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Review on Quorum Sensing; the Bacterial Language and its Role as a Target for Future Antimicrobial Therapy

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Abstract: Quorum sensing is a form of bacterial cell–cell communication in which a cell secretes a signaling molecule to communicate with other neighboring cells in a way that depends on the density of the cell population. The Process involves generation of a signal molecule, accumulation of those signals in medium to certain threshold concentrations, recognition of the signal molecule by a receptor and expression of a large array of genes in response to the concentration of the signal-receptor. With the help of this process, bacteria regulate myriad activities such as antibiotic resistance, biofilm formation, DNA transfer, survival in hostile environment, evasion of host defense and other virulence properties. Anti-biotic resistance is a global issue nowadays due to the emergence and spread of multi antibiotic-resistant bacteria. It is becoming more difficult to treat bacterial infections with currently available antibiotics. Thus, novel strategies which are targeted against bacterial quorum sensing to fight against infectious diseases should be designed. Therefore in this review, the mechanisms of bacterial Quorum sensing and its role on virulence are discussed and potential anti-virulence strategies that specifically block this mechanism (Quorum sensing inhibition/ Quorum Quenching) are suggested as future therapies.

Key words: Quorum Sensing · Virulence · Bacteria · AIPs

INTRODUCTION

In the conventional view of prokaryotic existence, bacteria live unicellular, with responses to external stimuli limited to the detection of chemical and physical signals of environmental origin. This view of bacteriology is now recognized to be overly simplistic, because bacteria communicate with each other through small 'hormone-like' organic compounds referred to as auto inducers. These bacterial cell-to-cell signaling systems were initially described as mechanisms through which bacteria regulate gene expression via cell density and, therefore, they have been collectively termed quorum sensing (QS) [1].

The functions controlled by quorum sensing are varied and reflect the needs of a particular species of bacteria to inhabit a given niche. Quorum sensing, or the control of gene expression in response to cell density, is used by both Gram-negative [2] and Gram-positive bacteria to regulate a variety of physiological functions. In all cases, quorum sensing involves the production and detection of extracellular signaling molecules, the auto inducers (AI) [3].

Recent studies show that quorum sensing modulates both intra- and inter-species cell-cell communication and it plays a major role in enabling bacteria to architect complex community structures. Many bacteria use cell-cell communication to monitor their population density, synchronize their behavior and socially interact. This communication results in a coordinated gene regulation and is generally called quorum sensing.

The discovery of antibiotics has been a milestone in the history of medicine. With the introduction of antibiotics into clinical practice, infectious diseases that were once untreatable have become treatable and millions of lives have been saved by taking many dangerous bacterial infections under control. However, this medical miracle is being deteriorated by the development and rapid spread of bacterial resistance.

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Today, a global concern has emerged that we are facing a post antibiotic era with a limited capability to fight bacterial infections. The increasing occurrence of multi-antibiotic resistant pathogen strains has gradually made conventional antimicrobial treatment ineffective [4].

QS Signaling activation and biofilm formation lead to the antimicrobial resistance of the pathogens. With indiscriminate use of antibiotics, there has been an alarming increase in the number of antibiotic resistant pathogens. Antibiotics are no longer the magic bullets they were once thought to be and therefore there is a need for development of other novel strategies to combat the infections caused by multidrug resistant organisms.

Quorum sensing inhibition or quorum quenching has been pursued as one of such novel strategies [5]. Anti-QS agents can abolish the QS signaling and prevent the biofilm formation, thereby reducing bacterial virulence without causing drug-resistant to the pathogens, suggesting that anti-QS agents are potential alternatives for antibiotics. While antibiotics kill or slow down the growth of bacteria, quorum sensing inhibitors or quorum quenchers attenuate bacterial virulence. Quorum sensing inhibitors are attractive alternatives for controlling human, animal and plant pathogens and their utility in agriculture and other industries [5].

Therefore, the objectives of this review were to,

- Discuss the mechanisms of bacterial Quorum sensing
- Suggest potential anti-virulence strategies that specifically block this mechanism to control virulence.

Quorum Sensing: Overview: Quorum-sensing is a process of cell-to-cell communication that relies on the production and release of extracellular signaling molecules termed auto inducers, whose concentration increases as a function of cell density. Quorum sensing is a mechanism that bacteria use to ensure that sufficient numbers of those bacterial cells are present for eliciting a biological response to an external stimulus. It includes expression of large number of genes that allow bacteria to work in unison to avert any kind of catastrophe during microbe-microbe or host-microbe interactions [6].

Quorum sensing process involves generation of a signal molecule, accumulation of the signal molecule in medium to certain threshold concentrations, recognition of the signal molecule by a receptor and expression of a large array of genes in response to the concentration of the signal-receptor complex. With the help of this process, bacteria regulate myriad activities such as virulence, biofilm formation, luminescence, DNA transfer. QS is known to overcome the host defense barriers by affecting the host transcriptional programs, detecting the host cytokines and stress hormones and capture when the host is most vulnerable [7]. QS Signals can transgress the interspecies and inter-kingdom barriers, when the bacterial population densities are low; the expression of virulence genes is not activated so as to avoid the detection of pathogen and immune stimulation against the pathogenicity factors. This gives ample time to bacteria for colonization and establishment in the host [8].

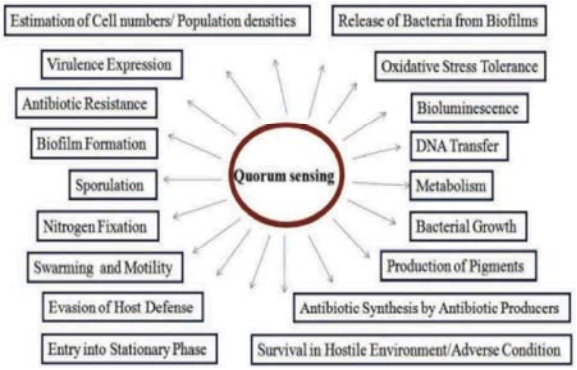

Fig. 1: Quorum sensing: A central component of multiple functions in bacterial communities [8]

Quorum Sensing in Gram Positive and Gram Negative Bacteria

Quorum Sensing in Gram Positive Bacteria: The Bacterial signaling molecules in this group of bacteria are called auto inducers small post-translationally modified peptides called auto inducing peptides (AIPs) which are central to this process and are often integral elements of a histidine kinase two-component signal transduction system.

When released into the surrounding environment they are either detected at the bacterial surface or re internalized via an oligopeptides transport system upon reaching a threshold level and activates quorum sensing genes. In the latter case, imported peptides interact with cognate regulators (phosphatases or transcriptional regulators) that modulate the expression of target genes. These regulators help control crucial functions such as virulence, persistence, conjugation and competence and have been reported in bacilli, enterococci and streptococci. There are two major pathways of QS unique to Gram-positive bacteria. In the first pathway, AIPs are

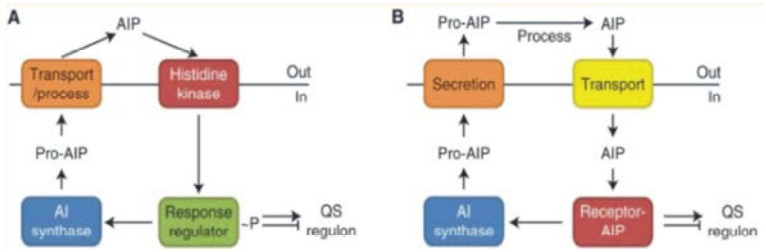

Fig. 2: Canonical quorum-sensing circuits in Gram-positive bacteria [9]

ribosomally synthesized as pro-peptides and then modified post-translation. They are secreted via dedicated ABC transporters and oftentimes undergo cleavage by secreted proteases to mature into AIPs. Once the concentration of AIPs reaches a certain threshold, they are recognized by specific cell surface receptor kinase, in turn activating the kinase via phosphorylation on a conserved His residue. The activated kinase subsequently activates a downstream intracellular regulatory receptor by transferring the phosphoryl group to an Asp residue. The activated intracellular regulatory receptor eventually regulates transcription of specific target genes as well as those of AIP secretion pathway itself. Given that this pathway has two key elements, namely the Histidine (His) kinase at the membrane and the intracellular regulatory receptor, it is commonly referred to as two-component pathway [9].

Gram-positive bacteria synthesize oligopeptides that are typically modified at specific amino acids and are actively secreted. Detection occurs via a two-component signal transduction circuit, leading to the phosphorylation of a response regulator protein, which can bind promoter DNA and regulate transcription of target genes (xyz). [10] Quorum sensing in Gram negative bacteria

The most common signaling molecules found in Gram-negative bacteria are N-acyl derivatives of homoserine lactone (acyl HSLs). Modulation of the physiological processes controlled by acyl HSLs (and, indeed, many of the non-acyl HSL-mediated systems) occurs in a cell density- and growth phase-dependent manner. This type of quorum sensing represents a dedicated communication system that enables a given species to sense when it has reached a critical population density in a host and to respond by activating expression of genes necessary for continued success in the host. Acyl-homoserine lactone signaling in the opportunistic animal and plant pathogen Pseudomonas aeruginosa is a model for the relationships among quorum sensing, pathogenesis and community behavior. In the *P. aeruginosa* model, quorum sensing is required for normal Biofilm maturation and for virulence. There are multiple quorum-sensing circuits that control the expression of dozens of specific genes that represent potential virulence loci [11].

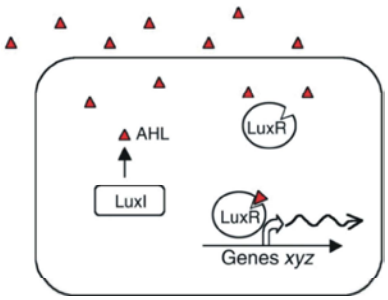

Fig. 3: Canonical quorum-sensing circuits in Gram-negative bacteria [11]

AHLs (red triangles) are produced by LuxI-like proteins and are detected by LuxR-type proteins. AHLs freely diffuse across the cell membrane and increase in concentration in the environment in proportion to cell growth. LuxR-type proteins, when bound to cognate auto inducers, bind specific promoter DNA elements and activate transcription of target genes (xyz). [10].

Quorum Sensing Signals: There are different types of QS systems based on the kind of auto inducer (AI) employed [12]. The bacterial QS signals mainly consist of acyl-homoserine lactones (AHLs), auto inducing peptides (AIPs) and autoinducer-2 (AI-2) and participate in the various physiological processes of bacteria including Biofilm formation, plasmid conjugation, motility and antibiotic resistance by which bacteria can adapt to and survive from disadvantages [13].

The Gram-negative and Gram-positive bacteria have different QS signals for cell-to-cell communications. The AHL signaling molecules are mainly produced by Gram-negative bacteria [14] and AIP signaling molecules

are produced by the Gram-positive bacteria and both Gram-negative and Gram-positive bacteria produce and sense the AI-2 signals [15]. These three families of QS signals are gaining more and more attention due to their regulatory roles in bacterial growth and infection.

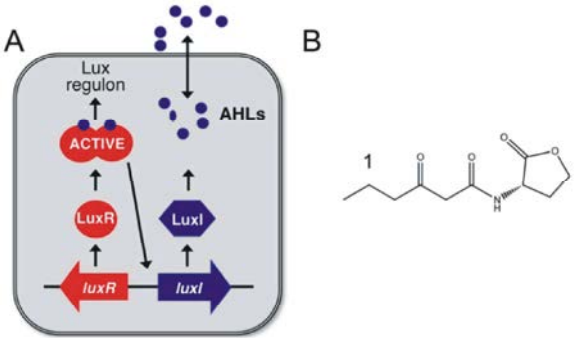

Fig. 4: Signaling molecule in Gram negative bacteria [15]

AHL quorum sensing in *Vibrio fischeri*. AHL signals [solid blue circles] are synthesized by LuxI family signal synthases and specifically interact with LuxR family transcription factors. When the population reaches high cell density, accumulated AHLs interact with LuxR homologues. AHL interaction causes the LuxR protein to change conformation and become active, which induces target gene regulation. (B) Structure 1, the Vibrio fischeri AHL, 3OC6-HSL. AHLs can vary in the side chain length and substitution at the third carbon position of the acyl chain and this variation dictates the specificity of the system [14].

Auto Inducer Type 1 (AI-1) System: N-acyl homoserine lactone (AHL) class of molecules acts as signal molecules. Lux-I (auto inducer synthase) type AHL synthase circuit has been considered as the QS signals producer in the Gram-negative bacteria such as *V. fischeri*, *E. coli*, *P. aeruginosa*, *Agrobacterium tumefaciens* and *Erwinia carotovora* [16]. Once the AHLs accumulate in the extracellular environment and exceed the threshold level, these signal molecules will diffuse across the cell membrane and then bind to specific QS transcriptional regulators, thereby promoting target gene expression [17].

The *luxI* gene encodes AHL synthase/I protein responsible for the production of AHL molecules whereas *luxR* (activator) encodes the receptor for AHL. The AHL molecules are composed of a homoserine lactone (HSL) ring with a side acyl chain varying in the chain length (4-18 carbons), the degree of saturation and the number of oxygen substitutions. AHLs with small fatty acid chains are soluble and freely diffusible molecules that can pass the cell m embranes to sense the bacterial densities. AHLs with long side chains require efflux pumps for their export outside the cell [18, 19].

LuxR is a cell-density de-pendent transcription regulator. When the densities reach a particular threshold value, AHL accumulation triggers the corresponding receptors. Binding to AHL stabilizes LuxR allowing the receptor to fold properly, bind DNA and activate transcription of the target genes [20]. The AHL-LuxR protein complexes not only act as co-activators for the promoter sites of the QS-responsive operons in a bacterial cell, they also act as positive regulators for the AHL synthesis itself. There-fore, the entire system is amplified via a process of auto induction not only in AI-1 system but also in all other QS. AHLs can be the targets for diagnosis of bacterial infections as well as for drug development as these molecules were detected in various infection models. For example, AHLs were detected in mice infected with *Yersinia enterocolitica* [21], lung tissues of mice infected with *P. aeruginosa* [22].

Auto Inducer Type 2 (AI-2) Systems: The system was discovered in marine bioluminescent bacteria *V. harveyi* based on the observation that AHL-deficient bacteria were also capable of producing bioluminescence. This indicated presence of another QS system which was found to make use of luxS genes and related homologues. AI-2 is a unique class of auto inducers in the sense that it is common to both Gram negative as well as Gram-positive bacteria and is the most ubiquitous system [23]. This fact that has led many researchers to call it a “universal language” of cross-talk extending to even inter-species communication[24, 25].

4, 5-dihydroxy-2, 3-pentanedione (DPD) serves as common precursor molecule in AI-2 sensing and is synthesized by LuxS (S-ribosyl homocysteine lyase), a protein that is ubiquitous in bacteria. *LuxS* gene encodes a key enzyme S-ribosyl homocysteinase (LuxS) involved in production of DPD and a detoxifying enzyme that mediates conversion of the toxic intermediate S-adenosyl-L-homocysteine to homocysteine, an activity central to the important metabolic pathways where methyl groups are attached to nucleic acid precursors, proteins and other metabolites. Therefore, it appears that AI-2 system might have an important role in metabolism as well as QS [26]. AI-2 is composed of a receptor-kinase network and the signal is made up of complex, multi-ringed, cyclical furanosyl molecules containing a Boron atom.

AI-2 is therefore a collective term that involves a group of inter-convertible furanones derived from spontaneous cyclisation of DPD due to high reactivity of its 2, 3-dicarbonyl motif. Receptor constitutes two component receptor-kinase signal transcription complexes. For example, in *Vibrio* sp. it is a membrane-bound molecule with two domains (Lux PQ complex) where LuxP is the signal-binding domain and Lux Q has the kinase-phosphatase activity depending on its folding.

AI-2 system is found in large number of bacteria including *E. coli*, *S. typhimurium* and *V. harveyi* and plays a role in Biofilm formation of oral bacteria like *Actinomyces naeslundii* and *Streptococcus oralis* (8). Deletion of *LuxS* influences Biofilm formation in *Streptococcus gordonii* and *S. mutans* [27]. In *S. typhimurium*, the Lsr (LuxS-regulated) transporter system has also been characterized which helps the bacterium to internalize and degrade AI-2 signals from other bacteria. Both *E. coli* and *S. typhimurium* have evolved this AI-2 system for destruction of AI-2 signals from other bacteria. Thus bacteria might also use AI-2 signals from the other bacterial species to their advantage and disrupt/hijack their signal system thus cheating other bacteria. Therefore, while AI-1 is proposed to be intra-species mode of communication, AI-2 can be considered a mode for inter-species communication [28]

Auto Inducer Type 3 (AI-3) System: Like AI-2, this system uses a two component receptor kinase intracellular signaling complex to activate genes of the virulome. Signal molecule in this system is not yet clearly defined but is probably similar to catecholamine. In AI-3 system of enterohemorrhagic E. coli (EHEC), QseA regulates the locus of enterocyte effacement (LEE) Pathogenicity Island and QseBC regulates the activity of flagella and motility genes. QseBC complex has been shown to be the periplasmic receptor that senses both AI-3 signal and human hormones epinephrine and nor epinephrine. QseC is the sensor kinase and QseB is the phosphorylated response regulator that regulates the virulome. AI-3 system has been only detected in Gram-negative enteric organisms and is shown to be essential for the pathogenesis of EHEC and *Shigella* spp. [29].

AI-3 works in synergy with the human stress hormones epinephrine or nor-epinephrine to signal the system. Treatment of E. coli luxS mutants with purified epinephrine or nor epinephrine was shown to restore the activity of LEE important for virulence of EHEC. Addition of AI-3 signal molecule or epinephrine led to an increase in the expression of the locus of LEE. Epinephrine has been shown to be a global virulence signal suggesting an inter-kingdom cell-to-cell communication between AI-3 of EHEC and the hormones of the human host [30].

Biofilm Formation and Virulence: Bacteria widely exist in the natural environment, on the surface of hospital devices and in the pathological tissues [31]. Biofilm formation is one of the necessary requirements for bacterial adhesion and growth. The Biofilm formation is accompanied by the production of extracellular polymer and adhesion matrix and leads to fundamental changes in the bacterial growth and gene expression [32]. The formation of Biofilm significantly reduces the sensitivity of bacteria to antibacterial agents and radiations and seriously affects public health. Some formidable infections are associated with the formation of bacterial biofilms on the pathological tissues and most infections induced by hospital-acquired bloodstream and urinary tracts are caused by biofilms-coated pathogens on hospital medical devices. A large number of studies [33] have shown that bacterial quorum sensing (QS) signaling plays important roles in Biofilm formation. Specific QS signaling blockage is considered an effective means to prevent the biofilms formation of most pathogens, thereby increasing the sensitivity of pathogens to antibacterial agents and improving the bactericidal effect of antibiotics [34].

The virulence factors produced by different strains are different. For example, Gram-negative Pseudomonas aeruginosa produces virulence factors, such as pyocyanin, elastase, lectin and exotoxin A and Gram-positive *Staphylococcus aureus* produces virulence factors such as fibronectin binding protein, hemolysin, protein A, lipase and enterotoxin [35]. Studies have shown that the production of these virulence factors is regulated by the bacterial QS signaling systems [36]. Disruption of QS to control the production of virulence factors seems to be an attractive broad-spectrum therapeutic strategy.

Quorum Sensing Inhibition (Anti-virulence Strategies): The mechanism through which bacteria are made “silent” by blocking quorum sensing system is called as quorum quenching. In this era of antibiotic depletion, world is searching for new remedies against bacterial infections. Quorum sensing targeted antibacterial therapy has evolved new revolution in this field. Bacteria affect the

host tissues by using virulence factors. Its virulence depends on the species and their population in the initial exposure. Once the infection begin in the host these microbes rapidly activate the target genome and produce virulence factors that facilitate the microbe to invade the host, initiate the infection and defend host immune system [37]. These virulence factors include: Adherence Factor, Invasion Factors, polysaccharide capsules, lipopolysaccharide Toxins and Siderophores [38].

Inhibiting the expression of these virulence factors, without killing causes less evolutionary pressure for the emergency of resistant genes, makes the bacteria less prone to invade the host. Among the main anti-virulence approaches are inhibition of quorum-sensing compound [39]. There are a number of ways to inhibit cell to cell communication the main strategies are: repressing signal generation, blocking signal receptors or disrupting QS signals and provide an alternative approach to control microbial pathogenesis thereby reducing the virulence of bacteria without affecting their growth or killing them and the reduced pressure may minimize the increasing resistance. Quorum sensing is a strong target for therapeutic intervention of bacterial infections and therefore Quorum sensing inhibition can be used as novel class of antimicrobial drugs.

Interfering with the Signal Generation: The acyl-homoserine lactone molecules not only participate in bacterial communication but also play roles in conversations with eukaryotic cells. AHLs can regulate the signaling pathways in epithelial cells and affect the behavior of innate immune cells [40]. Inhibiting the synthesis of AHLs is a direct strategy to reduce AHL-mediated virulence factors and prevent pathological damage. AI-2 compounds have been claimed as "universal" signal molecules involved in inter- and intra-bacterial species communication. This is supported by the fact that luxS gene homologs are widely distributed among bacterial genomes [luxS encodes the S-ribosyl homocysteine lyase (LuxS) enzyme, which synthesizes AI-2 [15].

Two main enzymes participate in AI-2 biosynthesis: Methylthioadenosine/S- adenosyl homocysteine nucleosidase (MTA/SAH nucleosidase) and LuxS. Both enzymes are involved in the activated methyl cycle and they therefore influence bacterial metabolism. Strategies focused on inhibiting AI-2 production have, therefore, targeted these enzymes [41]. MTA/SAH nucleosidase has been identified in several bacterial species but is absent from mammalian cells [42]. It is also linked to the acyl-HSLs biosynthesis pathway; therefore, MTA/SAH nucleosidase inhibition could interfere with the production of these quorum-sensing signals [43].

Degradation of the Signal Molecule: One of the most extensively studied QSI strategies to date is degradation and modification of the quorum-sensing signals. Degradation of QS signals by enzymes can effectively disrupt the "communication" among the bacteria without causing any selective pressure to the bacteria. Inactivation or complete degradation of the AHL signal molecules can be achieved by either of these methods: chemical degradation, enzymatic destruction or metabolism of the AHL molecules. In nature, the AHL-degrading enzymes have been identified in the bacterial pathogens like A. tumefaciens and P. aeruginosa that pro-duce AHLs [44].

Four different types of chemical reactions are observed behind enzymatic quorum sensing they are decarboxylation, deaminisation acylase and lactonase activity. So far enzymes those found degrading signal molecules are studied under three categories which is constituted by lactonase enzymes, acylase enzymes and oxydoreductase enzymes [45].

AHL lactonase are metallo proteins that hydrolyze the ester bond of the homoserine lactone ring to yield the corresponding acyl homoserine molecule. Hydrolysis of this ester bond can also occur spontaneously at alkaline pH and acidic conditions can restore the bond and AHL signaling activity following biological or abiotic hydrolysis [46]. AHL acylase hydrolyze the acyl-amide bond between the acyl tail and lactone ring of AHLs in a nonreversible manner, resulting in the release of a fatty acid chain and a homoserine lactone moiety. Unlike lactonase, acylase can exhibit substrate specificity. The oxidoreductases do not degrade the AHL but rather modify it to an inactive form by oxidizing or reducing the acyl side chain and these are the least abundant and least studied of the AHL-targeting enzymes identified to date [47].

QS Signal Inhibition/Interfering with Signal Reception: One widely explored method is to block the receptor with an analogue of the AHL signal molecule. There are basically three ways to develop on the AHL scaffold: introduction of substitutions in the acyl side chain which at the same time maintain the lactone ring, introduction of substitutions and alterations in the lactone ring which at

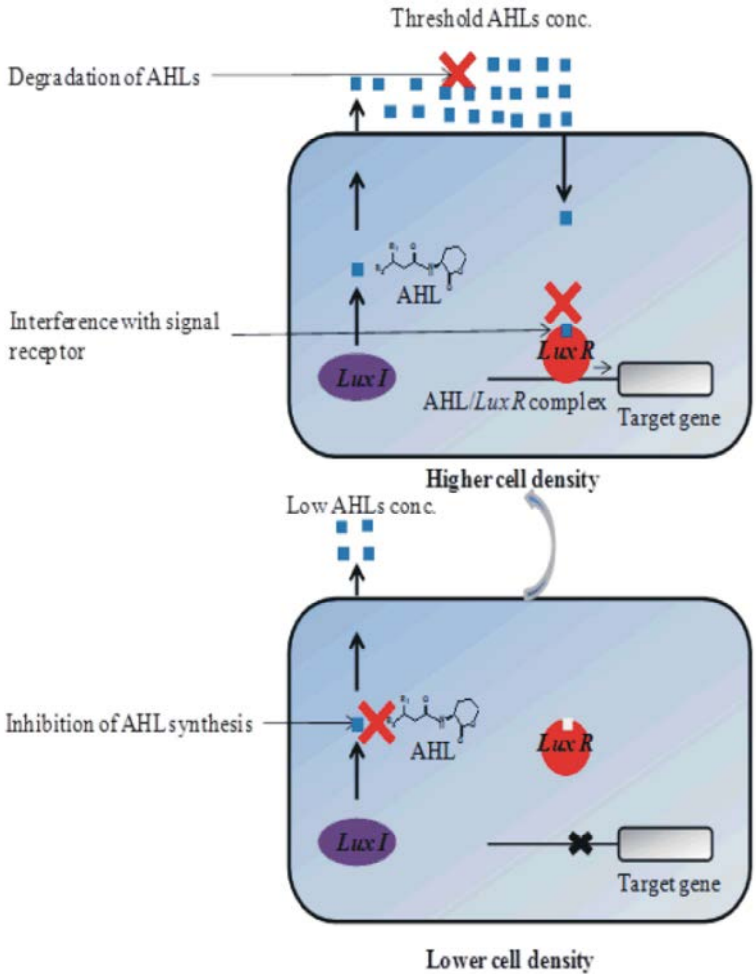

Fig. 5: Inhibition of quorum sensing in gram negative bacteria [49]

the same time leave the acyl side chain unchanged and finally extensive modifications in both the acyl side chain and the lactone ring. The alga *Delisea pulchra* is known to produce halogenated furanones with structures similar to AHLs which act as antagonists for QS and inhibit colonization, swarming and Biofilm formation by Gram-negative bacteria [48]. Furanones displace AHLs from their receptors [49].

Three quorum quenching strategies have been used for attenuating AHL-mediated phenotypes; (i) Inhibition of AHL synthesis (ii) Degradation of AHL signal molecules (iii) Interference with signal receptor [50].

CONCLUSION

QS Signaling activation and biofilm formation lead to the development and proliferation of anti-biotic resistant bacteria. With the emergence and spread of multi antibiotic-resistant bacteria, it is becoming increasingly more difficult to treat bacterial infections with currently available antibiotics. Antibiotics are no longer the magic bullets they were once thought to be.

In line with this conclusion the following recommendations are forwarded:

- New anti-virulence strategies should be designed to fight against infectious diseases.
- Future treatment strategies should target Quorum sensing, the magical language of bacterial pathogens.
- Further researches should be conducted on this area of science to design a novel therapeutic strategy that selectively blocks this language without putting pressure on the host being treated.

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