Regulation of Biofilm Formation By Quorum Sensing: Implications For Pathogenesis and Antibiotics Resistance

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***Abstract*—Biofilms are collections of microorganisms in a matrix of extracellular polymeric material made up of polysaccharides, proteins, lipids, as well as nucleic acids. Many bacteria may transition among planktonic and biofilm forms. Planktonic bacteria have reproduction rates and relatively fast cell growth, which reduces their chances of survival but they are capable of adapting to different environments. The biofilm formation state appears to be a natural besides prevalent condition of microorganisms.**

The biofilm formation important because it increases bacterial tolerance to hostile environmental conditions lets microorganisms avoid being washed away by merely attaching to a surface or tissue, and most likely, by limiting their diffusion, the extracellular polymeric matrix protects bacterial cells in deeper layers against antimicrobial agents. Primary contact/attachment to the surface, micro-colony development, maturity and construction of the biofilm architecture, and ultimately detachment and dispersion define the phases in biofilm formation.

Once a biofilm is established, bacterial mobility decreases while cell density increases. Bacteria communicate within the biofilm through quorum sensing (QS), a signaling mechanism that regulates biofilm formation and the production of virulence factors. QS relies on the secretion and detection of autoinducers, which facilitate intercellular communication. In Gram-negative bacteria, the major QS signaling molecules include acyl-homoserine lactones (AHLs), autoinducing peptides (AIPs) in the Gram-positive bacteria and autoinducer-2 (AI-2), which is produced by both types of bacteria.This review aims to highlight the regulatory role of QS in biofilm formation and its impact on pathogenicity and antibiotic resistance .

Keywords- QS, biofilm, antibiotic resistance

INTRODUCTION

Several bacteria coordinate their cooperative behaviors and biological processes by means of technique termed quorum sensing (QS), wherein microbial cells interact by releasing, detecting, and responding to small diffusible signaling molecules. The capacity of microorganisms to engage in collective behavior akin to a multicellular creature has conferred significant benefits in host colonization and biofilm production (1).

Bacterial biofilms consist of intricate microbial colonies enclosed in extracellular polymeric materials. Their formation constitutes a multistage process. Biofilms present a considerable obstacle in the management of bacterial infections and are a principal factor in the persistence of diseases (2). Estimates indicate that biofilms account for 65% to 80% of all microbial diseases in hospitals, influencing humans (3,4).

Infections associated with biofilms represent a persistent challenge in contemporary medicine. In numerous microorganisms responsible for chronic infections, the principal virulence factor is the development of biofilms (5,6). The heightened demand for implantable medical devices as well as the rising incidence of microbial resistance render biofilm development by bacteria a significant health threat (7). Biofilm formation on implanted devices can occur because of harmful bacteria (8). Bacterial biofilm, composed of microbes embedded in an extracellular polysaccharide matrix on the catheter surface, is responsible for several bloodstream as well as urinary tract infections attached with internal healthcare devices (9,10). This review aims to elucidate the intricate relationship between quorum sensing and biofilm development in relation to antibiotic resistance.

The life cycle of biofilm

The biofilms are defined as bacterial communities comprising several bacterial colonies or a singular type of bacterial cells that coexist closely by encasing themselves in an extracellular matrix (ECM) consisting of nucleic acids, lipids, sugars,

proteins (11), and extracellular polymeric substances (EPS), adhering to a substrate or to one another. These substances display phenotypic heterogeneity and are essential in biofilm development, comprising 90% of the total organic matter in the matrix, which is the primary structural characteristic of microbial biofilms that enables surface adhesion (12). Bacterial proliferation inside biofilms is a naturally taking place process, wherein the entire bacterial community can dynamically cling to the infection location. The capacity of bacteria to inhabit their surroundings and mature as biofilms on surfaces is a survival strategy of living organisms (13).Biofilm production involves microorganisms existing as structured aggregates on various surfaces and unique growth phase in contrast to free-swimming planktonic cells. Biofilm development is a multifaceted and cyclical process that encompasses transport, diffusion, chemical interactions, and ecological mechanisms, regulated by factors such as adhesion, transport, quorum sensing, detachment, cell death, as well as dispersion. Biofilms are structural assemblies of microorganisms that continuously evolve to adapt to their environment (14).

Cellular Attachment

The initial phase of biofilm formation is the adherence of microbes to a surface (15). In order for an organism to adhere to a surface, it must overcome the repulsive forces produced through the negatively charged microbial membrane in addition to the surface (16). The phase of attachment that includes fundamental support is termed reversible attachment. The attachment is reversible, as bacteria exhibit weak attachment to a surface and can detach at this phase. The microbes departing from a surface revert to their planktonic mode of existence (17).

Microcolony Formation

Next microbial cells have irreversibly adhered to a surface, they commence division as well as the production of extracellular polymeric substances (18). extracellular polymeric substances production leads to the formation of a biofilm matrix that serves as a'shelter' for all attached cells (19). EPS facilitates cell adherence to surfaces, leading to persistent attachment (20).

Biofilm Maturation

Cellular division and the ongoing construction of EPS lead to the formation of an initial biofilm, which evolves over time into a three-dimensional structure. The extracellular polymeric substances produced by the implanted cells adds to the previously described three-dimensional structure and is responsible for its maintenance (21). To facilitate quorum sensing, cells within the biofilm produce signaling molecules termed autoinducers (22, 23.) As illustrated in Figure 1

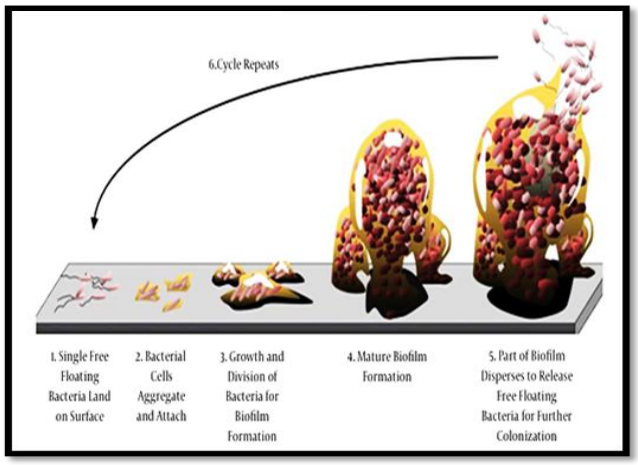

Figure.1: The biofilm life cycle [26].

Biofilm Dispersal

Biofilms mature and then disperse. At this stage, several cells detach from the biofilm and revert to a planktonic existence (24). Upon reverting to their free-floating condition, these cells may adhere to a different surface, thus initiating the cycle again (25).

The Gene Regulation of Biofilm

Biofilm development is controlled by a variety of internal and extracellular pathways of signaling (27). Quorum sensing, bis-(3′-5′)-cyclic diguanosine monophosphate (c-di-GMP) signaling, and non-coding short RNAs (sRNA) are the key signaling mechanisms responsible for the production and assembly of different matrix components during biofilm development (27). Quorum sensing allows bacteria to detect changes in cell density using autoinducers and respond by changing the expression of genes (28). Modification of intracellular c-di-GMP levels results in a varied gene activity pattern. Higher concentrations of c-di-GMP limit motility and stimulate the formation of matrix-associated polysaccharides and adhesions (27.)sRNAs have been shown to control exopolysaccharide production and export, amyloid expression, and motility (27).

Mechanisms of resistance to antibiotics via biofilm

Numerous studies on the connection between biofilm forming ability and antibiotic resistance have shown conflicting results. According to news reports, the creation of biofilms increases bacterial resistance through a number of mechanisms, including slower growth rates and decreased antibiotic diffusion (29, 30).

In polymorphonuclear leukocyte cases, these cells may be recruited to the biofilms and undergo bacteria-induced necrosis, causing the release of host eDNA. Research indicates that within the CF lung, eDNA synthesized by P. aeruginosa alongside host eDNA is capable of creating a barrier that defends the biofilm against immunological assaults from tobramycin and host immune cells (31).

Quorum sensing (QS)

Quorum sensing (QS) is a cellular communication method whereby microorganism's synthesis and emit signaling molecules known as autoinducers. As bacterial cell density grows, the concentration of signaling molecules rises,

prompting collective bacterial responses upon reaching a minimal threshold concentration. Quorum sensing assists microorganisms in modulating traits for instance biofilm formation and pathogenicity in a coordinated fashion, contingent upon species complexity and cell density (32-34).

Below are three essential ideas of bacterial quorum sensing:

The initial aspect is the concentration-dependent response to autoinducers, which are secreted extracellularly and elicit specific reactions within the bacterial community based on their concentration levels; the subsequent aspect involves specialized receptors found in the cytoplasm or cell membrane of microbes that can sense as well as respond to autoinducer concentrations, facilitating the initiation of quorum sensing pathways; finally, the third aspect pertains to the activation of the quorum sensing loop, which regulates bacterial virulence factors and behaviors upon detection of autoinducers by receptors (35).

QS Was identified in the marine bacterium Vibrio fischeri in 1960 (36). Since that time, QS research has broadened to encompass numerous bacterial species, including both Gram-positive and Gram-negative varieties. In the Gram-negative bacteria, acyl-homoserine lactone (AHL) molecules predominantly facilitate quorum sensing (QS), while the Gram-positive bacteria primarily utilize autoinducing peptides (AIPs) (37-40) (Figure 2). Notwithstanding the diversity of quorum sensing (QS) signaling molecules, the fundamental concept of QS remains uniform, enabling bacteria to perceive population density and modulate behavior to optimize survival strategies under fluctuating environmental situations.

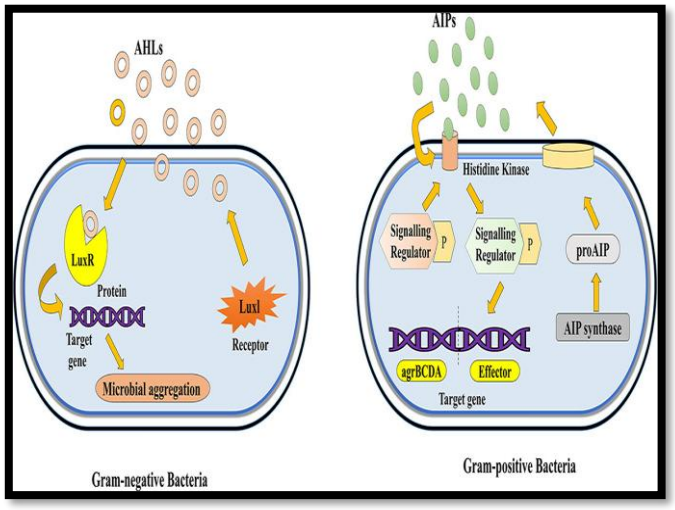

Figure 2: shows quorum sensing using AHLs in gram-negative bacteria and AIPs in gram-positive bacteria [40].

Quorum sensing Regulation of the Biofilm Formation in Gram-Negative Bacteria

The quorum sensing systems in Gram-negative bacteria that have been studied the most are the identical LuxR-LuxI system and the signalling molecules that are linked to it, called N-acyl homoserine lactones (AHL). It works like the process that was first seen in the sea bacteria Vibrio fischeri. However-AHL is used as a signaling molecule in the majority of Gram-negative bacteria quorum-sensing methods that have been investigated. When these molecules reach high enough amounts, they can link to and activate transcription activators, also known as R-proteins. This makes target genes start to work (41).

Quorum sensing Regulation of the Biofilm Formation in Gram- Positive bacteria

Gram-positive quorum sensing systems employ different signaling molecules than Gram-negative bacteria. These bacteria employ short signal peptides that undergo post-translational modification for quorum sensing. Atwo-component histidine kinase-signaling pathways sensory component responds to these peptide signals. Research showed that Gram-positive bacteria contained two transcription factor families, RNPP and Rgg, with binding domains. The RNPP protein family comprises Rap, NprR, PlcR, and PrgX. This class covers all Gram-positive quorum-sensing systems that use their signaling peptide within the receiving cell. RNPP controls sporulation, conjugation, biofilm growth, and pathogenic responses (42).

Mechanisms of quorum sensing to antibiotic resistance

QS is critical for the development of antibiotic resistance in polymicrobial illnesses involving many microbial species. In such infections, QS facilitates interactions between diverse bacterial species, increasing their combined ability to resist antibiotic treatment. Understanding the complex interplay between QS and antibiotic resistance in polymicrobial illnesses is critical for creating new therapeutic methods. Targeting QS pathways with quorum sensing inhibitors (QSIs) may make bacteria more sensitive to antibiotics (43-44).

Biological Competition and Quorum Sensing

Toxin production is commonly associated with the stress response to ecological competition, which is common in bacterial communities and usually involves both foreign and established genotypes (45).Toxin regulation of microbial diversity is elucidated by bacterial populations as a function of QS. The breakdown of individual cells of various genotypes is facilitated by bacterial toxins, which in turn cause harm to other bacteria. Typically, bacteria produce toxins that kill other bacteria. One example is bacteriocin, an antibiotic with a narrow spectrum that targets other microbes; another is pyocyanin, which may have multiple effects on nutrition and metabolism; and finally, toxins like these help us understand how microbes have evolved to interact with one another and how to eradicate them (46).

Here is how toxins control the variety of microbes: Microbes can use QS-mediated information about the community microbial population size to identify ecological competition. Toxin actions are modulated by the density of self-cells. Keeping a sufficient number of identically genotyped microbes in a community is an important goal of QS control (47).

Quorum Sensing signal degradation

Many prokaryotes and eukaryotes generate enzymes that break down Quorum Sensing signalling molecules. Four enzymes have the capacity to break down AHLs: acylases and lactonases hydrolyze the amide bond and HSL ring of AHL, respectively; oxidases and reductases alteration AHL activity but do not break it; and oxidoreductases particularly AI-2 target [48]. Many strains of bacteria have been demonstrated to have lower biofilm generation with the administration of these QQ enzymes that break down biofilms. QQ enzymes disturbs the

biofilm architecture and increases the sensitivity of the cells to antibiotics. *P. aeruginosa* showed similar behavior after lactonase treatment (50). It is being demonstrated that the oxidoreductases *Klebsiella oxytoca* and *Klebsiella indica* transform the signaling molecules AHL and AI-2 to hydroxy-derivatives that are QS-inactive (49,51).

There are numerous primary mechanisms of QS suppression (52-55) (Fig.3).

Suppression of signal molecule production (for example, inhibition of Lux operon proteins)The inactivation or enzyme breakdown of signal molecules Competing with signal molecules, receptor analogs; Blocking the transmission of signals cascades, such as preventing the creation of AI-receptor complexes.

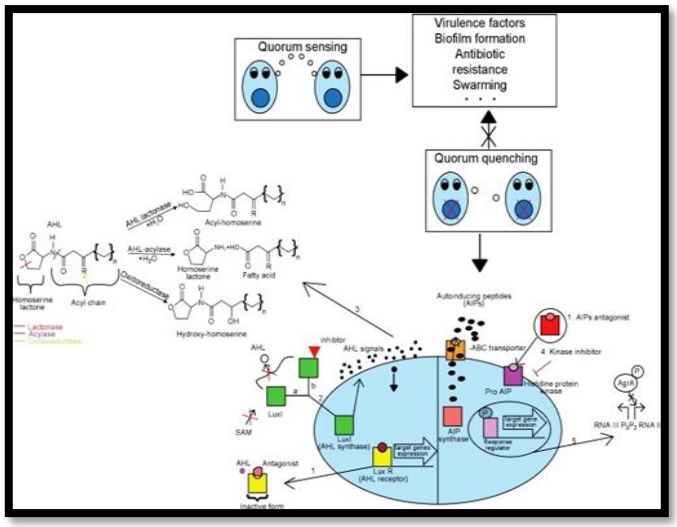

Figure 3 : Mechanisms of blocking quorum sensing in Gram-negative and Gram-positive bacteria (48).

Future Outlook

Quorum sensing, a new study topic in microbiological research, has been gaining popularity during the 1990s. Several relevant studies are now underway, and resistance to drugs is an emerging trend within the subject of quorum sensing. Despite extensive research, the regulating mechanism of quorum sensing in microbial resistance remains unknown. As may be observed. Additional research into quorum sensing within the area of resistant microbes offers potential as well as obstacles. To further address this tendency, subsequent studies on quorum sensing in resistant microbes must concentrate on these areas: (1) Despite the incompleteness of current QS-related regulatory mechanisms, molecular biology-based studies could be enhanced. (2) Ge should focus on doing pertinent research on bacterial quorum sensing because of the complexity of the bacterial resistance to drugs mechanism. (3) It is imperative to concentrate on creating newer more efficient QSI screening technologies due to the inefficiency of the current QSI screening methods. (4) Given the extensive probable of quorum sensing systems in synthetic biology, study and development of numerous QS regulatory mechanisms should focus on strict regulation of target genes to satisfy the variety of engineering microbes in actual construction (56-57).

CONCLUSION:

Microbes use quorum sensing to regulate a wide collection of functions, such as biofilm formation as well as pathogenicity. Therefore, using QS inhibiting drugs, for example QS inhibitors (QSIs) in addition to (quorum quenching (QQ) enzymes, to limit or even entirely suppress dangerous microorganisms formation of biofilm appears to be a potential method to controlling microbial infections.

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