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Quorum sensing: A molecular cell communication in bacterial cells

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ABSTRACT

Background

Quorum sensing is a cell-to-cell communication, which is extensively observed in bacteria. This process allows the cell to detect, analyze, share and act upon various environmental stimuli based on cell density. The molecular aspect of this process is the secretion and detection of chemical signaling molecules called autoinducers (AIs), which act upon the gene expression. The quorum sensing signaling pathway is specifically observed only bulk population or in other words, the quorum sensing is effective only in high cell density. The quorum sensing circuit in the bacterial population is widely studied under the following heading; quorum sensing in Gram positive bacterium, Quorum sensing in Gram negative bacterium and the Quorum sensing with respect to Interkingdom communication. These models are studied using the widely studied models like *Vibrio fischeri* in Gram negative QS circuit, *Staphylococcus aureus* in Gram positive QS circuit and *Vibrio harveyi.* This review paper details the introduction of quorum sensing and their gene level explanation and how they effect on the virulence of a particular species of bacteria. This paper also throws light on the realization that the bacteria has the capable of performing coordinated activities that was so long contributed to the eukaryotic cell performance.

Keywords

Autoinducers, Bacterium, Gram positive, Quorum sensing, *Staphylococcus aureus*, *Vibrio fischeri*, *Vibrio harveyi*

Introduction

Communication or basic form of speaking and exchanging information is a sign of life and is one of the identifying factors in the living organisms. It was thought that only advanced forms of life were capable of any form of communication, but in the advent of detailed and sciences which expertise at extreme levels of life, i.e., at microscopic levels and in cosmic levels, it was found that microscopic prokaryotic forms of life "speak and communicate" with each other. In the conventional point of view, the prokaryotic bacterial form of life live unicellularly and react to external stimuli by detecting the chemical signaling molecules and physical stimuli in the form of changes with respect to the original state. For many years it was thought of that the prokaryotes are self-sufficient and are thought to be strictly self-oriented and unicellular. This wide belief was deeply rooted due to the golden criteria of the pure culture paradigm of pathogenic organisms to cause disease in a host by Robert Koch. Although his golden criteria were an important tool in the identification of pathogenic bacteria and in the development of the antibiotic treatment in the control and prevention of diseased condition, this failed in the successful explanation of the lack of naturally occurring pure cultures of pathogenic microorganisms. In fact, they are found to be present in a complex and dynamic surface associated colony or community known as biofilms. What has been seen is that the individual bacterial components of such biofilms do not randomly stick to each other as they may be seen, but rather maintain intimate and strong relationship with each other.

The communication between these bacteria does not in literal sense mean in physical touch, this communication is achieved via the secretion of small extra cellular biochemical compounds, which help in the identification and further response. This kind of communication in bacterial colonies to react and reflect on defined environment with a particular threshold of signaling molecules and the 'quorate' population of the bacterial population in conducting activities in coordinated manner and in making decisions in high cell density conditions. Such decisions are termed to be a group-based decision and high cellular density dependent communication. Such extracellular signaling molecules are known as auto inducers (AIs) [1-3]. The further detailed and in-depth study of this biofilm colony formation and their communication form has brought to lime light the advanced eukaryotic like features of these bacterial microorganism and their unexpected high degree of coordination. Further they have exhibited well monitored and regulated physiological and group activities which were governed by a process now known to be quorum sensing where the cell secretes extracellular signaling molecules by which they detect and respond to their environmental stimuli. It has also been observed that this quorum sensing has also been a key player in the establishment of pathogenic conditions in a particular host. This observation has also been supported by the fact that for an infectious state to be established a particular threshold of cell density has to be achieved before the virulence and its symptoms are observed.

History

As mentioned above, the communication in bacterial cell through quorum sensing system is mainly responsible in many character expressions. This QS circuit has been scientifically established in many phylogenetically diverse microorganisms. There has been the identification of many gene families like the LuxR/I gene system, the LuxS system and many of their homologs in the maintenance, regulation of the gene regulation and protein synthesis of the targeted character. The phylogenetic tree analysis of the gene systems involved in the quorum sensing in bacterial species have shown that the LuxS and the LuxR/I tree show similarity and agreement to the ribosomal RNA tree; this indicates to the path of evolutionary aspects in bacteria like Probacteria and Firmicutes. The evolutionary study of the genes involved in the QS circuit has suspected to undergo a number of modifications like ancestral duplication and gene loss within the main genus.

The first ground-breaking solid explained proof in the field of cell-to-cell communication in the bacterial field was done by study of the bioluminescence in a Gram negative marine bacterial system of *Vibrio fischeri* [2]. This bacterium was found living symbiotically on Hawaiian squid for the luminescence at the nighttime for the hunting purpose. The light emission was explained at molecular aspect in credit to the luciferase operon with the LuxR/I gene system and the autoinducer being Acyl- Homoserine Lactone (AHL).

The initial ideology was that only the *Vibrio fischeri* and its counterparts of the same family where capable of this circuit, but with advancement in the research and experimental work, it was seen that homologous systems with diverse biological purposes of the quorum sensing signaling pathway was observed in many probacterial and bacterial species. Few of such observations included the expression and regulation of virulence and pathogenic aspects in the human pathogen *Pseudomonas aeruginosa* [3, 4], the expression and regulation of a range of enzymes to attack the plant host and the production of antibiotics by a phyto pathogen Erwinia carotovora [2,5,6] Another important and still widely studied and used phyto pathogenic bacteria Agrobacterium tumeficiens was observed to have a LuxR/I gene system if Qs circuit system in its plasmid region which helps in the conjugal transfer of the plasmid into wounded dicot plants and establishing a diseased condition [7].

The experimental studies showed that the QS circuit in different species shows the production of different autoinducers which is responsible for the expression and the regulation of different phenotypic characters via the same QS outline circuit. This was explained by the use of marine Gram negative bacteria *Vibrio fischeri* and *Vibrio harveyi*, these two bacteria use the same LuxR/I gene system but the

autoinducers in both bacterium are different; the former uses acyl-Homoserine lactone as the signaling molecule for the expression of bioluminescence character whereas the latter uses furanosyl borate diester as the signaling molecule for the expression of virulence character [8-11]. Another characteristic feature of the quorum sensing signaling pathway is the presence of LuxS gene in many species of the bacterial population which was explained to be the reason for the expression of autoinducers which aid in the interkingdom and interspecies communication. LuxS gene system in many bacteria has been found to have same biosynthetic pathways, but the targeted gene by the autoinducers produced by it has been attributed to different areas like few target the respiratory track of the host like Clostridium perfringens by producing toxins in that region; whereas in case pathogen like *Vibrio cholerae* and *Streptococcus typhimurium* , the LuxS gene system is responsible in the expression and establishment of the virulence cascade [12-13].

Many such gene systems and the QS circuit system trees are analyzed and studied using phylogenetic and evolutionary sciences. The recent development in the field of Proteomics and Bioinformatics have also played a very major role in the establishment in the similarity between different family trees and establishing their evolutionary relationships.

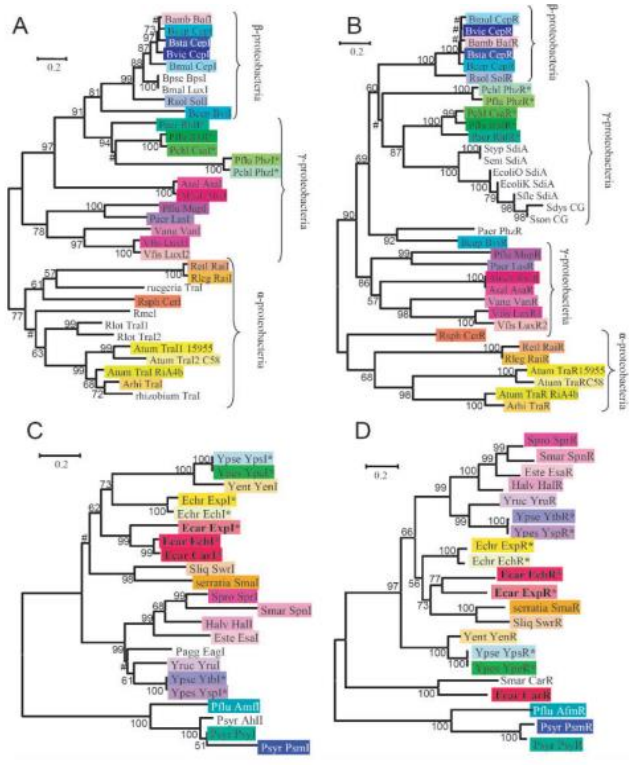

Figure 1: familial trees with similar QS circuit genes coding

This image shows the various familial trees with similar QS circuit genes coding for the corresponding proteins which play an important role in cell signaling process [13].

Figure 1 shows the various family trees of bacterial colonies with similar protein alignment by a particular QS circuit gene. The figure A denotes the tree with similar protein alignment with respect to the LuxI of the A family; the figure B denotes the tree with similar protein alignment with respect to the Lux R gene system of the A family; the figure C denotes the tree with similar protein alignment of the LuxI gene system of the B family and figure D denotes the tree with similar protein alignment with respect to the LuxR gene system of the B family [14].

The presence of homologous systems of the gene system in the QS circuit in the different species of bacteria explains the ability of the organism in adapting to new target genes with respect to its target host organism. The system thereby helps us in understanding more in the aspect of communicative relation of the bacteria with its environment and its host organism, be a prokaryotic or a eukaryotic system.

Working mechanism of quorum sensing process

The primary action of quorum sensing has been seen in the bacterial gene regulation mechanism via cell density. Thereby, three models of quorum sensing mechanism have been established; one for the Gram negative bacteria, one for Gram positive bacteria and one of universal nature.

The basic working mechanism of quorum sensing is the production, secretion and detection of autoinducers. These AIs start accumulating in the external environment of the cell as the cell density increases and the bacterial cell uses this increase or decrease in the chemical moieties in its external surrounding in tracking and analyzing the cell population and aptly change its gene expression as per the situation. Quorum sensing is only possible in large number of population and this process is governed by gene which functions at bulk level gene expression. Many physiological processes like bioluminescence, sporulation, competence, antibiotic production, biofilm production, symbiosis, conjugation, motility, and more. The generalization of the autoinducers has been classed as the use of acylated homoserine lactones in gram negative bacteria and oligo-peptides in gram positive bacteria. The old observation had been that the autoinducers are specialized to a particular strain of bacteria, but the recent discovery has seen that the cell –to-cell communication via autoinducers facilitate both within the same species and as well between different bacterial species.

The autoinducers show host specific responses in general. Even though the nature, the relay mechanism, the gene target mechanism, differs in each bacterium, the quorum sensing system allows in each case the ability to communicate within the same strain as well as with different microorganisms by coordinating the gene expression with the help of the autoinducers. This allows

the prokaryotic cells to behave as a eukaryotic cell in bulk cell density.
The quorum sensing evolution and its effect on the prokaryotic cell to exhibit qualities of eukaryotic cell directs to the evolutionary indication and development of multicellularity.

The quorum sensing pathway:
The quorum sensing mechanism in general can be divided into four main steps;

i) The production of small biochemical signal molecules by the bacterial cell.
ii) The release of the signal molecules by active or passive mode, into the external environment.
iii) The recognition of these secreted signaling molecules by specific receptors on the cell membrane receptors, once they cross a threshold concentration, that is, in bulk cellular density.
iv) This is an important step, as these AIs enter the cell, they influence the gene expression and they express a particular cell behavior.
One of the commonly and often observed consequences of the quorum sensing is the gene regulation in the increased synthesis of the proteins involved in the signaling molecule production. The stronger the signaling molecules, the more the synthesis of the signaling molecule proteins; this causes a positive loop feedback. This is the reason for the term autoinducers; the signaling molecule initiates the synthesis of the protein of the signal molecules.
Like mentioned above, the quorum sensing system has been classified into three systems, the LuxR/I gene system in Gram negative bacteria, the LuxS/AI-2 gene system in the Gram positive bacteria and the AI-3/epinephrine/norepinephrine interkingdom signaling system used by the bacteria for interspecies communication. These gene systems used by the different strains of bacteria for the quorum sensing has been discussed below.

The quorum sensing system in gram negative bacteria and in gram positive bacteria.
The gram-negative bacteria use small molecule autoinducers for their communication. These autoinducers are produced and secreted by the cell into its external environment and when these molecules reach a particular threshold, they bind to the membrane receptors and they are taken into the cell. Here they help in gene regulation in the quorum sensing circuit and thereby help in the expression of various phenotypic characteristics in the bacterial cell. In few cases of Gram negative bacteria, there are two compounds in the detection of AIs which function analogously.

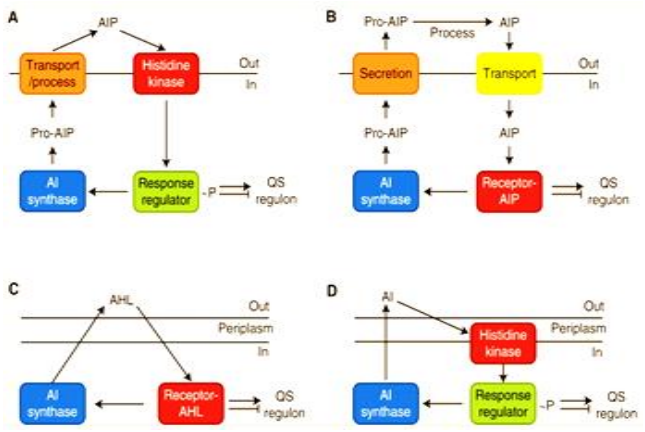

Figure 2: Paradigmatic quorum sensing circuits

The above figure depicts four paradigmatic quorum sensing circuits followed in Gram positive and Gram negative bacteria. The image A depicts the two-component signaling process; the image B depicts the AIP-binding transcription based QS regulation; both occurring in gram positive bacterial cell. The gram negative bacterial follow a different set of pathways in regulating the QS circuit namely the LuxL-LuxR type system depicted in the image C and the two-component system as depicted in the image D.
The gram positive, unlike the gram negative bacteria, use a different quorum sensing system. The gram positive use peptides as autoinducers and as signaling molecules. The autoinducers when bound to the membrane receptors, they undergo auto phosphorylation due to the activity of the receptor kinase enzyme. Upon the phosphorylation, they pass the phosphate to cytoplasmic response regulators which activate the required genes in the quorum sensing regulon.

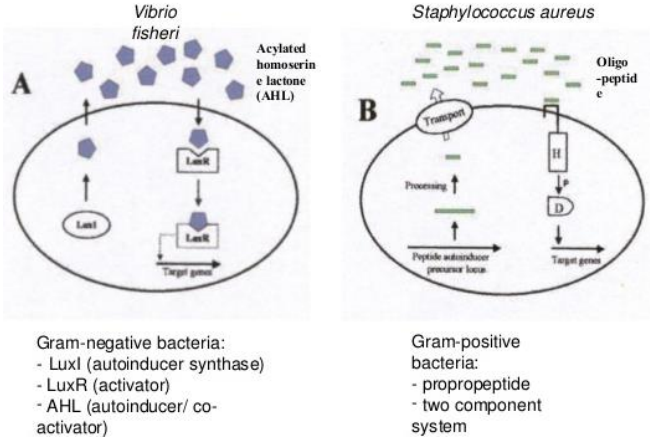

Figure 3: Quorum sensing – autoinducer systems

The above image depicts the classic example of the quorum sensing in gram positive bacteria namely the *Staphylococcus aureus* and the gram negative bacteria namely *Vibrio fischeri.*

The above image takes the commonly studied examples of the QS circuit in both Gram positive and Gram negative bacterium to explain the varied range of characters expressed by this quorum sensing system. the above taken examples are observed in detailed manner in the following matter.

Quorum sensing in gram negative bacteria:

Like mentioned above, the quorum sensing in gram negative bacteria is via the AHL autoinducer. The gene regulation in gram-negative bacteria is governed by the LuxR/I gene system. This model was first discovered in a marine Gram negative bacteria, *Vibrio fischeri* [15].

The gram negative bacterium, *Vibrio fischeri*, is a marine bacterium found in the Hawaiian squid and is known for its striking bioluminescence in coordinating group behavior. The genes responsible for the bioluminescence are principally governed by the LuxR/I gene system. The luciferase system in this QS circuit has two main proteins, LuxR and LuxI. The LuxI is responsible for the synthesis of AHL signaling molecule. AHL stands for Acyl-Homoserine Lactone molecule. LuxR, when activated by the AHL autoinducer, helps in the transcription of the luciferase operon. This LuxR/I gene system has been found in other bacteria and its components have been observed to be performing the same functions as stated above; AHL as the autoinducer and LuxR being responsible for the transcription of the operon. The only change observed in the different Lux R/I systems are the different phenotypic characters that they code for. For example, this system codes for

- Antibiotics production in Erwina.
- Motility in Yersinia pseudotuberculosis.
- Bioluminescence in *Vibrio fischeri*.
- Pathogenesis/ virulence factor and biofilm formation in *Pseudomonas aeruginosa*.

The Lux I as mentioned above, synthesizes a protein called AHL synthase which produces the AHL autoinducer signaling molecule. The AHL molecule has a cons2erved homoserine lactone ring which is connected by amide bond to acyl ring. This acyl chain may have varying carbon chain length from C4-C18. The carbon at 3rd position may be altered or modified by functional group like carbonyl, hydroxyl group or may be completely reduced. These different modifications in the acyl chain are what give different AHL signaling molecule. These different AHL molecules are recognized by different and compatible LuxR protein. This ensures the expression and regulation of different phenotypic characters in the bacterial cell.

The substrate for the Lux I protein to synthesize the AHL signaling molecule was found to be S- adenosyl methionine (SAM) for the homoserine lactone ring and the lipid metabolic pathway intermediates for the synthesis of the acyl chain.

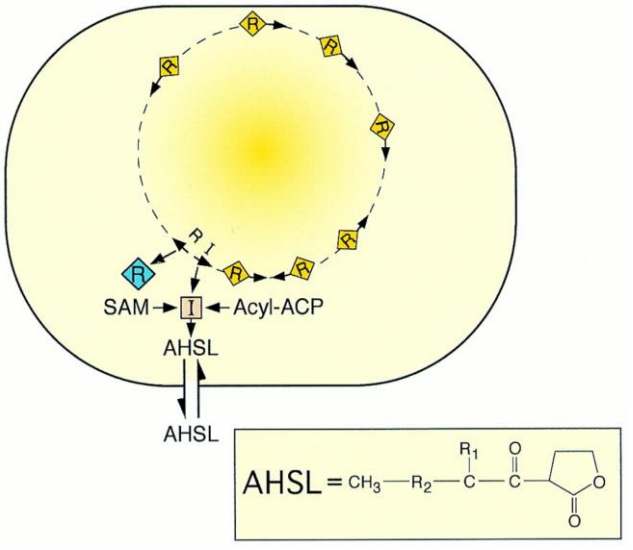

Figure 4: Generalized scheme for an acyl homoserine lactone QS circuit in a bacteria

The above image shows the generalized scheme for an acyl homoserine lactone QS circuit in a bacterial cell. The orange square denote the AHL –Lux I homolog and the diamond symbol denotes the LuxR homolog activates by the AHL signaling molecule. The arrows in the circular manner are the QSC genes in the chromosome. The AHL can easily diffuse in and out of the cell and the substrates for the AHL signaling molecule are acylated acyl carrier protein (acyl-ACP) and A-adenomethionine (SAM).

The below image explains the quorum sensing circuit in *Vibrio fischeri* for the phenotypic character of bioluminescence. It is observed that the *V. fischeri* do not exhibit bioluminescence at low cell density but only at high cell density. At HCD, the autoinducers in the external environment of the cell reaches the maximum threshold and this causes them to enter into the cell. They then influence the gene regulation of the luciferase operon and bring about light phenomenon.

The LuxR proteins are basically transcription factors which get activated by the AHL signaling molecule and this causes the stabilization of the LuxR proteins. The nature of this class of transcription factors is being specific to a particular class of AHLs and this nature allows the bacteria in a signaling system which associated to intraspecies signaling system. But there are few LuxR proteins which are known to facilitate the recognition of more than a specific AHL molecules and thereby helping in the communication between interspecies microorganisms. This is a naturally found mechanism, due to the presence of the bacterial colonies in mixed manner and not in pure form, which is in a biofilm case.

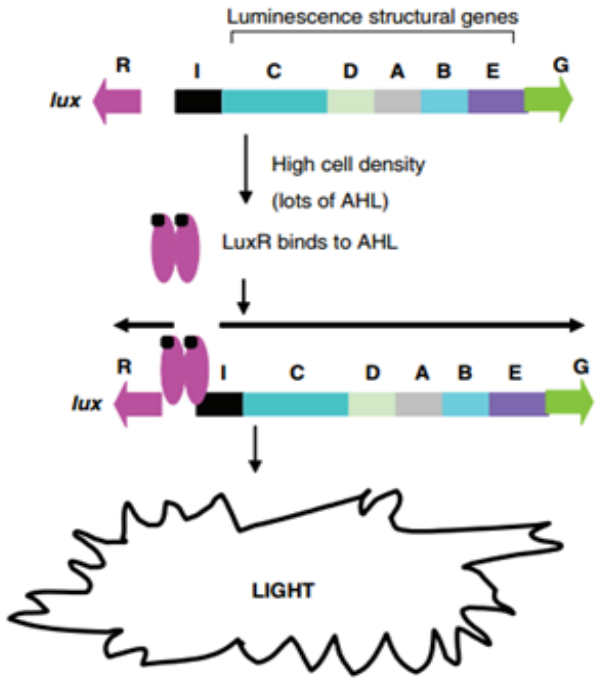

Figure 5: Bioluminescence activation in *Vibrio fischeri*

The image depicts the model of bioluminescence activation in *Vibrio fischeri* by the LuxR/I quorum sensing system. In high cell density, the acyl-homoserine lactone (AHL) autoinducer binds to LuxR, LuxR complexed with AHL then activates the transcription of itself and the luciferase operon.

The best explained and studied case of the LuxR/I gene system of the quorum sensing is in *Pseudomonas aeruginosa*. The quorum sensing in *P. aeruginosa* uses many genes which is helpful for the pathogen to colonize and sustain itself inside the host organism. In other words, the QS circuit in *P. aeruginosa* expresses the virulence or the pathogenicity of the bacteria. The nature of this pathogen is opportunistic in nature with respect to the immunological system of the host [16, 17]. The quorum sensing of this pathogen facilitates the production an array of toxins and the formation of biofilms in immunologically compromised host organism [18-19]. The nature of the QS circuit in *P. aeruginosa* is complex; the cell produces two AHLs N-(3-oxododecanoyl)-L-homoserine lactone (3OC12-HSL) and N-butanoyl-L-homoserine lactone (C4-HSL) [20-21]. These AHL molecules then activate the LuxR transcriptional factors. These transcriptional factors coupled with homoserine lactone causes the transcription of rhlR and rlhI. The AHL- LuxR complex is sometimes known to activate the LuxI system which causes the AIs to surround the cell in large amount [22-24].

There have been instances in few bacteria which have the ability to degrade the QS circuit by degrading the AHL signaling molecule. This is due the bacterial enzyme lactonase, which degrades the lactone ring of the acyl-homoserine lactone ring thereby rendering the QS circuit ineffective. This concept has been incorporated into transgenic plants; the transgenic plants are made into expressing the bacterial enzyme lactonase and these plants have shown resistance against those pathogenic bacteria which depend on the quorum signaling for the expression of their pathogenic character and the infection factor [25]. Following this, there are a growing numbers of reports of using these bacterial AHLs in the expression of gene expression of cytokines in immune mammalian cells [26-30].

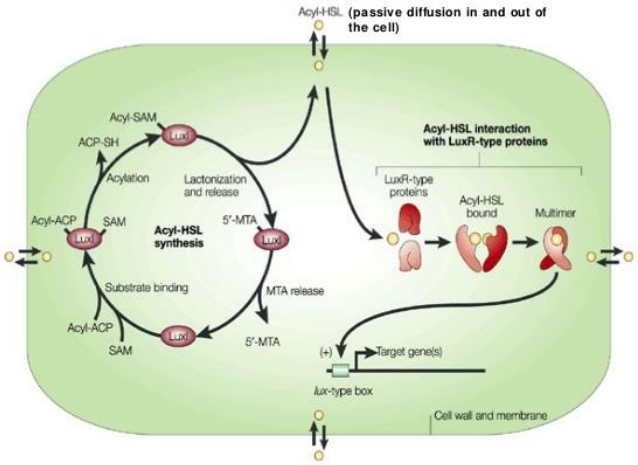

Figure 6: LuxR/Luxl quorum sensing – Gram-negative bacteria

The above image explains the entire QS circuit in gram-negative bacteria with the autoinducers and the transcription factors that play an important role in the initiation and the regulation of the pathway and the operon system.

Quorum sensing in gram positive bacteria.

As of now, there are many gram positive bacteria which employ the quorum sensing systems for their gene regulation and expression. Unlike the gram negative bacterial QS circuit, the Gram positive bacteria uses peptide transcription factors as the signaling molecule for their QS circuit this is due to their thick chemical composition of their cell membrane. This remains impermeable to the AHL and AHL like molecules for the signaling purpose. So the gram positive bacteria utilizes small post translationally modified peptides as autoinducers.

The gram positive bacteria QS signaling pathway based on the type of the peptide which is used as the autoinducers is classed into two categories. The signaling peptide may either act on the outside or the inside of the cell. Like the quorum sensing in gram negative bacteria, the autoinducers in the gram positive QS circuit upon binding causes the auto phosphorylation of the histidine- kinase and this is then followed by the transfer of the phosphate group to a cytoplasmic response regulator. These activated response regulator then bind to the DNA and cause the translation of

the desired and targeted gene. Few examples of such system are the Agr- type and Gly-type peptide signaling system.

Among the main expressed traits, the quorum sensing system in gram positive bacteria expresses the virulence factor of the pathogen. The most commonly studied model for the study of quorum sensing in gram positive bacteria is done using *Staphylococcus aureus*, a commensal bacterium found in human system. But these gram positive bacteria are also known for being the cause of few of the fatal diseases like pneumonia, endocarditis, wound infection and the recently arising Multiple drug resistant *Staphylococcus aureus* and many more. The QS circuit in this bacterium involves a protein system called the accessory gene regulator (Agr) which regulates the expression of toxins and protease. At low cell density, the bacterium has protein secretion for the establishment and the colonization of itself. But as the cell density increases, the protein concentration in the environment increases and causes the establishment of symptoms and disease condition.

The peptide signaling system of the bacterium is controlled by Agr D gene. This is then modified by the addition of a thiolactone ring by the Agr B gene. This complex is then transported outside the cell. Now this complex bind to sensor kinase Agr C receptors on the membrane. Now as soon as this coupling occurs, the Agr C transfers the phosphate group to Agr A. This activated Agr A gene activates the transcription of the Agr operon and produces a regulatory protein RNA III. This leads to the repression of cell adhesion factor and increases the expression of secreted factors [31]. The unique nature of the QS circuit in S. aureus is that noncognate AIP repress the other AIPs by competitive binding. This allows the microorganism to evolve and adjust to a suited environment.

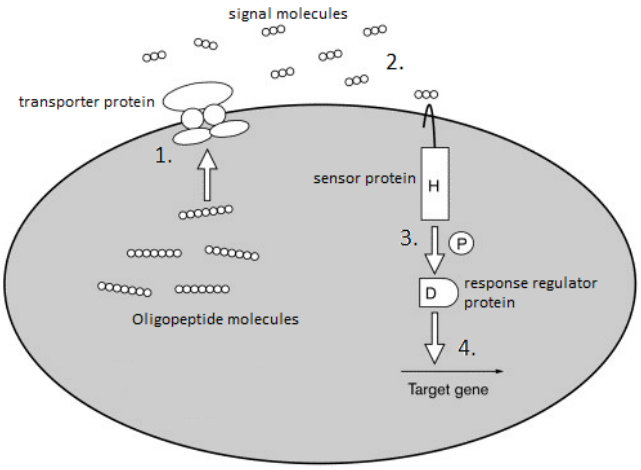

Figure 7: QS circuit in a Gram positive bacterium

The above diagram shows the QS circuit in a Gram positive bacterium in generalized manner. The following image shows the Agr operon based QS circuit which is widely studied in a human pathogen *Staphylococcus aureus*.

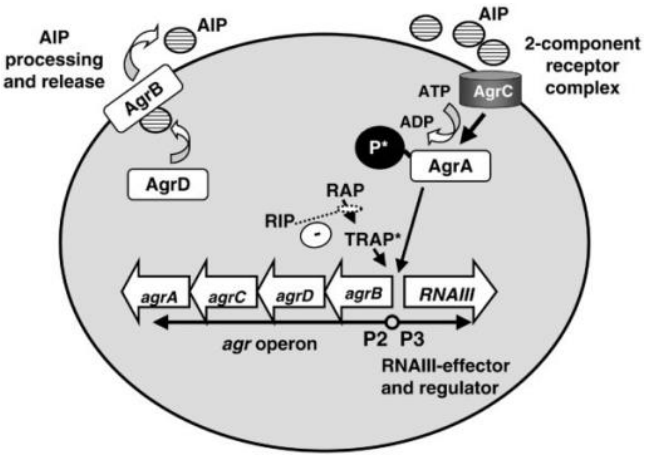

Figure 8: Agr-QS circuit in *Staphylococcus aureus*.

This diagram is a detailed explanation of the Agr-QS circuit in a Gram positive bacterium, *Staphylococcus aureus*. The above system uses a two compound regulatory system for the detection the peptide signaling molecule.

Quorum sensing by the lux s/ai-2 signalling system:

The Lux S/AI-2 signaling system is widely studied for understanding the universal communication of the bacterium. The most widely studied model for this signaling system is *Vibrio harveyi*, a marine bacterium. This bacterium uses the *Vibrio harveyi* QS system for bioluminescence. This QS system was found to a mi between the QS circuit found in Gram positive and negative bacterium. This bacterium has two QS systems; system 1 similar to the Qs circuit found in Gram negative bacteria using the AHL signaling molecule for the intraspecies communication and system 2 where the autoinducer is a furanosyl borate diester involved in interspecies signaling [32-34].

This bacterium has two hybrid sensorkinase systems one LuxN and one LuxQ which recognizes AI-1 and AI-2 respectively. These, when not present, have intrinsic enhancer binding proteins like LuxU and LuxO gets phosphorylated. Upon phosphorylation, these activated complexes activate the transcription of small regulatory RNAs. These upon activation, degrades LuxR protein, which is a main protein in bioluminescence and there by curbing the active transcription of the luciferase operon. Now in the other scenario, in the presence of cognate autoinducers, the sensor behaves as phosphatase and the system gets dephosphorylated and allows the active translation of the luciferase operon. The AI-2 receptor is a periplasmic protein LuxP and requires LuxS enzyme for its synthesis. The LuxS enzyme is involved in the metabolism of SAM and yields a very unstable compound called 4, 5-dihydroxy-2, 3-pentanedione (DPD). The DPD reacts with water to crystalize into various forms of furanones [35-37]. Several character expression are attributed to this AI-2

system in organisms by the comparison of the LuxS mutant in the wild type to the organism.

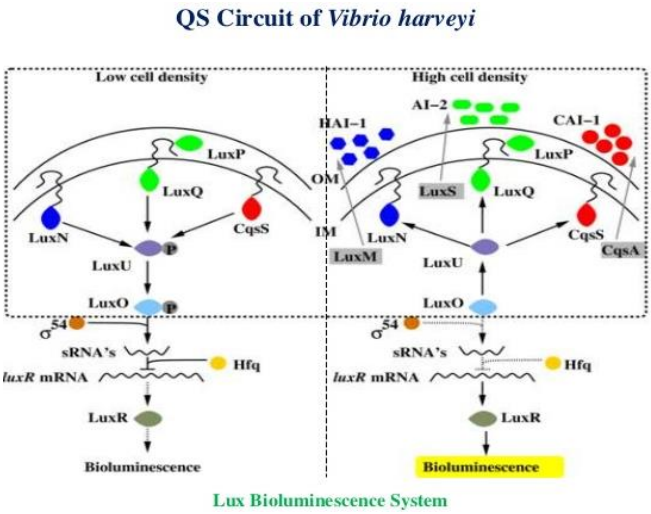

Figure 9: The above diagram explains the complex detailed QS circuit found in *Vibrio harveyi* with the auto-inducers and the transcription factors that responsible for triggering the QS circuit and its regulation.

AI-3/ epinephrine/ norepinephrine signaling cascade:

A Quorum sensing signaling cascade used for universal communication. Another QS circuit found in the intestinal flora of human gut is the AI-3 /epinephrine/norepinephrine signaling system. This is an enzyme activated methyl pathway which involves the synthesis of methionine and SAM. The gene expression is controlled by the mutated LuxS and the gene expression is affected per se due to the interruption in the normal metabolic pathways. AI-3 was explained by a compound expressed by the QseC gene system [38]. The synthesis and the molecular configuration of the signaling molecule of this pathway is still to be correctly explained. This pathway uses negative feedback mechanism and the denovo synthesis of amino acids like methionine and the accumulation of S-ribosyl – homocysteine in the cell. Along with this, the structural configuration of the AI-3 shows that the compound is an aromatic compound and not a carbon based chain like the AI-2 signaling molecule. AI-3 signaling pathway plays an intrinsic role in the interkingdom communication along with the intraspecies communication in the bacterium. AI-3 also crosslinks with hormones like epinephrine and norepinephrine present in gut region of the host. So based on the functioning level of these hormones aids the bacteria in studying the metabolic state of the host and thereby acting to the situation as per requirement.

The commonly studied model of this system of QS circuit is the Enterohemorrhagic E.coli.

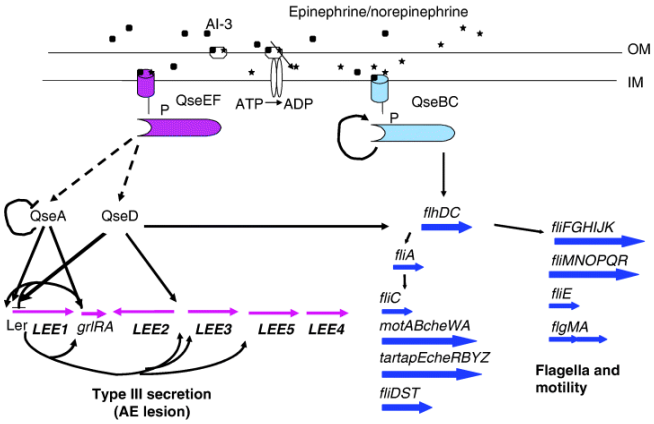

Figure 10: Model of quorum sensing signaling in Enterohemorrhagic Escherichia coli. This model explains the role of the hormones Epinephrine and norepinephrine in the process of the cell signaling pathways and circuit.

Both AI-3 and epinephrine/norepinephrine seem to be recognized by the same receptor, which is probably in the outer membrane of the bacteria. These signals might be imported to the periplasmic space where they interact with two major sensor kinases. QseC might be the sensor kinase transducing these signals towards activation of the flagella regulon, whereas QseE might be the sensor kinase transducing these signals to activate transcription of the locus of enterocyte effacement (LEE) genes. QseC phosphorylates the QseB response regulator, which binds to the promoter of flhDC to activate expression of the flagella regulon. QseB also binds to its own promoter to positively autoregulate its own transcription. QseE is the sensor kinase and its predicted response regulator is QseF. At what levels QseF regulates transcription of the LEE genes remains to be established. QseA is one of the transcriptional factors involved in the regulation of ler (LEE1) transcription in two levels, by binding and activating transcription of LEE1 and by activating transcription of the grlRA operon, where GrlA and GrlR positively and negatively regulate expression of ler, respectively. Then, in a cascade fashion, Ler activates transcription of the other LEE genes. QseD is a second LysR-like regulator, involved in modulating expression of the LEE and flagella genes.

Further studies have shown that this AI-3 signaling system has been found in many bacteria like Shigella, Salmonella, Yersinia, and many other , thereby helpful in the conclusion that the signaling cascade helpful in the interkingdom species is not only restricted to E.coli.

Conclusion

Cell signaling and communication is a vital process for the survival and establishment of the bacterial cell in its environment. The basic idea of communication is usually misconceptionalized to occur only in the eukaryotic cells and not to a great extent in prokaryotic cells. But with the groundbreaking discovering the process of quorum sensing

in the *V.fischeri* , a marine gram negative bacterium, the new world of bacterial communication in a coordinated group communicative process which is similar to the communication and activity in eukaryotic cells. The quorum sensing signaling pathway is responsible for the expression and regulation of many cell phenotypes like the symbiosis, competence, virulence, antibiotics production, mobility, sporulation, biofilm formation, bioluminescence, and many more. The QS circuit is found in many Gram positive and Gram negative bacteria. Even though the general principle of the quorum sensing circuit sticks on the same principle, the autoinducers (the signaling molecule) is different in each species and thereby responsible for the expression of different characters in the cell. The autoinducer in Gram negative bacterium is Acyl-Homoserine Lactone (abbreviated as AHL) and the Gram positive bacterium, due to the different nature of cell membrane, uses processed oligo-peptides as the signaling autoinducers.

The quorum sensing process can be differentiated into three groups; one, Quorum sensing circuit in Gram positive bacterium. Two, Quorum sensing circuit in Gram negative bacterium and the final being the Quorum sensing circuit used by the bacterium for interkingdom communication. Such diverse and complex pathways governing the activity of such unicellular organisms can be conferred to the expression of characters in them which are like that of multicellular organisms.

In the evolutionary aspect, the Quorum sensing circuit holds the key answers to the question of the rate of evolution and the transformation and slide from the life from the state of unicellular nature to that of the life in the form of multicellular nature.

Upon the discovery of Quorum sensing, the concept of Anti-Quorum sensing mechanism has also been observed. The host organism and antagonistic organisms have developed and expressed natural machineries in them which help them in rendering the Quorum sensing cascade in the bacteria useless and thereby making them ineffective. This process may employ the degradation or alteration of the autoinducer or by the host producing autoinducer antagonistic compounds which compete with the original autoinducer which fiddles with the QS circuits.

These natural machineries which render the ineffectiveness of the QS circuit are being extensively studied and are now being implemented in situations to counter act on the adverse or fatal effect of the bacteria which employ quorum sensing signaling pathway.

Being said this, the study of the quorum sensing and their evolutionary aspect helps us in the better understanding of life around us and thereby helping us understand our being in a better manner.

Abbreviations

Acyl- Homoserine Lactone (AHL), auto inducers (AIs), S-adenosyl methionine (SAM)

Authors' contribution

All authors contributed equally

Competing interests

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