



REVIEW ARTICLE

A comprehensive review on communication method in bacteria

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Abstract

Quorum Sensing (QS) represents a pivotal mechanism by which bacteria regulate gene expression in response to population density via the production and detection of small signaling molecules known as autoinducers. Numerous bacterial characteristics that are essential to their survival and pathogenicity, such as bioluminescence, biofilm formation, virulence factor expression, antibiotic resistance and environmental adaption, are regulated by this intercellular communication. Gram-positive bacteria use oligopeptides as autoinducers, while Gram-negative bacteria usually use N-acyl homoserine lactones (AHLs). In addition to aiding microbial pathogenicity, the QS system is crucial for bioremediation, plant-microbe interactions that increase agricultural output, tailored drug delivery in nanomedicine and global biogeochemical cycling that controls nutrient turnover. Research on QS as a potential target for antimicrobial therapeutics has increased in response to the escalating Antimicrobial Resistance (AMR) challenge. The ability of QS Inhibitors (QSIs) and Quorum Quenching (QQ) enzymes to interfere with bacterial communication and reduce virulence without applying selection pressure that increases resistance is being studied. Both synthetic and natural QSIs, as well as delivery techniques based on nanotechnology, have demonstrated promise in the fight against infections that are resistant to several drugs. Furthermore, using QS circuits in biotechnology opens up possibilities for improving the manufacture of medicinal biomolecules and biofuel. Ultimately, QS is a key area of focus for expanding our knowledge of microbial ecology and creating sustainable solutions for business, agriculture and medicine. Future research directed towards unraveling QS complexities and refining QQ strategies holds the potential to revolutionize microbial management and therapeutic interventions.

Keywords

Gram-negative bacteria; Gram-positive bacteria; signalling; QS

Introduction

"I think that a multiple of bacteria is stronger than a few and thus by the union can overcome obstacles too great for the few." (Smith 1905)

Communication between unicellular and multicellular microorganisms, such as bacteria, was puzzled in the latter half of the 20th century. For a very long period, it was thought that bacteria were separate cells that existed solely to acquire nutrients and proliferate and that only multicellular organisms could engage in coordinated activity, but the recent discovery of communication between cells among bacteria has led to the revelation of bacteria being capable of this. It includes the development and detection of extracellular signalling molecules referred to as auto-inducers in every documented instance. Their concentration increased with increasing bacterial populations. Autoinducers are tiny, self-generated signal molecules that serve as the foundation for the "language" that underlies this intercellular communication. Bacteria can control their behaviour based on population density using autoinducers (1). The mechanism of QS has been diagrammatically explained in Fig. 1.

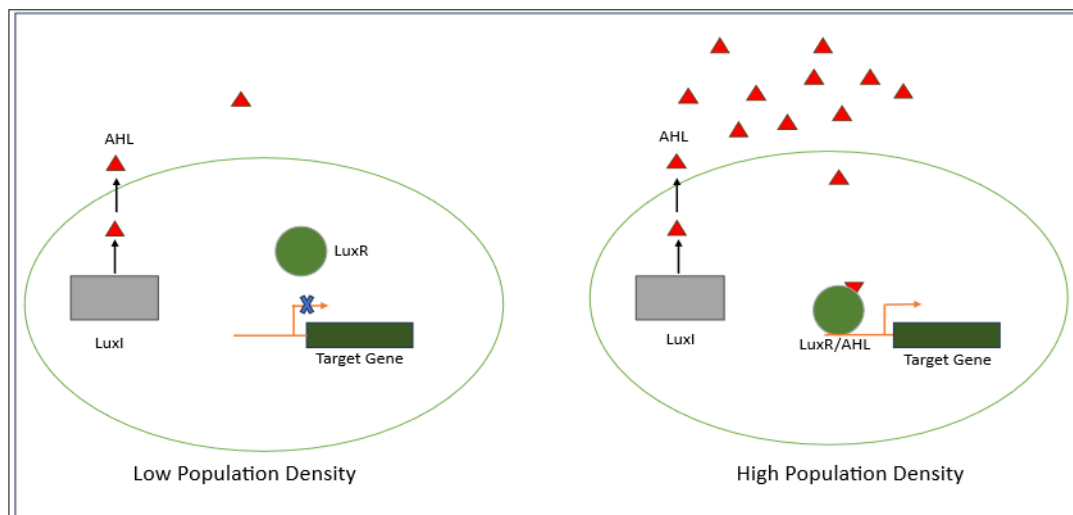


Fig. 1. Representation of quorum sensing's dependence on cell population density.

Signalling

The enzyme accountable for emitting light in *Vibrio fischeri* species is encoded by the luciferase structural operon luxCDABE and light emission was determined to occur only at high cell population density in response to the accumulation of secreted auto-inducer signalling molecules (1). QS is a form of bacterial intercellular interaction (2). The concept of 'quorum sensing' was introduced in 1990s and thereafter a lot of papers have been come upon and the growth is always seen to be exponential. Numerous tiny molecules are produced by bacteria, such as metabolic byproducts, signalling molecules and compounds like secondary metabolites including antibiotics, siderophores (compounds that bind iron), etc. These signalling molecules, known as autoinducers or pheromones, possess the capability to induce their creation. They frequently aid bacteria in determining the density or size of their population. These chemicals are emitted into the surroundings as the bacterial culture develops and accumulate over time (3).

The QS phenomenon, sometimes referred to as cell-to-cell communication, is based on the theory that when a single

bacterium releases autoinducers into the environment, their quantity is too low to be detected.

In Gram-negative bacteria

Many bacteria, such as *Vibrio fischeri*, use AHL as an autoinducer. These AHLs are density-dependent and initially have a lower concentration. This regulation depends on the increase in the AHLs concentration within the cells. Transcription occurs when its concentration increases (4). One of the main categories of human pathogens that exhibit significant levels of antibiotic resistance is gram-negative bacteria, which requires careful investigation (5). Gram-negative bacteria produce and react to particular AHL autoinducers to produce QS (6). In 1975, Nealson and Hastings identified QS in the bioluminescent marine bacterium *V. fischeri*, fundamentally altering the perception of bacterial communication and coordinated environmental responses (7). The action mechanism of bioluminescence in *V. fischeri* through LUX I/ LUX R signalling is diagrammatically represented in Fig. 2. The functions of several important Gram-negative bacteria are presented in Table 1.

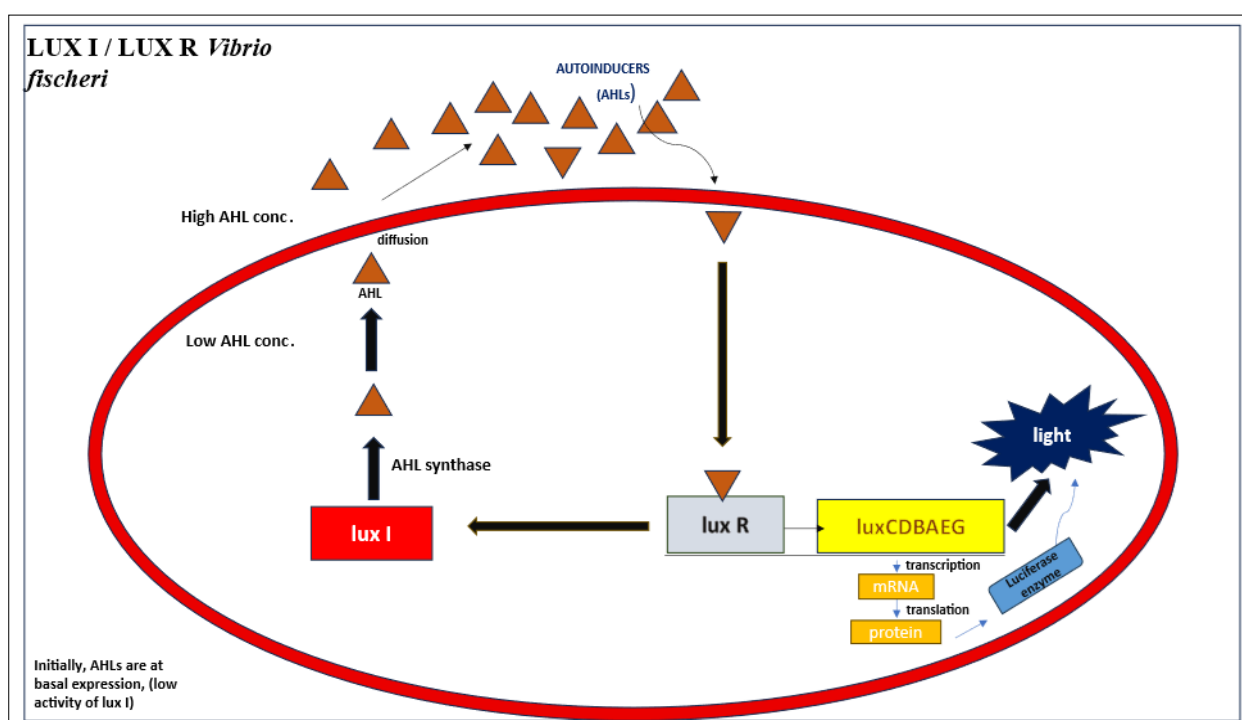


Fig. 2. LUX I/LUX R signalling in *Vibrio fischeri*, showing bioluminescence.

Table 1. Functions of QS in some Gram-negative bacteria

Bacterium	Function	Reference
<i>Vibrio fischeri</i>	Regulates bioluminescence	(7)
<i>Pseudomonas aeruginosa</i>	Controls virulence factors and biofilm formation	(8)
	Regulates rhamnolipid biosurfactant synthesis	(9)
	Modulates virulence and biofilm maturation	(10)
<i>Agrobacterium tumefaciens</i>	Mediates conjugal transfer of Ti plasmid	(11)
<i>Erwinia carotovora</i>	Controls production of plant cell wall-degrading enzymes	(12)
<i>Vibrio harveyi</i>	Regulates bioluminescence and virulence factors	(13)
<i>Vibrio cholerae</i>	Regulates virulence factors and biofilm formation	(14)
<i>Yersinia enterocolitica</i>	Controls motility and possibly other functions	(15)
<i>Acinetobacter baumannii</i>	Regulates biofilm formation and virulence factors	(16)
<i>Salmonella enterica</i>	Regulates virulence gene expression	(17)
<i>Escherichia coli</i>	Involved in interspecies communication	(18)

In Gram-positive bacteria

Oligopeptides are utilized as autoinducers. These results show two-component signalling. They typically use small signal molecules that have undergone translational processing. These peptide signals communicate with the sensor kinase signal transduction system. Based on the characteristics of peptide signalling molecules and their receptors, Gram-positive bacteria's QS pathways are divided into two categories (19). These peptide signals, which are necessary for the activation of QS, are first created by ribosomal synthesis as precursor peptides and frequently go through post-translational changes. Following transcription and translation, a specific ATP-binding cassette (ABC) transporter is usually used to transform the precursor peptide into its mature form and transport it outside the cell. Both linear and macrocyclic structures can be found in these mature peptide signals (20).

With increase in cell density, processed peptide signals' concentration increases too. Then after, reaching threshold, peptide binding occurs on the receptor that's specific to the peptide binding with, this is regulated either by a self-signalling mechanism or a two-component system. Named for important response regulators found in several bacterial species, such as Rap (*Bacillus subtilis*), Rgg (*Streptococcus*), NprR (*Bacillus cereus*), PlcR (*Bacillus cereus*) and PrgX (*Enterococcus faecalis*), the self-signalling pathway is called the RRNPP protein family. The species that developed this signalling circuit were the pioneers to be found to have these regulators (21,22). Functions of key Gram-positive bacteria are shown in Table 2.

Table 2. Functions of QS in some Gram-positive bacteria

Bacterium	Function	Reference
<i>Staphylococcus aureus</i>	Regulation of virulence factors	(23)
<i>Listeria monocytogenes</i>	Regulation of virulence and adaptation	(24)
<i>Enterococcus faecalis</i>	Regulation of gelatinase and serine protease production	(25)
<i>Streptococcus pneumoniae</i>	Induction of genetic competence	(26)
<i>Bacillus subtilis</i>	Induction of genetic competence	(27)

QS significance in bacteria

QS plays an essential role in bacterial behaviour, including biofilm formation, virulence, antibiotic resistance, symbiosis, etc.

Bioluminescence

The function of bioluminescence, which was initially noticed in the marine bacteria *Vibrio fischeri* in the early 1970s, is among its most well-known applications. The importance of QS in microbial communication and coordinated activity has been highlighted by this discovery, which has made *V. fischeri* a paradigm for research on QS in Gram-negative proteobacteria (28).

Biofilm formation

The capability to form biofilms is a key factor contributing to the virulence of opportunistic human pathogens. QS controls the development of biofilms in many important diseases. The formation and growth of biofilms, which are ordered bacterial communities, depend on efficient cell-to-cell communication. The effectiveness of traditional antibiotics is hampered by the development of biofilms. Biofilms are a breeding ground for antibiotic resistance (29).

Biofilm generation is a crucial virulence mechanism in the pathogenesis of several medically important bacteria, such as *Pseudomonas aeruginosa* (*P. aeruginosa*), *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*). Many diseases, including otitis, conjunctivitis, vaginitis, colitis, ventilator-related pneumonia, gingivitis and urethritis, are associated with or brought on by biofilm infections. The presence of biofilms in lungs of people with cystic fibrosis is one biofilm-related infection that doctors are particularly concerned about. An opportunistic bacterium known as *P. aeruginosa* has been connected to lung infections, both acute and chronic, which can significantly increase morbidity and mortality (30).

Pathogenesis and virulence regulation

Several pathogens use QS for regulation of the expression of virulence factors. QSIs are being explored as anti-virulence therapies. Numerous virulence factors produced by *S. aureus* are controlled by QS. Autoinducing cyclic peptides often mediate QS control in Gram-positive bacteria. Through the Agr system, which depends on the Autoinducing Peptide (AIP), QS specifically regulates the development of virulence components for *S. aureus*, including hemolysins, leukocidins, cell surface adhesins, exoenzymes and biofilm formation. AgrD encodes AIP, which has a 5-membered

thiolactone ring and seven to nine amino acids (31). The membrane protein AgrB secretes this peptide and the AgrC sensor kinase activates it (32).

Antibiotic resistance

QS influences antibiotic gene resistance in bacterial communities; therefore, the disruption of QS pathways can increase antibiotic efficacy. Nowadays, antibiotics are utilized extensively worldwide and antibiotic resistance is growing more quickly than ever (33). Due to selection pressure brought on by the millions of tons of antibiotics used since their inception, practically all harmful bacteria have become resistant to widely used antibiotics (34). Most antibiotics on the market today are made to directly eradicate harmful bacteria by disrupting essential protein synthesis and damaging cell membranes (35). The widespread utilization of antibiotics has resulted in significant problems with germ resistance, which is encouraged by the "life or death" selection pressure. "Superbugs" that are not susceptible to a variety of widely used antibiotics have surfaced globally in recent years (36).

Bioremediation

Certain bacteria use QS modulation to break down harmful pollutants, which could be utilized to clean oil spills and effectively treat waste. The process of bioremediation uses microorganisms to break down environmental pollutants into less harmful or non-toxic forms (37). One of the latest technologies that take advantage of microorganisms' capacity to efficiently, economically and environmentally break down environmental pollutants is bioremediation (38). Because of their ease of growth and genetic modification, these bacteria are appropriate for bioremediation. Microorganisms, food and nutrients referred to as the bioremediation triangle are the three main elements needed for bioremediation (39).

QS as a means of biological control in agriculture

QS is a mechanism used by many plant-associated bacteria to control characteristics that facilitate their symbiotic or pathogenic lives. In terms of agriculture, inoculation-based technological methods of specific microbes can produce a higher yield in a sustainable manner (40). We define plant disease prevention and plant growth promotion as novel approaches that alter the plant's microbial population to support its growth and resilience to unfavourable conditions (diseases, pathogens, drought, etc.) (41).

The microbiota of multicellular organisms forms a holobiont, which significantly influences their physiology and development (42). The network between the microbial population and the plant host is crucial to the holobiont's constitution and is closely linked to QS signalling systems. Plant growth and immunity are influenced by the balance between pathogenic or helpful bacteria and their host plants, which is influenced by interkingdom signalling. Although more research is necessary to completely understand the precise biochemical pathways by which bacterial AHL signals affect plant performance, it has been noted that these signals have an impact (43).

Nanomedicine

Since the 1990s, there significant progress has been made in the application of nanotechnology to the prevention and treatment of human diseases. Traditional molecular medications currently dominate research on drug design and development. However, to increase effectiveness and reduce adverse effects, nanotechnology

is frequently used in conjunction with this study. Because of their characteristics (size of 10–100 nm; huge surface-area-to-volume ratio; flexibility of surface functionalization and wide reactivity), nanotherapeutics do, in fact, typically show enhanced effects when compared to standard medications. These characteristics give nanotherapeutics improved pharmacokinetics, minimal toxicity, increased bioavailability and therapeutic efficacy. Furthermore, improving current treatments for many human diseases still primarily involves the efficient transport and release of medications to a target. One intriguing method for improving drug delivery, targeting and protection is the use of NPs as "transporters" (44).

Virulence

A highly opportunistic bacteria called *Pseudomonas aeruginosa* is known to cause serious nosocomial infections in people who are critically ill and immunocompromised. Chronic infections are challenging to treat because of the pathogenic bacteria's capacity to manufacture virulence factors and their growing resistance to several medications (45).

P. aeruginosa is one of the three critical priority diseases that the World Health Organization (WHO) has determined urgently need new medications to combat. *P. aeruginosa* possesses a wide range of virulence factors that fall into three main categories: bacterial surface structures like flagella, pilli and lipopolysaccharides that aid in adhesion or the colonization to the hosts; secretion systems delivering toxic substances into the host, including pyocyanin that damages host cells and suppresses the immune system; exotoxin A that inhibits protein synthesis and causes cell death; and bacterial cell-to-cell interactions, such as QS and biofilm, that provide bacterial communication and drug resistance (46).

Because of this, methods that try to lessen pseudomonal infectivity by destroying or impairing bacterial virulence factors are superior to traditional antibiotic treatment (46). When bacterial virulence is disrupted, the bacteria are more susceptible to the immune system or antibiotics and there is less selective pressure on their survival, which reduces the likelihood that drug resistance will develop (47).

Biotechnological applications

QS circuits can be engineered to optimize metabolic pathways in cell factories, which can later be utilized to make consortiums to produce biofuels. Marine bacteria produce Extracellular Polymeric Substances (EPS), which have been discovered and used for a variety of purposes across multiple industries because of biotechnological developments in QS. An important example is the EPS that *Alteromonas infernus* and *Vibrio diabolicus* make when they are isolated from deep-sea hydrothermal vents. This EPS has therapeutic regenerating qualities. Because of their low immunogenicity, the glycosaminoglycans found in these EPS are advantageous for tissue remodelling and repair. Hyaluric acid is one such product made from these EPS; it uses hyaluronic acid to help with joint injuries, embryogenesis and tissue remodeling. Like a combination of hyaluronan and non-sulfated chondroitin units, the EPS is made up of high molecular weight linear tetrasaccharidic repeating units of glucuronic acid and hexosamine (N-acetyl-glucosamine and N-acetyl-galactosamine) (48).

QS and biochemical cycling

It has been discovered that QS systems are crucial for controlling the microbial activity engaged in the ocean's biogeochemical cycling. *Vibrio* sp., *Pseudomonas*, *Pseudoalteromonas*, *Marinobacter*,

Roseobacter and some cyanobacteria are among the many marine bacterial species that are important regulators of biogeochemical cycles and engage in QS. QS-mediated gene regulation affects how vital elements like carbon, nitrogen, phosphorus and sulfur cycle in marine ecosystems. For instance, QS regulates the synthesis of extracellular enzymes that break down complex organic materials, enabling bacteria to effectively use these substrates for acquiring nutrients and energy (49).

QS as a novel target for antimicrobial therapy

QS has become an attractive target in the search for new medicines owing to the emergence of drug-resistant bacteria. Global health is seriously threatened by AMR, which might have dire repercussions. A global reaction to lessen the impact of the developing antimicrobial agent resistance has been prompted by global concern. Many parties, including governments, legislators, scientists and researchers, are committed to making sure that this menace doesn't jeopardize lives and undermine the progress of contemporary medicine. Under the "one health" paradigm, which recognizes the close ties between animal, human and environmental health, these collaborative efforts seek to significantly impact the fight against AMR (50).

Given this, QSIs are being considered more as possible anti-virulence drugs that have the ability to disarm pathogens without applying the kind of selection pressure common to traditional antibiotics (51). Recent developments have shown that both natural and synthetic QSIs are effective at preventing bacteria from communicating with one another, which reduces virulence factors like motility, biofilm formation and toxin production (52). Furthermore, delivery systems based on nanotechnology have shown promise in improving the stability and targeted distribution of QSIs, hence expanding their therapeutic potential in the fight against infections resistant to several drugs (53).

Quorum quenching: disrupting bacterial communication

QS is an essential mechanism used by bacteria to regulate gene expression based on population density. However, disrupting this communication process termed quorum quenching (QQ) has emerged as a promising strategy for controlling bacterial virulence, biofilm formation and pathogenicity. Unlike traditional antibiotics, which exert selective pressure leading to resistance, QQ targets bacterial signalling pathways, making it an alternative approach for antimicrobial therapy and industrial applications (54).

QQ refers to a range of biological mechanisms that prevent QS signals from being synthesized, accumulated, or received, hence impairing bacterial communication (55). It acts as a natural inhibitor of bacterial coordination, frequently offering microbial communities a competitive edge and showing promise for use in industry, biocontrol and medicine (56).

Conclusion

Our knowledge of bacterial communication has been completely transformed by QS, which shows that bacteria may produce and detect autoinducers to coordinate their actions in response to changes in population density. Numerous bacterial functions, such as bioluminescence, biofilm formation, antibiotic resistance, virulence regulation and bioremediation, depend heavily on this phenomenon. QS has implications for biotechnology, nanomedicine, agriculture and even global biogeochemical

cycles, demonstrating its importance beyond microbiology. The emergence of bacteria resistant to antibiotics has made QS a viable target for innovative antimicrobial treatments. It may be possible to lessen bacterial infections by interfering with QS pathways without applying selection pressure that increases resistance. Furthermore, QS-based approaches in the environmental and agricultural sectors highlight its potential for long-term improvements. Future studies will probably concentrate on creating novel QSIs, enhancing microbial interactions for advantageous uses and utilizing QS in biotechnology as investigations into the complexities of QS and its wider ramifications continue. QS is a key component of contemporary microbial research since it may be used to understand and control bacterial communication, which can lead to discoveries in industrial microbiology, environmental science and medicine.

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Authors' contributions

All authors made substantial contributions to conception and design, acquisition of data or analysis and interpretation of data. All authors read and approved the final manuscript.

Compliance with ethical standards

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