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Article

Quorum Sensing and Antimicrobial Resistance in Bacteria

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Abstract: *is the process of modifying gene expression in reaction to changes within the population of cells density. Gene expression is impacted by an autoinducer's minimal threshold stimulatory dosage. Each Gram-positive and Gram-negative bacterium employs quorum sensing signaling circuits to regulate various kinds of biological functions. Acylated homoserine lactones are frequently by bacteria that are gram-negative as autoinducers. Another means of communication involving microorganisms that are Gram-positive and Gram-negative is through processed oligo-peptides. According to current study, autoinducer-mediated cell-cell interaction occurs both inside and as well as amongst bacterium species, growing proof that bacterial autoinducers cause distinct reactions in their hosts. Bacteria are able to coordinate gene expression through mutual interaction, although the target genes, signal relay systems, and chemical signals mediated by bacterial quorum sensing systems differ, and so the collective response of society in any given circumstance. Therefore, one of the earliest steps toward multi-cellularity may have been the emergence of quorum sensing systems in bacteria. We will review in this article the mechanism of both quorum sensing and Autoinducers and explain the role of both gram negative and negative bacteria according to their transcription factor and the advantage that they have been effect on life.*

Keywords: *Autoinducers; Quorum-sensing; LuxR, LuxI, Acyl homoserine lactone; Bacterial signaling*

1. INTRODUCTION

Quorum sensing (or Quorum signaling) is the biological capacity of a cell to detect and react to the density of its cell population through gene regulation. QS (Quorum sensing), for instance, allows genes to be expressed only in high cell densities in bacteria where the ensuing phenotypes would be most advantageous [1].

When the photo luminescent marine bacteria *Aliivibrio fischeri* showed signs of conditioning in the media in which it had developed, Terry Platt, J., and Kenneth Nealson observed quorum sensing for the first time in 1970. In a freshly inoculated culture, these bacteria did not produce luciferase, which prevented them from glowing, but only after the bacterial population had risen greatly. Since the medium's conditioning was linked to the increased cell population, they named the process auto induction [2].

The bacterial population's local density in the immediate surroundings serves as the basis for the quorum-sensing function. It can happen between different species of bacteria as well as within a single type of bacteria. Although quorum sensing is used by each of gram-positive and gram-negative bacteria, there are some significant distinctions in their methods [3].

2. MATERIALS AND METHODS

Bacteria require three qualities in order to employ quorum sensing constitutively: they need to secrete an autoinducer and a signaling molecule, be able to detect changes in

the quantities of these molecules, and be able to respond by controlling gene transcription [4].

This strategy has a major impact on how the signaling molecules diffuse. QS Signaling molecules are typically released in small amounts by specific bacteria. The molecules will just spread out freely at low cell densities. If there is high cell density, The threshold limit of the local concentration of signaling molecules will be exceeded, triggering gene expression changes as shows in Fig. 1, [5].

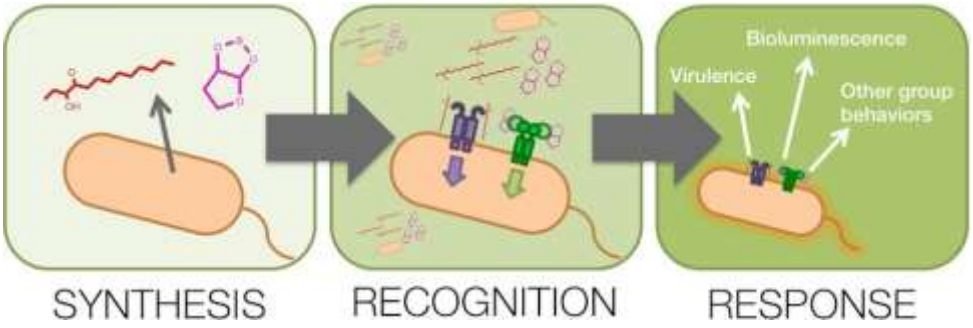

Fig. 1 Mechanism of quorum sensing

2.1 Gram-positive Bacteria

Autoinducing peptides (AIP) are utilized through gram-positive bacteria as inducers Gram-positive bacteria become aware of a high AIP concentration in their surroundings; they bind to a receptor and trigger a kinase. A transcription factor that controls gene transcription is phosphorylated by the kinase. A two-component framework is what it's called. Another possibility is that AIP binds to a transcription factor directly after entering the cytosol, causing the transcription to start or stop as shows in Fig.2,

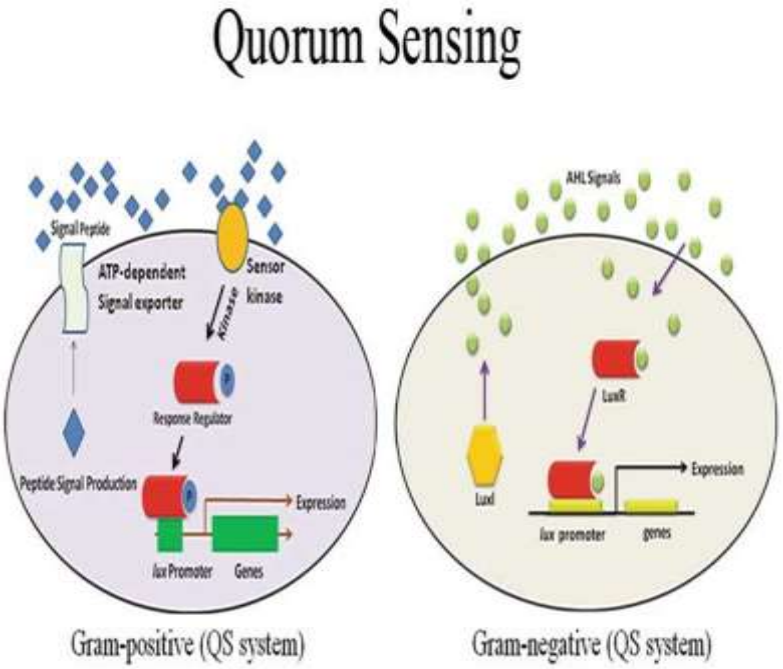

Fig. 2 Quorum sensing arrangement

2.2 Gram-negative Bacteria

N-acyl homoserine lactones (AHL) are a kind of signaling molecule created by bacteria that are classified as gram-negative. AHLs bind to transcription factors directly to control the expression of genes; they are often not digested. The two-component system can also gram-negative bacteria make use of it as shows in Fig. 3.

3. DISCUSSION

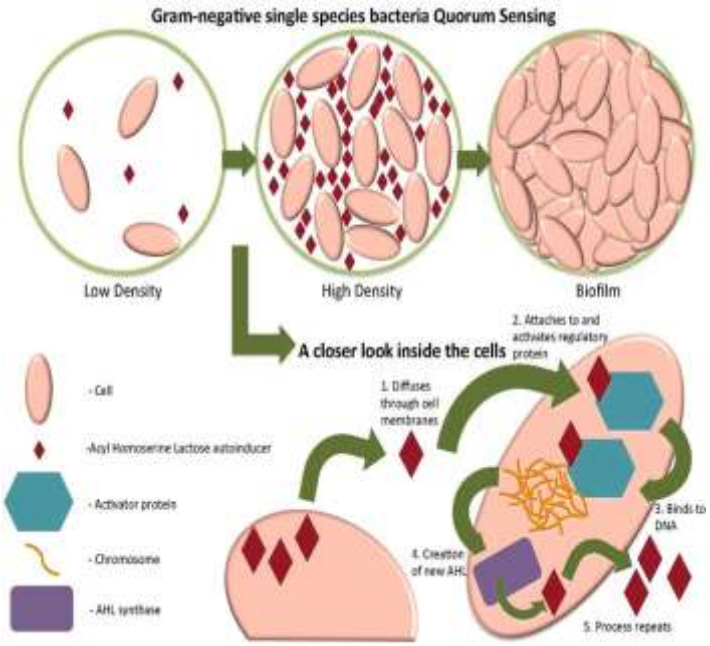

Fig. 3 Quorum sensing arrangement

2.3 Sequence analysis

The "two-gene" paradigm—autoinducer synthase combined with a receptor molecule used by the majority of Gram-negative Proteobacteria quorum sensing systems is comparable to that of the *Vibrio fischeri* system.

This suggests that quorum sensing mechanisms are very old, and that they first appeared in the Proteobacteria lineage. Although it is visible in the LuxI, LuxR, and LuxS phylogenies, horizontal gene transfer is not very widespread. This observation aligns with the understanding that many different genes' expression is regulated by quorum sensing genes dispersed across the bacterial genome.

It will not be possible to have acquired horizontal gene transfer in such a recent manner. Given that most autoinducersynthase/receptor combinations in bacterial genomes are found in tandem, switching partners is uncommon, so pairs appear to coevolve. Gamma proteobacteria have a functioning pair of quorum sensing genes called LuxI/LuxR., It comprises *Escherichia coli* and *Pseudomonas aeruginosa [6]*. LuxI is the autoinducer synthase and LuxR is the receptor. The quorum sensing genes found in Gamma Proteobacteria are unusual in that they are functionally identical to the LuxI/LuxR genes but have a significantly different sequence The gamma Proteobacteria progenitor may have given rise to the homologs of quorum sensing; nevertheless, It's yet unknown what causes their remarkable sequence divergence and functional similarities. Furthermore, nearly all members of the gamma Proteobacteria use multiple discrete quorum sensing systems.

3. Autoinducers

Autoinducers belonging to the AHL class are the most prevalent in Gram-negative bacteria. They have a variable -4 to -18 carbon acyl chain and a core N-acylated homoserine-lactone ring. LuxI-type synthases are the ones that create these AHLs found in hundreds of bacterial species. Stability can be influenced by acyl chain length, which might have an impact on signaling dynamics [7], [8].

They are signaling molecules that are formed when the density of a cell population varies. The autoinducer concentration rises in proportion to the density of quorum detecting bacterial cells. As a result of bacteria detecting signal molecules, gene expression changes until the minimal threshold is met.

The process known as quorum sensing improves the finding of bacteria that are both Gram-positive and Gram-negative. And control each other's physiological activities.

Virulence, Symbiosis, biofilm formation, motility and antibiotic activity are examples of such activities [9], [10].

Depending on the species, autoinducers can have an extensive variety of sizes and forms, but their actions are essentially the same. Using autoinducers, bacteria may communicate within species as well as between [11].

This coordination changes gene expression and helps bacteria to increase synchronized reactions to their surroundings; similar to how higher organisms communicate and behave. It's not surprising that quorum sensing has been proposed as a significant evolutionary milestone in the evolution of multicellular life forms as shows in Fig. 4, [12].

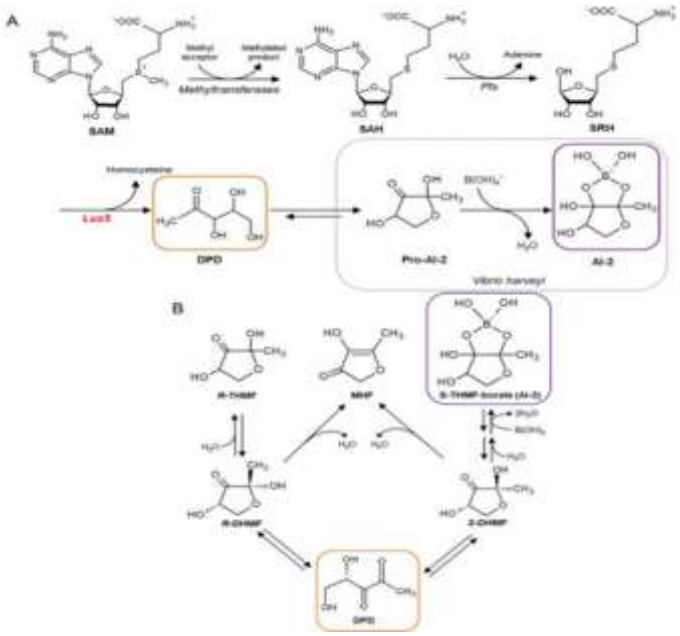

Fig. 4 The autoinducer-2 Biosynthetic pathway

3.1 Mechanism

Bacteria employ autoinducers in their most basic quorum sensing systems, which consist of just two parts. They'll require both a signaling mechanism and a signal responding mechanism. Changes in gene expression are often involved in these cellular systems, which are also closely organized [13].

The quantity of bacteria grows in density with the synthesis of autoinducers. Most signals are produced inside of cells and released into the extracellular environment. Popular techniques for identifying autoinducers include attaching to certain receptors and diffusing back into cells. Autoinducers often do not attach to receptors until a specific autoinducer concentration is attained. Bound receptors then modify gene expression whether directly or indirectly [14].

While A few receptors function as transcription factors on their own, many send out signals to transcription factors farther down the line. Autoinducers are frequently employed in forward feedback loops, where the output of a chemical signal is amplified to much larger levels from a low initial concentration of the autoinducer as shows in Fig. 5 [15].

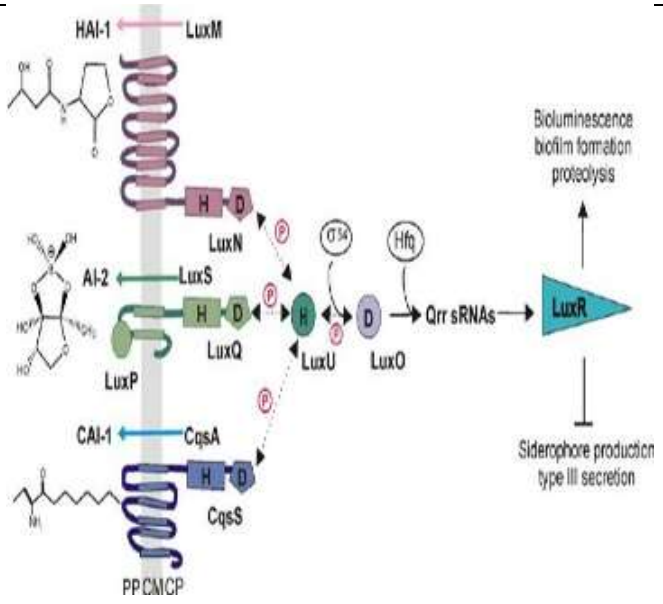

Fig. 5 The autoinducer-2 Biosynthetic pathway

3.2 Acylated Homoserine Lactones

Gram-negative bacteria are the primary producers of the tiny neutral lipid molecules known as acylated homoserine lactones (AHLs), which are composed of an acyl chain and a homoserine lactone ring. The acyl side chain, which typically has four to eighteen carbon atoms, differs in length and composition throughout Gram- negative bacterial species.

The formation of AHLs is the result of AHL synthases. They enter and exit cells via both passive and active transport channels. AHL receptors include transcriptional regulators named"R proteins," that is sensor kinases or DNA- binding transcription factors as shows in Fig. 6 [16].

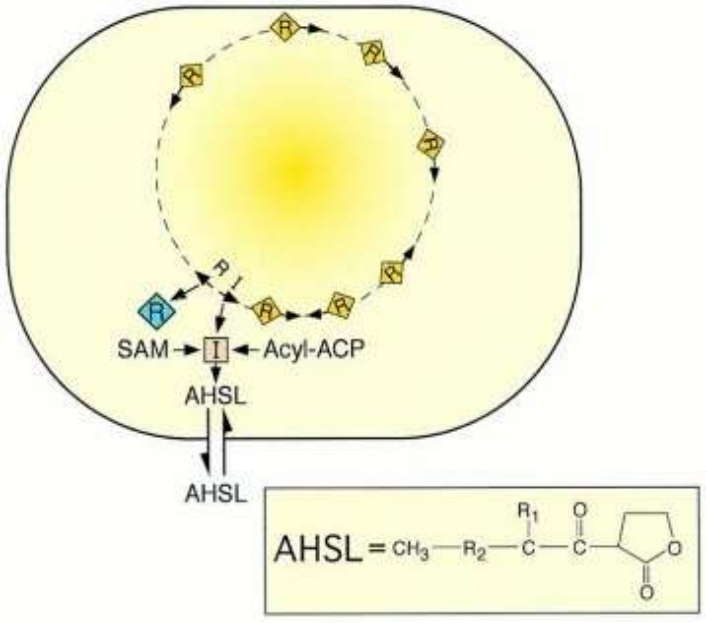

Fig. 6 Acyl-homoserine lactone quorum

Peptides Secreted oligopeptides are frequently used as autoinducers by quorum sensing gram-positive bacteria. Typically, a bigger precursor molecule is modified posttranslational to create peptide autoinducers. Gram- positive bacteria require certain export mechanisms in order to secrete peptides. For instance, ATP-binding cassette transporters release peptide autoinducers, which link cellular export with proteolysis processing. Following secretion, peptide autoinducers grow up in extracellular settings in a two-component regulatory system. The function of A histidine sensor kinase protein represent in monitors signals and delivers a signal to the cell when the signals exceed a threshold frequency.

The signal eventually influences gene expression, much like AHLs do. But most oligopeptides don't work as transcription factors as certain AHLs do [17].

3.3 Furanosyl borate diester

A different signaling molecule is used by the free-living, bioluminescent sea bacteria *Vibrio harveyi* instead of an acylated homoserine lactone. Known as AI-2 chemical is Autoinducer-2, a furanosyl borate diester. Since many different kinds of bacteria, can manufacture and use AI-2, it is thought to serve as a Genetic connection between the two main kinds of quorum sensing circuits [18].

Transcription factor

Proteins known as transcription factors contribute in the transcription of DNA into RNA. A vast array of proteins, with the exception of RNA polymerase, are known as transcription factors because they start and control the transcription of genes. [19].

In metabolic engineering, transcription factor-based ways of controlling microbial cell metabolism have been effectively implemented, leading to notable enhancements in the production and host cell tolerance of their target molecules. [20]

the bacterial regulation's trans-acting elements. The recruitment of the RNA polymerase holoenzyme to a particular location upstream of the gene, referred to as its promoter, marks the start of initiation.

Transcription factors are a significant subclass of bacterial regulators that normally activate or repress target gene transcription in response to a cellular or environmental stimulus.

Depending on the quantity of genes and range of cellular processes they target, these variables might be either global or local.

Through the use of signal-sensing protein domains, both global and local transcription factors' activity can be controlled at the post-transcriptional level or at the level of their own expression.

Not only do these global factors affect polymerase recruitment to promoters, but they also change the conformation of bound DNA, affecting other DNA-related processes like replication and recombination. These proteins are referred to as "nucleoid-associated proteins" and impose structural constraints on chromosomes, hence having an impact on further DNA-related activities like replication and recombination. [21]

It is not unexpected that transcription factor dysfunction is the root cause of many human illnesses and anomalies. likewise, chromosomal rearrangements or somatic mutations that impact certain transcription factors are important in the development of some human malignancies. [22].

Our knowledge of how cells work is hampered by the division between the domains of gene regulation and signaling, which TFs span perfectly. [23].

What is quorum sensing and how does it work?

During their reproductive phase, some bacteria create autoinducers. Gram-negative bacteria produced Acyl-homoserine lactone autoinducers and can diffuse passively via their thin cell walls [24].

Conversely, Gram-positive bacterial autoinducers consist of peptide and require continuous transfer through the ABC transporter mechanism via their peptidoglycan cell wall. When autoinducers arise in both scenarios, they move out of particular cells. The extracellular concentration of autoinducers rises in proportion to the bacteria multiply because more individual cells make them. This process eventually reaches a "critical mass" [25].

The intracellular concentration of intracellular autoinducers rises as a result of that threshold, which renders it energy inefficient for them to keep departing the cell (via transport or diffusion). When the intracellular of Autoinducers' concentration rises, they bind to their receptors and start signaling pathways that change the activity of transcription factors and, consequently, the expression of genes. Many bacteria experience downregulation of autoinducer production in a negative feedback loop when gene expression shifts as shows in Fig. 7 [26].

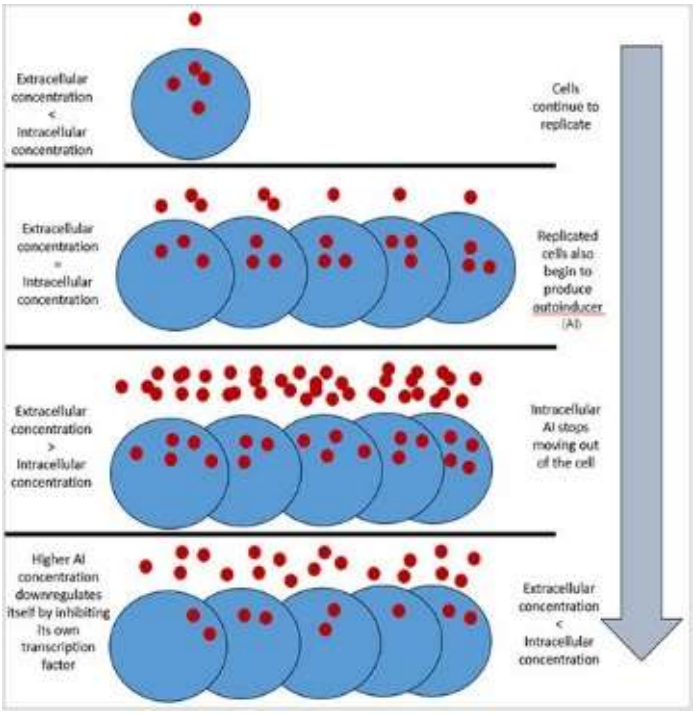

Fig. 7 Acyl-homoserine lactone quorum

Quorum sensing can assist in coordinating the spread of illness within a species. The gram-negative pathogenic bacterium *Vibrio cholerae* uses quorum sensing to increase its pathogenicity during cholera outbreaks. In order to assist move nutrients across colonies and ensure their safety, *V. cholerae* creates biofilms.

Bacteria's capacity to form biofilms inside of their hosts guarantees the bacteria's replication cycle and subsequent secretion of cholera toxin, two virulence factors combined that lead to 21,000 to 143,000 cholera deaths per year around the world as shows in Fig. 8 [27].

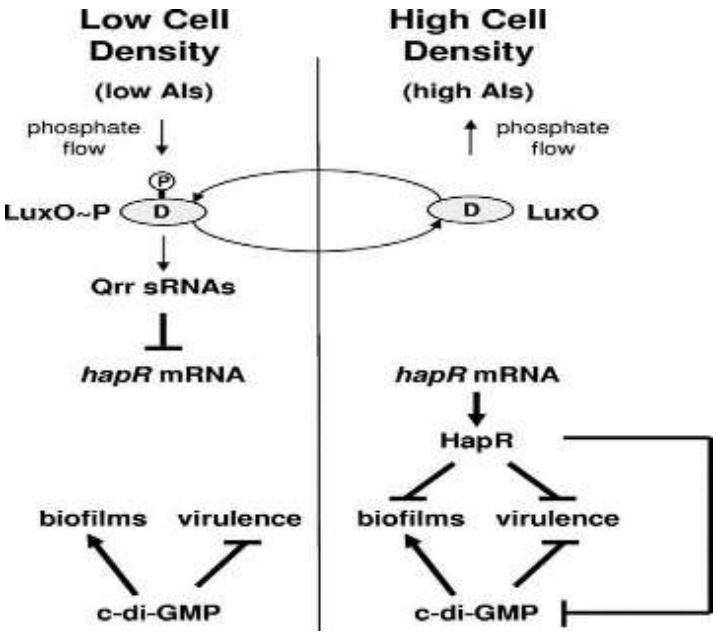

Fig. 8 The quorum sensing system in V.cholerae

The biofilm production of *V. cholerae* begins almost instantly after it reaches a person's small intestine. When *V. cholerae* reproduces, it produces species-specific autoinducers. LuxO controls *V. cholerae's* reaction to autoinducers. Autoinducer receptors function as kinases when autoinducers are not present in high intracellular concentrations, passing phosphate to LuxO (LuxOP). LuxOP encourages the development of proteins that aid in the formation of biofilms.

As *V. cholerae* multiplies the extracellular concentration of autoinducers rises and finally exceeds each bacterial factor's own autoinducer concentration. As a result, the concentration of intracellular autoinducer rises, Autoinducers bind to receptors and cause the receptor's kinase function to change to phosphatase.

Next, the receptors dephosphorylate LuxO, which inhibits the production of genes related to biofilms. At the same time, both *V. cholerae* bacteria cease to produce biofilms, and a novel quorum sensing sequence directs the bacteria through the infectious phase. With this knowledge, scientists are now investigating *V. cholerae's* quorum sensing system as a possible therapeutic target. For instance, overburdening *V. cholerae* with its autoinducer can completely halt the formation of biofilms,

So postponing the infectious process until human immune systems had time to adjust.

Disrupting bacterial contact is an innovative breakthrough and a realistic solution to the rapid increase in antibiotic resistance across bacterial species , as shows in Fig. 9 [28].

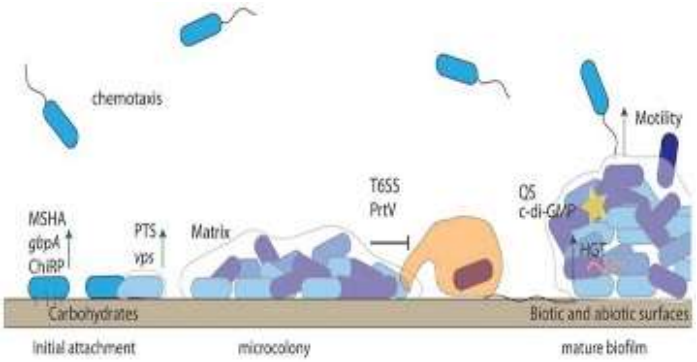

Fig. 9 *Vibrio cholerae* persistence

3.5 Interspecies quorum sensing encourages collaboration and competition

There is also quorum sensing for various bacterial organisms. Some animals possess receptors for the autoinducer molecules of other species, which enables them to detect and react to those in their surroundings, even though they are unable to produce their own autoinducers. Similar to us, bacteria are creatures that live in between individualism and collectivism.

This consistency can lead to confrontation, but it can also lead to teamwork and interspecies quorum sensing. Currently, quorum sensing is used by bacteria in the intestine in a never ending fight against dangerous bacteria. Bacillus spores in our intestine have been shown to inhibit *Staphylococcus aureus*, a frequent food poisoning is caused by bacteria that colonize the digestive system by destroying its quorum sensing system, according to one report.

S. aureus employs the quorum sensing pathway to promote inflammation and cause symptoms similar to food poisoning in order to boost its nutrition intake. Fengycin is a chemical produced by Bacillus sp. that has antifungal properties.

Certain bacteria, such us *Pseudomonas aeruginosa* and *Burkholderia cepacia*, which frequently coinfect the cystic fibrosis lungs patients, appear to employ quorum sensing to increase one another's pathogenicity.

Higher concentrations are obtained when *B. cepacia* is injected into *P. aeruginosa* conditioned culture medium, according one investigation. In vivo, both the siderophore and *B. cepacia* protease virulence factors were present at baseline levels in compa- rable amounts. The extracellular autoinducer that *P. aeruginosa* left behind in the conditioned medium changed the expression of the *B. cepacia* gene, making it more virulent [29].

Other investigations have shown that *Porphyromonas gingivalis* and *Streptococcus goronii* form symbiotic partnerships that result in a very powerful periodontitis confection by using the same autoinducer to form mixed species biofilms.

3.6 The Interactions Between Quorum-Sensing Molecules and Cells in Mammals have Applications in Medicine

Quorum sensing derived compounds, particularly peptides, are looking into usage in various therapeutic areas such immunology, CNS diseases, and cancer, in addition to their potential antibacterial capabilities. It has been demonstrated that quorum sensing

peptides engage with cancer cells and pass through the blood-brain barrier, allowing them to enter the brain parenchyma.

3.7 Signaling Molecule Degradation

Following the isolation of a well-researched quorum quenching bacterial strain (KM1S), AHL was examined using rapid resolution liquid chromatography (RRLC). RRLC effectively and sensitively distinguishes components of a mixture depending on their compatibility with different liquid phases.

It was shown that this strain's genome encodes an inactivation enzyme that targets the destruction of AHLs and has unique patterns.

3.8 Signaling Molecule Modification

N-acyl-homoserine lactones (AHL) are the Gram-negative bacteria's quorum sensing signalling agents, as previously mentioned. However, the functional groups on the acyl chain of these molecules can vary, as well as the length of the acyl chain. As a result, there are several AHL signalling molecules, such as 3-oxododecanoyl-L-homoserine lactone ($3OC_{12}$-HSL) and 3-hydroxydodecanoyl-L-homoserine lactone ($3OC_{12}$-HSL) ($3OHC_{12}$-HSL).

Another kind of quorum quenching is the change of certain quorum sensing (QS) signaling molecules, an oxido reductase activity can accomplish this.

The relationship between a host, vulgaris, Curvibacter spp. and Hydra, the main organism that colonizes its surface epithelial cells. So, These bacteria develop quorum sensing molecules called 3-oxo-HSL.

Activity of the polyp Hydra oxidoreductase, on the other hand, is capable of converting 3-oxo-HSL to their 3-hydroxy-HSL equivalents.

We may call this quorum quenching because there is an interaction with quorum sensing molecules.

In this case, the results are not the same as when the QS are inactivated. Curvibacter undergoes a phenotypic transition as a result of the host modification, which influences its capacity to colonize the surfaces of the epithelial cells Of *H. vulgaris*.

3.9 Quorum Quenching

Quorum quenching is the mechanism of blocking quorum sensing by suppressing signaling. Inactivation of signaling enzymes, the introduction among molecules that inhibit the receptors of signaling molecules by imitating them, the destruction of signaling molecules, or the modification of quorum sensing signals due to enzyme activity are all ways to achieve this as shows in Fig.10.

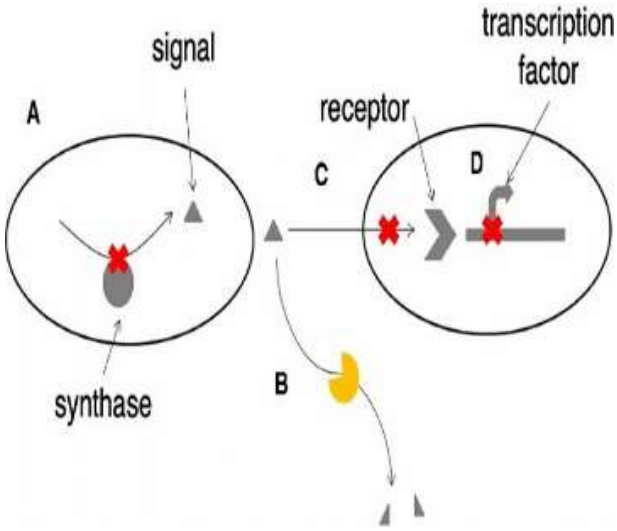

Fig. 9 Quorum quenching strategies

3.10 Robotics and Computing

Quorum sensing can be an effective technique for enhancing the performance of self-organizing networks, such the environmental monitoring system SECOAS (Self-Organizing Collegiate Sensor).

There is a theory showing that individual nodes in this system are informed that there is a population of other nodes that have comparable information to report. There after, the population selects a single node to submit the data, conserving electricity. Add hoc Quorum sensing is advantageous for wireless networks as well since it enables the system to recognize and react to network conditions.

Autonomous robot swarms can also be programmed to behave in unity via quorum sensing. Robots may quickly decide as a group without the guidance of a controller by employing a mechanism like to that of Temnothorax ants.

4. CONCLUSION

Acute During our brief existence on this planet, humans have evolved into successful communicators. Our contact, on the other hand, pales in contrast to that of bacteria. Using autoinducers for quorum sensing, bacteria may interact both within and between organisms. Based on the autoinducer"call" they get, they may either compete or partner with other animals. Humans have a long way to go until our contact system matches that of bacteria, there is a lot of advantages include Increase pathogenicity, elude host defense, and improve overall surviving conditions by allowing a population of bacteria to arrange actions worldwide and function like a multicellular unit. (optimize and regulate a variety of activities, to interact with one another and change their behavior when other bacteria are present. and it has clearly know the diverse use of QS in Reduce microbial resistance, pathogenicity, virulence, etc.; reduce competition; stop bio-fouling; stop plant pathogen bio control; stop biofilm development on membranes in freshwater or wastewater treatment facilities; and so on.

We must made more investigation on the relations mediated by QS because it is still limited and more detailed for understanding the molecular mechanisms of quorum sensing signaling is necessary.

wide research of bacterial transcription factors can aid the development of new technique to stop or inhibit bacterial infections and give insights into stresses adaptation, besides using bacteria in many industries.

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Data Availability: All the data and materials in the manuscript are available upon request.

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