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Review Article

Quorum Sensing and its Correlation with Virulence Factors

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Abstract: Quorum sensing (QS) is cell to cell signaling mechanism that enables bacteria collectively control gene expression in response to their population density, or it is bacterial communicate with one another using chemical signals. There are three types of signaling molecules: Acyl-homoserinelactonase (AHLs), Auto-inducer peptides (AIPs) and Autoinducer-2 (AI-2). Q.S was first observed and described in bioluminescence bacterium V.fischeri.In V. fischeri, several kinds of quorum sensing system were identified. At first, lux system was found and regulates the luciferase operon and light production. LuxIwas isolated as an AHL synthase while LuxR was isolated as a transcriptional activator of the luciferase operon. At low cell density, LuxOrepresses LitR, which is a positive regulator of the expression of LuxR. Quorum quenching (QQ) refers to the mechanism by which bacterial communication can be interrupted, or it is the process of preventing QS by disrupting the signaling.The first major QS-disrupting strategy that has been studied is the interference with the detection of the AIs and the second one is the inactivation/degradations of the signal molecules.

Keywords: Quorum sensing (QS), V. fischeri, gene expression, AHLs, AIPs, Autoinducer-2 (AI-2), Quorum quenching (QQ).

INTRODUCTION

Quorum sensing (QS) is cell to cell signaling mechanism that enables bacteria collectively control gene expression in response to their population density, or it is bacterial communicate with one another using chemical signals (Abisado *et al*., 2018). It is very important to recognize that this type of communication is achieved only at high cell densities. Bacteria release various types of molecules called autoinducers in the extracellular medium, these molecules are mediators of quorum sensing (Borges and Simões, 2019).The bacteria produce signaling molecules that accumulate during specific stages of growth, although their production level can also be influenced by the environment. At a threshold concentration, the signals activate a regulator that can induce or repress target genes. Usually processes that are regulated by QS are beneficial when a group of bacteria acts together. For example in the marine bacterium, QS regulates luminescence in the squid light organ (Bose *et al*., 2011).

Bacteria use QS for many activities including; conjugation, releasing or expression of virulence factors such as toxins, hemolysis, swarming and motility biofilm formation, antibiotics resistance, bioluminescence, sporulation and many other activities. The bioluminescent Gram-negative bacterium *Vibrio. fischeri* is the first organism in which QS was observed (Schuster *et al*., 2010**)**.

In the late 1960s, Hastings was studying bioluminescence in the marine bacteria *Vibrio fischeri.* He and his post-doc, Kenneth Nealson, discovered that bacteria could communicate by secreting a small peptide. This allowed *V. fischeri* to sense the concentration of their fellow bacteria and, when the density reached a critical level, turn on bioluminescence (Gupta and Gupta, 2021). Hastings named this process autoinduction, also known as quorum sensing. Quorum sensing has since been shown to play a critical role in bacterial behaviors such as toxin production and biofilm

formation.Hastings hypothesizes that luciferases, and thus bioluminescence, evolved as a mechanism to protect bacteria from oxidative damage as the Earth's atmosphere became oxygenated 2.5 billion years ago (Brackman *et al*., 2011).

1- Quorum sensing mechanism (Q.S.)

When bacteria use Q.S it constitutively produces and secrete signaling molecules called autoinducers or pheromones. These bacteria have a receptor that can specifically detect the signaling molecule inducer, when the inducer binds the receptor it activates transcription of certain genes including inducer synthesis system (Abisado *et al*., 2018) were observed (Fig. 1).

A variety of ways for bacterial populations to coordinate their activities have been discovered. Cell density-dependent regulation in these systems appears to follow a common theme (Chen *et al*., 2002). First, the signal molecule (a post transnationally processed peptide–pheromone) is secreted by a dedicated ATP-binding cassette (ABC) exporter. The role of the secreted peptide pheromone is to function as the input signal for a specific sensor component of a two-component signal-transduction system (Chong *et al*., 2013). Co-expression of the elements involved in this process results in self-regulation of peptide–pheromone production. Peptides are secreted and processed under various conditions that are further recognized by the cell (Abisado *et al*., 2018). Next, in response to pheromone, cells swim in a coordinated fashion, thereby forming a kind of wall surrounding rings of bacteria having the same exploration behavior (Chong *et al.*, 2013).

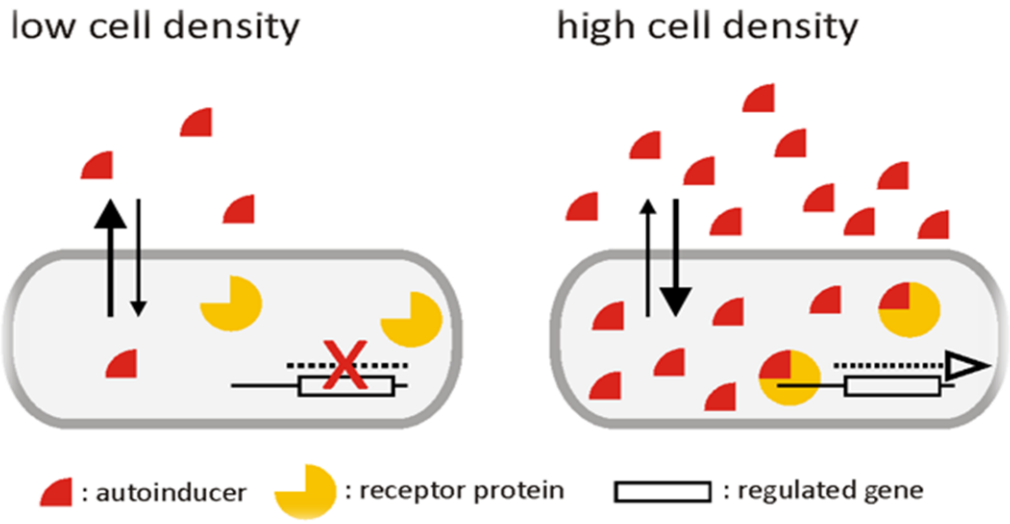

Fig-1: Effect of cell density on quorum sensing expression (Chong *et al*., 2013).

2- Q.S Signaling Molecules (Autoinducers)

There are three types of signaling molecules:

1. Acyl-homoserinelactonase (AHLs)
2. Auto-inducer peptides (AIPs)
3. Autoinducer-2 (AI-2)

3.1- Acyl-homoserinelactonase (AHLs).

AHL signaling molecules are mainly produced by Gram negative bacteria that synthesized by AHL synthase (I protein) encoded by a gene referred to as and I gene (luxI in *V. fischeri*and lasI in *P. aeruginosa*) which mediate intracellular communication and able to diffuse through membrane (passive diffusion).When the population density reaches the threshold, these AHL molecules exceed the threshold concentration and are recognized by specific receptors that belong to a large class of DNA-binding transcription factors named (regulatory protein, R-proteins) such as *LuxR*in *V. fischeri* and *LasR*in *P. aeruginosa*(De Kievit and Iglewski, 2000).

N-acyl-L-homoserine lactone (AHL) mediated gene expression is one such bacterial quorum sensing system that has received an enormous amount of attention primarily owing to the direct role of many of the regulated phenotypes to human and plant infection. AHL mediated gene expression involves the production of AHLs by an AHL synthase enzyme most commonly encoded by a homologue of the *luxI* gene of the marine symbiont *Vibrio fischeri* (Calatrava-Morales *et al*.,2018). AHLs typically diffuse through cell membranes and increase in concentration in the local extracellular environment if there are many producing cells in one location and there are barriers to diffusion preventing AHL loss from that location. Once a threshold intracellular concentration is reached, AHLs interact directly with

transcriptional regulators encoded by homologues of the *luxR* gene of *V. fischeri* resulting in a transcriptional response. In the case of *V. fischeri*, in which AHL mediated gene expression was discovered, the transcriptional response encodes for the production of light that forms the basis of symbiotic interactions with marine fish and the bobtail squid *Euprymnascolopes*(Chong *et al*.,2013) were observed (Fig. 2).

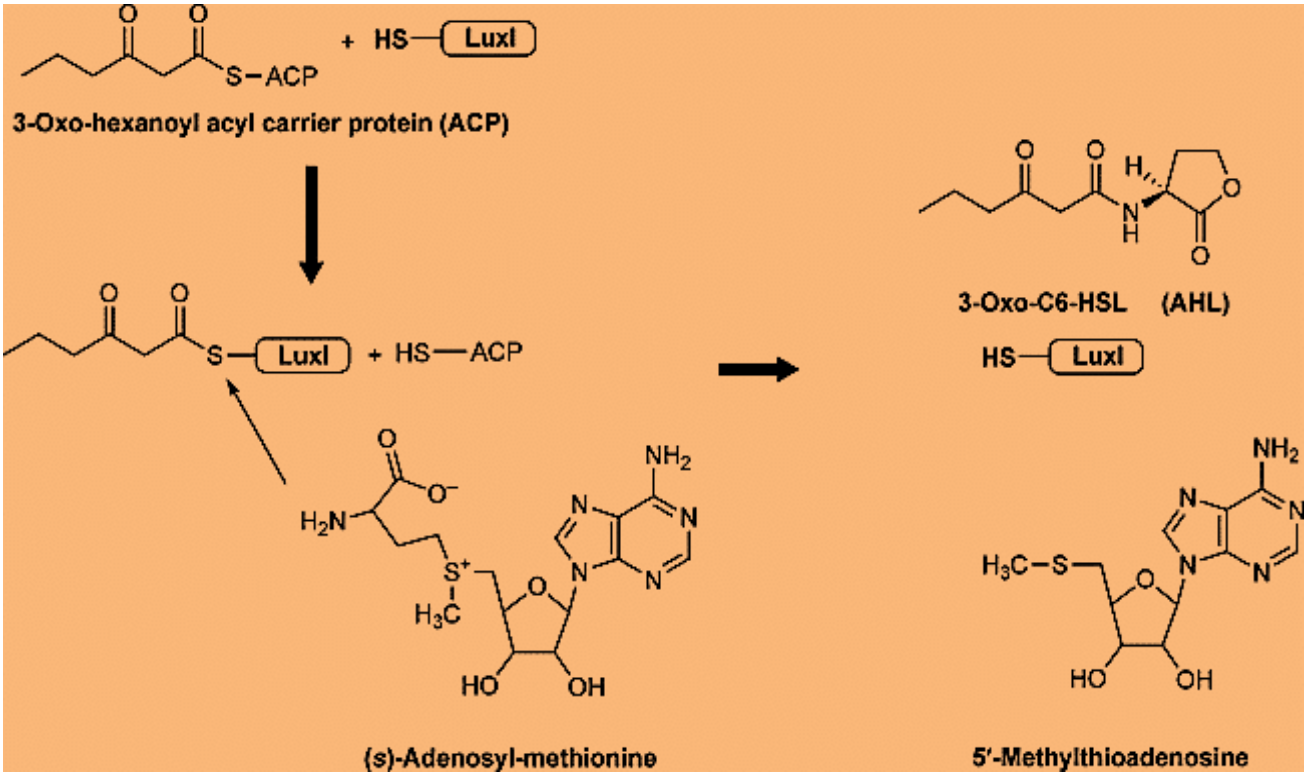

Fig-2: The synthetic pathway of AHL (3-oxo-C6-HSL in this case) (Horng *et al*., 2002).

3.1.1- *Vibrio fischeri*Q.S

Q. S was first observed and described in bioluminescence bacterium *V.fischeri*. It is a symbiotic bacterium isolated from a light organ of a squid (*Euprymnascolopes*). In *V. fischeri*, several kinds of quorum sensing system were identified. At first, *lux* system was found. The *lux* system regulates the luciferase operon and light production. *LuxI*was isolated as an AHL synthase and directs the synthesis of N-(3-oxohexanoyl)-l-homoserine lactone (3-oxo-C6-HSL)(Hmelo, 2017).

*LuxI*binds an acylated ACP and S-adenosylmethionine. The acyl chain is transferred from ACP to *LuxI* and forms an amide bond with S-adenosylmethionine. Then, AHL is formed with the formation of lactone ring and release of 5′-methylthioadenosine (Chan, 2015) (Borges *et al*., 2016) were observed (Fig. 3).

*LuxI*consists of 193 amino acids including an active site for amide bond formation and a binding site of acylated-ACP. *LuxR* was isolated as a transcriptional activator of the luciferase operon. 3-Oxo-C6-HSL synthesized by *LuxI*binds to *LuxR* and the 3-oxo-C6-HSL–LuxR complex binds to DNA at the region named lux box and activates the transcription of the luminescence operon *luxICDABEG*. *LuxR* consists of 250 amino acids and has two domains. The N-terminal region is an AHL-binding site and the C-terminal region is a DNA-binding site with a helix–turn–helix motif. The *Lux* system also has effects on colonization factors (Chan, 2015).

AinS was also isolated as another AHL synthase in *V. fischeri*. *AinS* directs the synthesis of C8-HSL. While the *Lux* system regulates the bioluminescence at high cell density, the *Ain* system effects at lower cell density. These two quorum sensing systems are connected and regulate sequential induction. At low cell density, *LuxO*represses *LitR*, which is a positive regulator of the expression of *LuxR*. During the cell growth, even at the lower cell density, C8-HSL produced by *AinS* binds to *AinR*, which is a homologue of *LuxN*, and C8-HSL–AinR complex inactivates *LuxO*. Increased expression of *LitR*results in increased expression of *LuxR*. C8-HSL also binds to *LuxR* directly and slightly activates bioluminescencewere observed (Fig. 4). At high cell density, *Lux* system mainly regulates bioluminescence (Ampomah-Wireko *et al*., 2021).

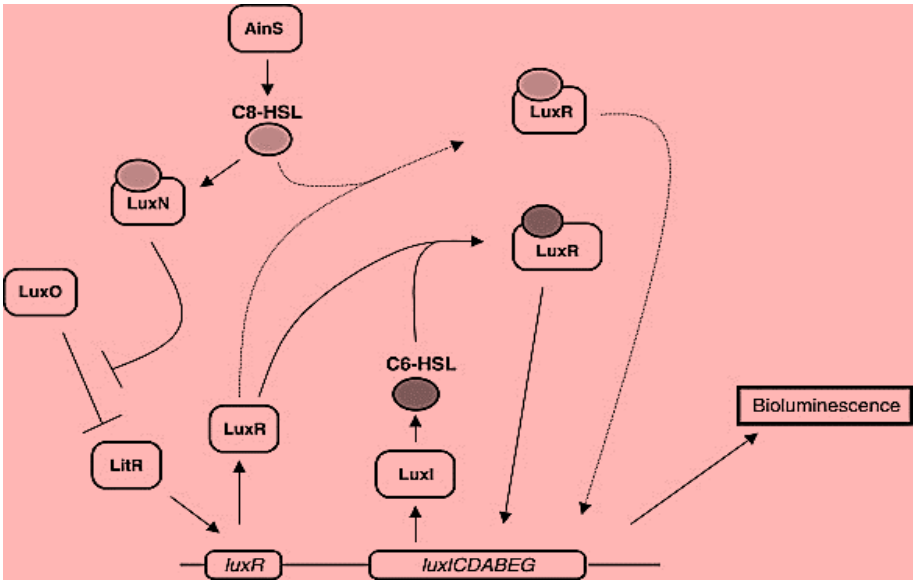

Fig-3: The relation of Lux and Ain quorum sensing systems in Vibrio fischeri for bioluminescence (Darch *et al*., 2012).

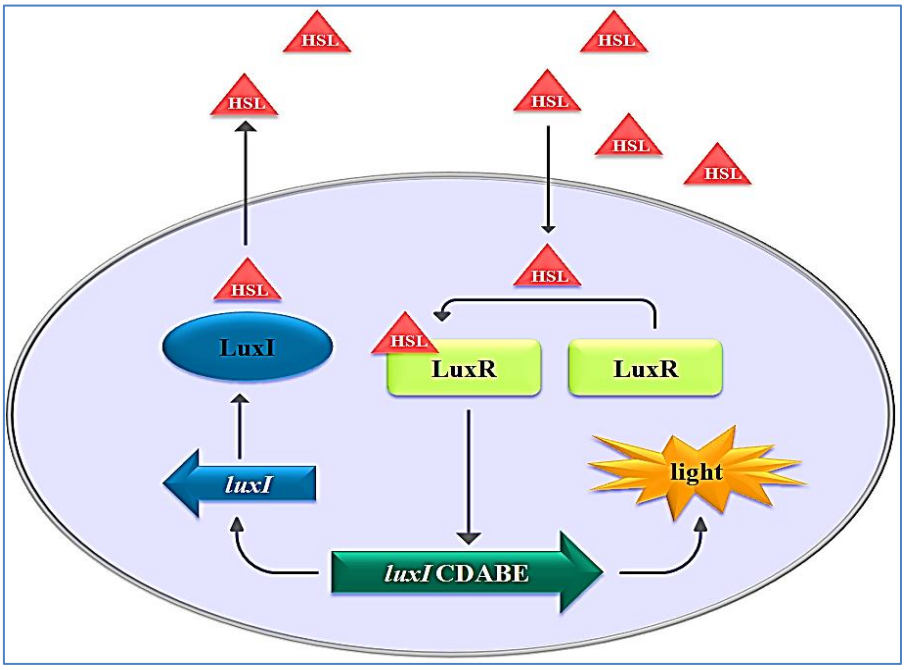

Fig-4: Acyl homoserine lactone (AHL)-dependent quorum sensing system as exemplified by LuxI/R system in *V. fischeri.* Gram-negative bacteria (Darch *et al*., 2012).

3.2. Auto-inducer peptides (AIPs)

AIPs are Small peptides regulate gene expression in Gram-positive bacteria such as *Staphylococcus aureus*and other Gram-positive bacteria. These molecules recognize by membrane bound histidine kinase as receptor. Signal transduction occurs by specific mechanism (via conserved phosphorylation /de-phosphorylation mechanism). In Gram-positive bacteria, secretion of peptides requires specialized export mechanisms. For example, some peptide autoinducers are secreted by ATP-binding cassette transporters (ABC channel) that couple proteolytic processing and cellular export (Kiran *et al*., 2008).

The induction pathway in the recipient bacterium called two component signal transductions composed of sensor kinase located in the bacterial cell membrane act as a receptor and response regulator that bind to promoter to activation gene expression. Following secretion, peptide autoinducers accumulate in extracellular environments. Once a threshold level of signal is reached, a histidine sensor kinase protein of a two-component regulatory system detects it and a signal is relayed into the cell, the signal ultimately ends up altering gene expression (Kleerebezem *et al*., 2001)were observed (Fig. 5).

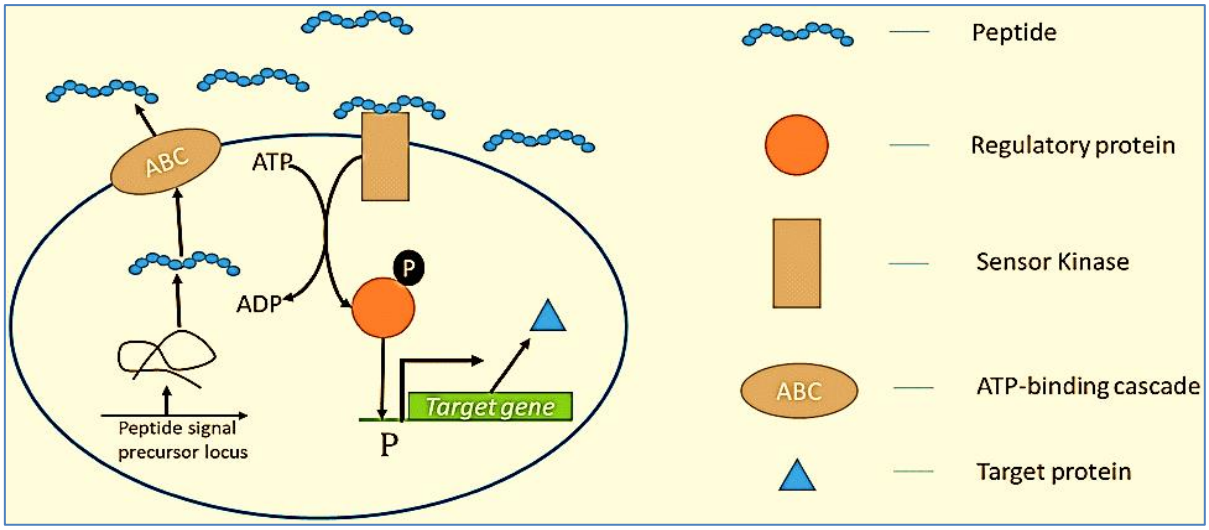

Fig-5: Quorum sensing in Gram-positive bacteria using Auto-inducer peptide signaling molecules (Kleerebezem *et al.*, 2001).

3.2.1. *Staphylococcus aureus* Q.S

S. aureus is found among the normal human skin flora. If the epithelial barrier is compromised, *S. aureus* can cause minor skin infections. These infections can lead to pneumonia, bacteremia, and sepsis (Soto, 2013). *S. aureus* is the leading cause of hospital-related infections in the United States. Its ability to cause disease depends on expression of an array of adhesion molecules, toxins, and compounds that affect the immune system. QS Regulates expression of genes encoding these virulence factors. The ability of *S. aureus* to cause a wide range of infections is attributed to its ability of virulence factors expression (adhesins, toxins, and enzymes), many of which are under the control of the quorum-sensing accessory gene regulator (*Agr system*) (Periasamy *et al*., 2012).

The Agr locus found to be widespread in *staphylococci*. The *Agr* system have a critical role in pathogenesis by regulating virulence factors, biofilm formation, and the heterogeneous resistance of methicillin-resistant Staphylococcus aureus (MRSA).The *Agr* system consists of an autoinducer peptide of *Staphylococcus aureus* (AIP) generated by *AgrD* and a two-component sensor kinase and response regulator, *AgrC* and *AgrA*, respectively. The *(AIP)* was secreted out of the cell through the action of the *AgrB*membrance protein. When the concentration increases, AIP binds to the histidine sensor kinase receptor *(AgrC*) and result in it autophosphorylation (Periasamy *et al.*, 2012). The phosphorylated *AgrC*that activates of response regulator *(AgrA)* gene which act with another regulator *SarA*, to transcription at P2 and P3 promoters resulting in elevated intracellular levels of Q.S amplification (RNAII) (Yarwood *et al*.,2004)were observed (Fig. 6).

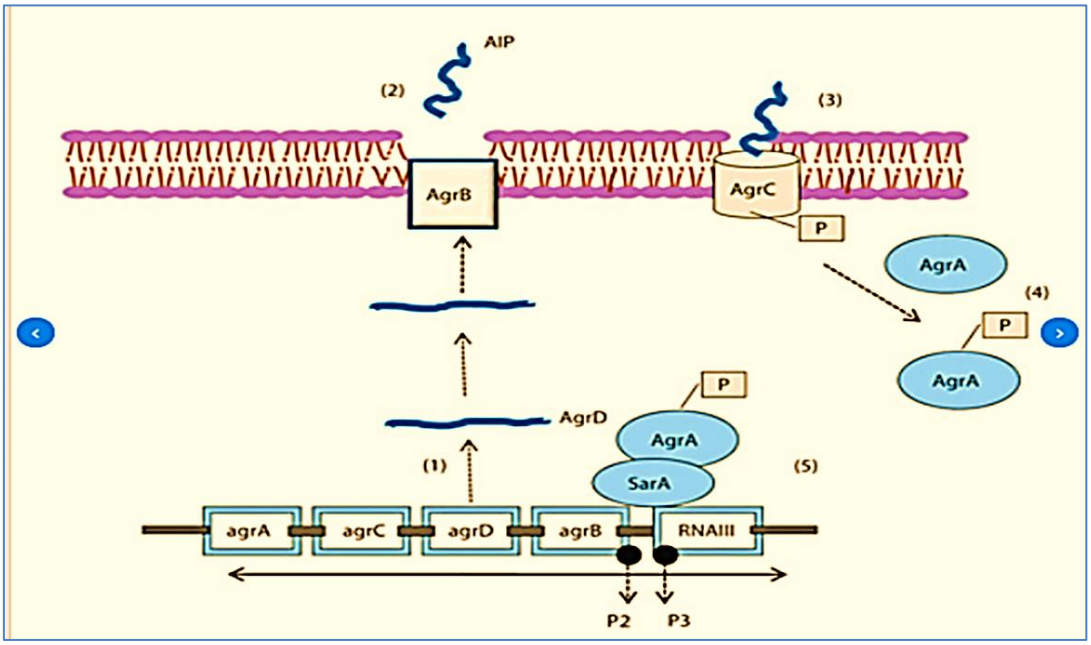

Fig-6*: Staphylococcus aureus*Quorum sensing (Yarwood *et al*., 2004).

3.3. Autoinducer-2 (AI-2) and multilingual bacteria

This type of autoinducers involve in interspecies communication among bacteria. It presents in both Gram-positive and Gram-negative bacteria. Multilingual bacteria also called (The universal *LUXs* language), *LUXs* involved in production of autoinducer-2 (AI-2). Different studies found that many bacteria possess a specific- specific language as well as a specific-nonspecific language; these findings ensure that bacteria can assess their own population and other population density of other bacterial species in their area.AI-2-mediated quorum sensing system was first found in *V. harveyi* (Henares, 2012).

3.3.1. *V. harveyi* Q.S.

It is a marine bioluminescent bacterium and regulates bioluminescence, production of siderophore, polysaccharide and metalloprotease, and type III secretion through quorum sensing.Despite its relatedness to *V. fischeri*, *V. harveyi* lacks a LuxI/R quorum-sensing system, and instead employs a hybrid quorum-sensing circuit, detecting its AI through a membrane-bound histidine kinase and using a phosphorelay to convert information about the population size to changes in gene expression (Heras *et al*., 2015). Since their identification in *V. harveyi*, such hybrid systems have been identified in many other bacterial species. *V. harveyi* uses a second AI, termed autoinducer-2 or AI-2, which is unusual because it is made and detected by a variety of different bacteria, both Gram-negative and Gram-positive. Thus, *V. harveyi* has been instrumental to the understanding and appreciation of interspecies bacterial communication (Yang and Defoirdt, 2015).

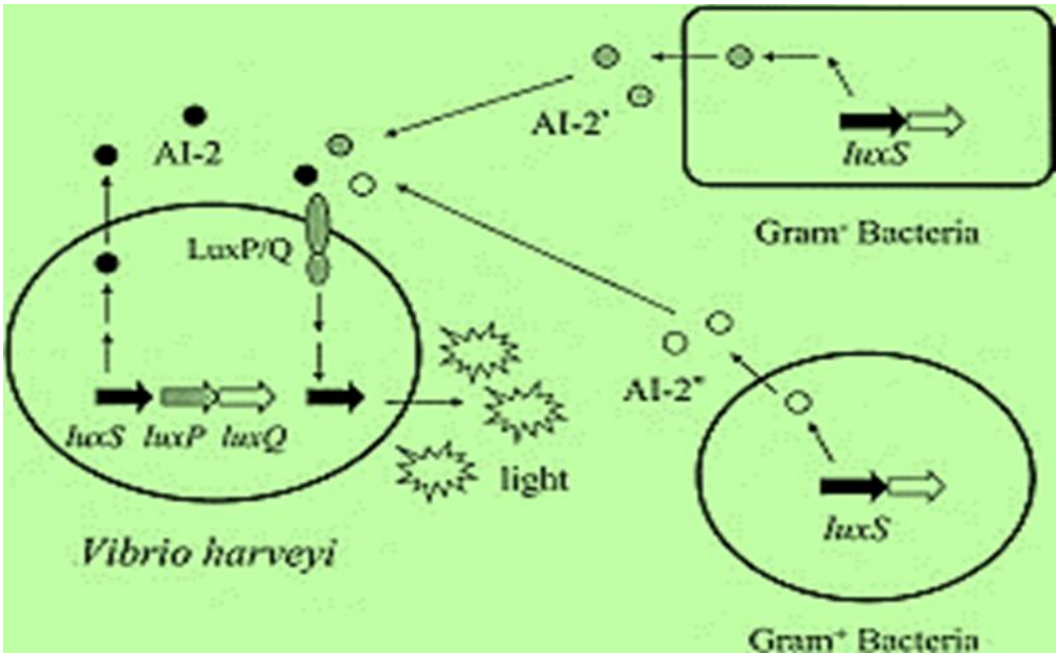

Fig-7: Multilingual language quorum sensing using by *Vibrio harveyi*bacteria (Yang and Defoirdt, 2015)

3-β-OH-C4-HSL is synthesized by *LuxM*. *LuxN* is identified as a receptor of 3-β-OH-C4-HSL. Without 3-β-OH-C4-HSL, that is, at low cell density, through *LuxU* and *LuxO*, LuxN leads to inactivation of LuxR, which is required for transcription of genes for bioluminescence, production of siderophore, polysaccharide and metalloprotease, and type III secretion.At high cell density, 3-β-OH-C4-HSL binds to *LuxN* and such 3-β-OH-C4-HSL–*LuxN* complex leads to inactivation of *LuxO t*hrough *LuxU* and then *LuxR* is activated to promote transcription of genes (Anetzberger *et al*., 2019)were observed (Fig. 7, 8, 9).

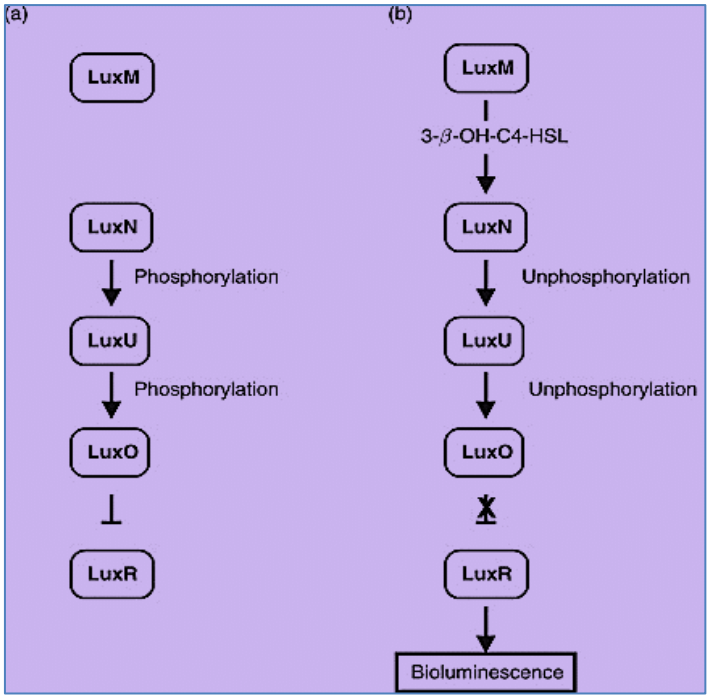

Fig-8: Regulation for bioluminescence in *Vibrio harveyi* (a) at low cell density and (b) at high cell density (Yang and Defoirdt, 2015).

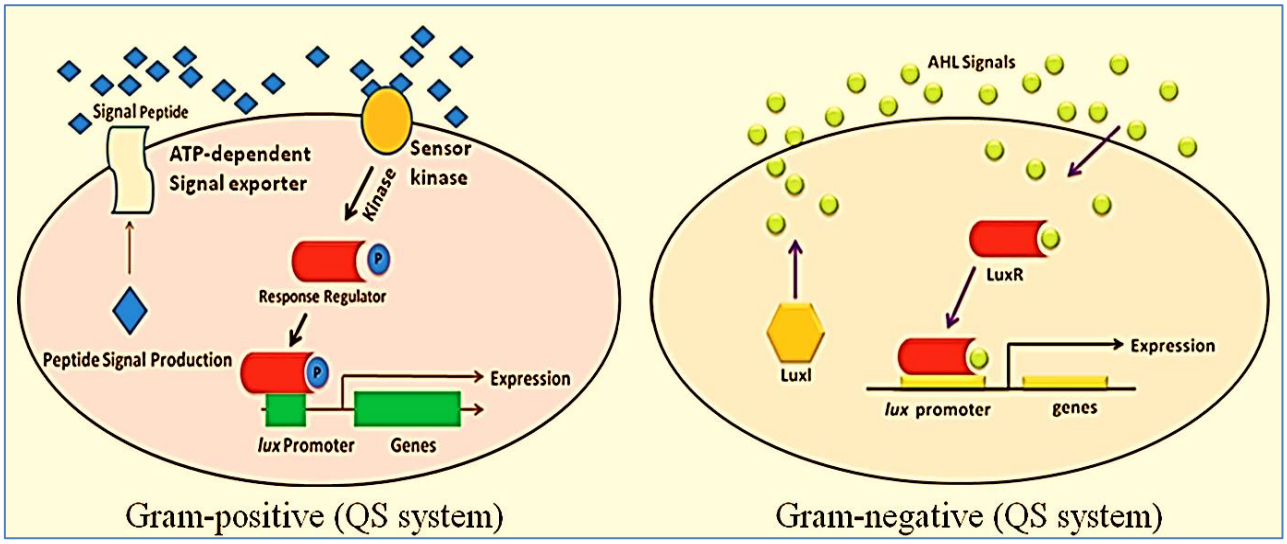

Fig-9: Quorum sensing in Gram-positive and Gram-negative bacteria (Whitehead *et al*., 2001).

3- Quorum sensing correlation with virulence factors and biofilm formation

Gram-positive and Gram-negative bacteria use quorum sensing communication circuits to regulate a diverse array of physiological activities. These processes include symbiosis, virulence, competence, conjugation, antibiotic production, motility, sporulation, and biofilm formation.Many studies have shown that bacterial quorum sensing (QS) signaling plays important roles in biofilm formation. Biofilm formation is one of the necessary requirements for bacterial adhesion and growth. It is accompanied by the production of extracellular polymer and adhesion matrix and leads to fundamental changes in the bacterial growth and gene expression.Several human pathogenic bacteria able to produce Acyl homoserine lactone dependent biofilm including *Burkholderiacepacia* and *serratiamarescens*(Galloway *et al*., 2011).

The formation of biofilm significantly reduces the sensitivity of bacteria to antibacterial agents and radiations and seriously affects public health. *RpoS* that regulation the slow growth rate of some cells in biofilm, which in turn leads to Q.S controlled expression (Srinivasan *et al*., 2021). Q.S controlled processes such as biofilm formation were dependent on efflux pump that HSL requires active transport through efflux pump to diffuse across the cell membrane, therefore increase in efflux pump activity could have several effects on biofilms formation through increase in inter and

throw of QS molecules. In *Staphylococci*, phenol-soluble modulin (PSM) peptides have surfactant molecule properties and are under transcriptional control of *AgrA*. Agr controls biofilm formation and in *S. aureus PSMs* regulated by agr contribute to biofilm detachment. Agr also regulates production of alpha-toxin, delta-hemolysin, and adhesins necessary for biofilm formation and maturation.Q.S via agr increases production of virulence factors, which include various enzymes and toxins. Coagulase is an enzyme that coats the cell surface in fibrin as protection from immune defenses like phagocytosis. Toxins include superantigens, proteases, exfoliative toxins, hemolysins (alpha, beta, gamma, delta), and leucocidin (Novick andGeisinger, 2008).

Among them, cell-to-cell communication in bacteria is crucial for their adaptation to different environments and is regulated by quorum sensing (QS) networks. This signaling process is also involved in the expression of genes important to the production of virulence factors, host colonization, biofilm formation and antibiotic resistance in a number of pathogenic bacteria. QS Systems play a central role in the ability of bacteria to promote pathogenicity and much attention on the development of new anti-infective agents has been focused on targeting these pathways. The best studied QS systems in marine microbial environments occur in surface-attached communities (biofilms) and depend on AHL signaling. The main role of AHL-QS in marine microbial communities is related to ecologically and biogeochemicallyprocess as well as to massive bioluminescence episodes associated with algal blooms (Williams and Cámara, 2009) were observed (Fig. 10).

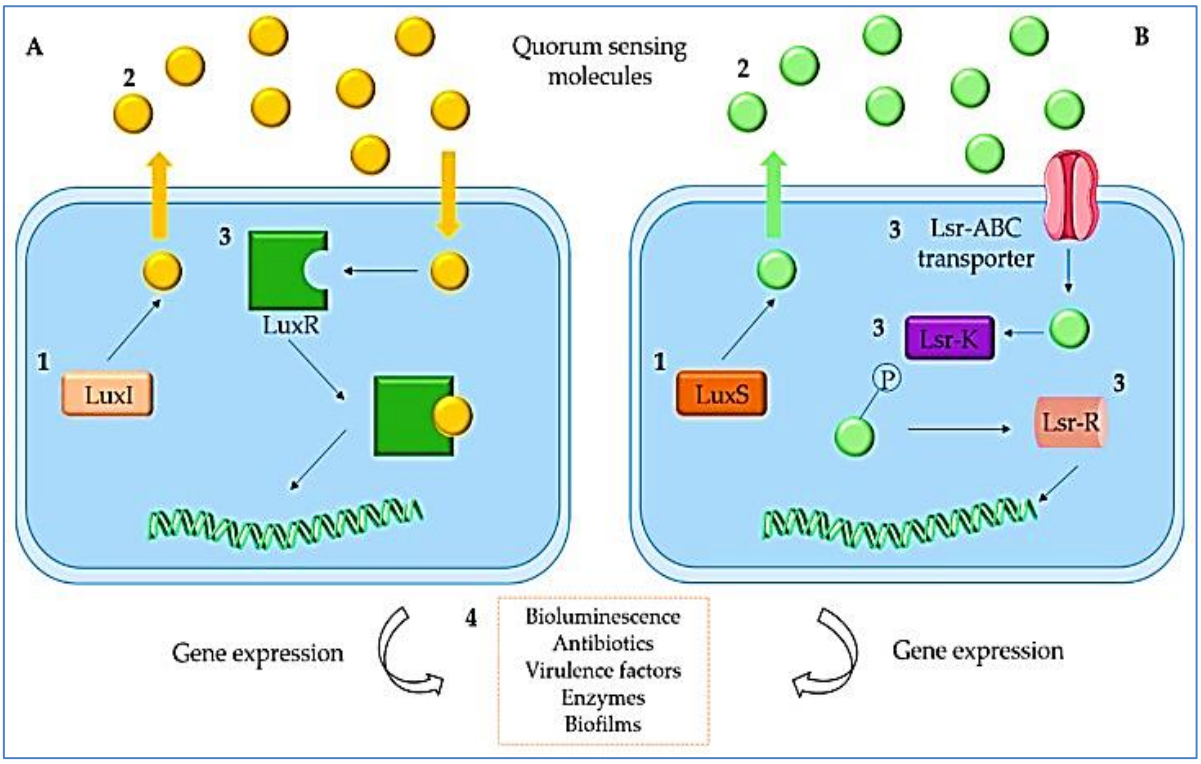

Fig-10: General scheme of the main QS mechanisms described for marine bacteria. (A) LuxI/R-type system; (B) LuxS/AI-2 system. 1—Signal synthase protein (LuxI, LuxS); 2—Autoinducers (AI-1, AI-2); 3—Response regulator protein/receptor (LuxR; Lsr-ABCKR); 4—QS regulated behaviors (Wang *et al*., 2020).

4- Quorum Quenching QQ

Quorum quenching (QQ) refers to the mechanism by which bacterial communication can be interrupted, or it is the process of preventing QS by disrupting the signaling. QQ can be achieved by inhibiting the production of auto-inducers, their detection by receptors, or their degradation and many other mechanisms. At higher pH and higher temperature AHL molecules undergo lactonolysis and this causing that it AHL molecules lost its activity. Also, the QS inhibitors have been synthesized and isolated from many natural extracts such as garlic extract. Some bacteria produce lactonolysing enzymes such as (AiiA) from *Bacillus cereus* and *B. thuriengiensis*(Uroz *et al.*, 2009).

Many organisms such as algae, plant and bacteria produce molecules that are structurally similar to AHLs, and therefore, competitively inhibit their binding to receptors.QS Inhibition strategies, also known have a multifaceted value, particularly in the present scenario of rising antibiotic resistance (Frederix and Downie, 2011). Such molecules are valuable to restrain or even preclude the impact of bacterial diseases in plants, animals or humans. In addition to their role in infection control, the signaling molecules can also influence other microbiological features, particularly microbe-microbe interaction, host-pathogen interaction, and microbial physiology. Microorganisms can develop signal

interference mechanisms to adapt to different environments, and compete for nutrients and ecological niches. In a clinical perspective, the most relevant aspects of this approach are their no-lethality and versatility, as it exerts a more restricted selective pressure on bacterial survival and can act on several molecular targets. Another proposed advantage is that QSIs can also favor the use of low doses of antibiotics, as they usually improve their effectiveness (Rutherford and Bassler, 2012).

They can be broadly grouped into two groups, the QSIs (non-enzymatic methods) and the QQ enzymes (enzymatic methods). QSIs generally englobe compounds that are *able to inactive AI synthases* or receptors by competitive binding/structural modification, while QQ enzymes switch off signal transmission by signal degradation (Frederix and Downie, 2011).

The first major QS-disrupting strategy that has been studied is the interference with the detection of the AIs and the second one is the inactivation/degradations of the signal molecules.His greatest part of the QQ enzymes are involved in AHL-degradation, which can be classified into three types based on their catalytic mechanism: AHL lactonase/paraoxonase (lactone hydrolysis), AHL acylase (amidohydrolysis) and AHL oxidase/reductase (oxidoreduction). Most of the described QS inhibition strategies have primarily targeted AI-1 and then AI-2 (Jiang *et al*., 2019) were observed (Fig. 11).

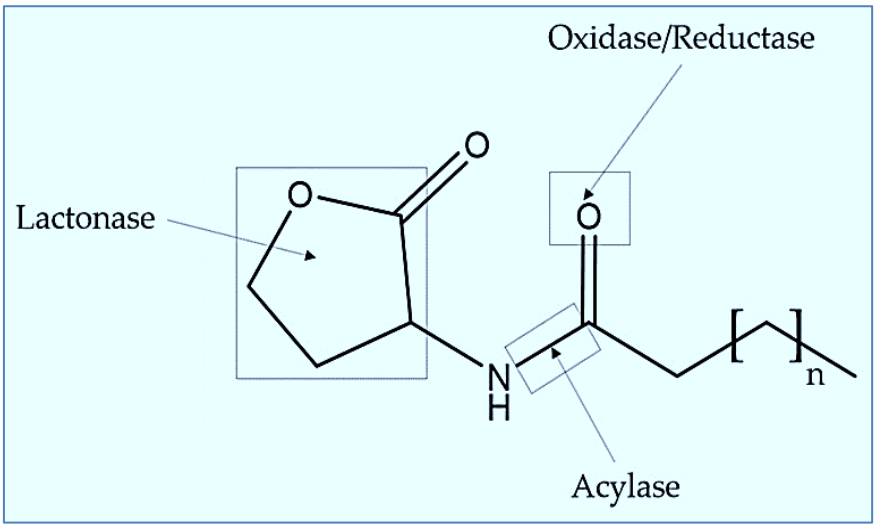

Fig-11: The AHL-degrading enzyme targets. Broken lines mark position of possible cleavages of N-Butyryl-l-homoserine lactone (C4-HSL) molecule by lactonase, acylase and oxidase/reductase (Wen, 2022).

5- ACKNOWLEDGMENTS

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