therapy. In this research-work authors concluded that *bap* protein is used as a biofilm forming factors participated in the interaction of *S. aureus* with host cells and showed that *bap* protein helps in adhesion with surfaces but prevents the entry of *S. aureus* into epithelial cells.

Authors found specific dual roles of *bap* protein first is attachment of persistent infections, and second is promoting the adhesion of *S. aureus* to epithelial cells of the mammary gland by impairing the bacterial internalization through the interaction and impairing host cell invasion [24]. Authors have divided bovine mastitis *S. aureus* isolates into 3 groups on the basis of genetic elements, these are important for biofilm formation i.e. group 1 (*ica*+, *bap*+), group 2 (*ica*+, *bap* negative), and group 3 (*ica* negative, *bap* negative) respectively. The bovine mastitis disease appeared due to biofilm formation in *S. aureus* strains and *bap* is the most important gene for that process of biofilm formation [25].

Bacterial biofilms are therefore to be dependent on *icaADBC* dependent and independent pathway. Therefore there could be the possibility of cross talk between the two pathways. Certain other protein factors are also found to have an important role in biofilm formation. Many types of regulatory pathway controlled by regulatory molecules, like- DNA binding protein *SarA*, regulatory RNAIII effector molecule of the *agr* system of growth process.

Increasing and decreasing regulating power is controlled by *SarZ* gene, i.e. a member of *SarA*/*MarR* family of transcriptional regulators. *SarZ* is a regulatory molecule of the regulatory phase and its increases to virulence factors that necessary for the biofilm development process of *S. aureus* infections. *SarZ* also shown the transcriptional and phenotypic analyses process in the *S. aureus* (MRSA and MSSA) both strains. However introduced mutation in *SarZ* gene is decreased *agr* transcription pathway. *SarZ* gene controlled the *sarA* and *agr* genes expression of virulence factors in biofilm formation phenomenon, like- *hla* and *sspA* [26].

Some other protein factors such as *cid* and *lrg* genes present in *S. aureus* bacterium and show opposing effects on the control of murein activity and lysis during the biofilm development in cells grown in planktonic culture. Similarly *Staphylococcus aureus* have also specific surface protein (*SasC*) factor which participate in the cell aggregation and biofilm production due to colonization and help in accumulation in pathogenic bacteria [27].

PSMs (biofilm maturation factor) also participate as a specific gene in biofilm maturation steps, characteristic development, channel-containing biofilm structure, and dissemination, control of biofilm expansion and biofilm detachment *in vivo* condition of *S. aureus.* Biofilm structure is dependent on biofilm maturation factor (PSM) expression of local differences, which is further proceeding by quorum-sensing (*agr*) activity.

It has been also concluded that intercellular adhesion (*ica*) gene promoted by *Aap* and *SasG* genes of staphylococcus species are also known as zinc zipper, in which Zn^{2+} ion is present in between self-association events stretches of B repeats on opposing *Aap* or *SasG* molecules. Studies on the molecular cross-talk of biofilm forming mechanisms of bacteria are not well known by scientists. Biofilm formation mechanisms are not well known due to deficiency of knowledge about biofilm structure, attachment, maturation and detachment process. It is also found in author's result; biofilm development process controlled by *agr* negative gene however *agr* mutant strains have capacity to formed thick biofilm.

The following experiments will be interesting to perform: preparation of recombinant strains of *Staphylococcus aureus* expressing full length and domain of proteins involved in *icaADBC* dependent biofilm forming pathway; preparation of recombinant strains of *Staphylococcus aureus* expressing full length and domain of proteins involved in *icaADBC* independent biofilm pathway and comparative investigations in the level of proteomics and transcriptomics of different recombinant strains to describe the possible interactions between proteins of *icaADBC* dependent and *icaADBC* independent pathway.

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