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Bacterial Social Engagements: Production and Management of Virulence in Pathogenic Bacteria of Quorum Sensing System (Interbacterial Communication) which was First Noticed in Oceans with Bioluminescence

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Abstract

Quorum Sensing System (QS) is a bacteria- bacteria communication process in which bacteria use the production and detection of extracellular chemicals called autoinducers (AIs) to monitor bacteria population density. QS allows bacteria to synchronize the gene expression of the group, and thus act in unison. Once the bacteria communicate and synchronize through the AHL molecules of the QS system, they perform their vital work and operations. By proving QS, it is claimed that bacteria are not asocial, they can calculate their numbers in the environment, and some researchers may even have a so-called artificial intelligence. In this review, the QS system of *Vibrio fischeri* bacteria is explained and the bioluminescence feature and virulence factors in QS management is explained. While the functions of bioluminescence are not known for all animals, frequently bioluminescence is used to warn or evade predators, to lure or detect prey, and for communication between members of the same species. It has been explained that pathogenic bacteria create virulence with the T1SS, T2SS, T3SS, T4SS, T5SS, T6SS, T7SS secretion system under the control of the QS system through AHL molecules and initiate the disease process.

Keywords: Quorum Sensing System, Interbacterial Communication, Bioluminescence, Virulence, *Vibrio fischeri*

INTRODUCTION

Signal transduction and gene regulation through the phosphorylation of two regulatory components is now recognised as one of the primary global regulatory networks in bacteria world [1]. However, not all types of sensor-regulator circuits relay information via phosphoryl transfer. Alternative signalling systems mediated by small diffusible molecules termed autoinducers or pheromones have long been recognised to be involved in the control of gene expression. Numerous signalling molecule-mediated sensing and response pathways have now been identified and many fall within the scope of a form of regulation which is known as Quorum Sensing Systems (QS). QS is commonly used to describe the phenomenon whereby the accumulation of a low-molecular-mass signal molecule enables individual cells to sense when the minimal population unit or quorum of bacteria has been achieved for a concerted action to be initiated [2]. This system relies on two major components, a small signalling molecule which accumulates in a population density-dependent manner and a transcriptional activator protein which, in concert with the signal molecule, activates the expression of relevant genes. This review will focus on the wide range of QS that employ *N*-acylhomoserine lactones (AHLs) as the signal molecule [3]. Detection of the QS system is a very important piece of evidence that reveals the socio-microbiological aspects of bacteria. This communication takes place both within and between species. The bacterial world thus becomes quite complex.

Vibrio fischeri bacteria, it has now become evident that AHLs are produced by a wide variety of bacteria including a lot of bacteria and they have been shown to control a diverse range of bacteria density dependent factors. Some bacteria produce multiple AHLs, each controlling different phenotypes. AHLs signalling was first described in *V. fischeri* and has become a model for studies of QS [3].

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Oceans samples taken from place on the world revealed the presence of bioluminescent bacteria, but at a rather low level of abundance, not more than a few cells per milliliter. A question frequently raised was what function the light emission might have in such free-living bacteria. The question was even more compelling because the maximum light emission of these bacteria under ideal conditions in the laboratory is about 10^3 to 10^4 photons $s^{-1}cell^{-1}$. Even at this level of luminescence, populations found free in seawater would produce nowhere near enough light to have physiological, biological or ecological significance. This answer, as well as new insights about bacteria-to-bacteria communication and critic genes regulation in very different bacteria, came from experiments designed to explain what seemed a curious phenomenon observed in laboratory. The initial research in this area was published in the early 1970s [4].

The first and basic observation was that in newly inoculated cultures of a luminescent bacteria like *V. fischeri*, the onset of exponential growth occurs without a lag but bioluminescence does not increase until mid-logarithmic phase. Taken from the original report of the phenomenon [5], in which the lag and subsequent sharp rise in luminescence were attributed to transcriptional regulation and referred to as autoinduction. The autoinduction was attributed to a substance produced by the bacteria themselves, which was therefore dubbed the autoinducers (AIs). Autoinduction showed characteristics of a developmental process and differential gene expression. This analogy to development did not catch on; at the time bacteria were generally viewed as undifferentiated cells with a single-minded program focused on growth and division. Held the fact that there was also some evidence suggesting a role for cell-to-cell communication signals in the control of competence gene expression in Gram-positive bacteria [6,4]. These first socio-bacteriological studies, which were the beginning of everything, were comprehensive and investigated in pathogenic bacteria. It has been reported that the QS system plays a very effective role in the killer mechanisms of bacteria and even initiates the disease process. Subsequent academic studies have revealed that Gram-negative bacteria also have a QS [7].

V. fischeri is a Gram-negative, rod-shaped bacteria found globally in marine environments [8]. This species has bioluminescent properties, and is found predominantly in symbiosis with various marine animals. It is oxidase-positive, heterotrophic, and motile by means of a polar flagella [9]. The bacteria is a main research organism for examination of microbial bioluminescence, QS, and bacterial-animal symbiosis [10]. *V. fischeri* bacteria also helped us to meet the QS system, which is an important part of this type of bacteriological life. *V. fischeri* is named after Bernhard Fischer, a German microbiologist [11]. Ribosomal RNA comparison led to the reclassification of this species from genus *Vibrio* spp. to the newly created *Aliivibrio* in 2007 [12]. However, the name change is not generally accepted by most researchers, who still publish *V. fischeri*.

At first *V. fischeri* this situation, which was noticed in, is being investigated in all bacteria. Both Gram-negative and Gram-positive bacteria use QS [13]. With the discovery of bioluminescence, it has now been proven that bacteria are not asocial, on the contrary, they are social creatures and cause disease by triggering critical gene expressions such as virulence factors with this QS system. Each bacteria causes disease with the virulence it produces in accordance with the characteristics of its own species. This process is the responsibility of QS. The aim of this review article is to explain the QS-directed bioluminescence first noticed in *V. fischeri* in the oceans, and starting from here the virulence it creates with QS, the interbacterial communication system in other pathogenic bacteria.

The purpose of this review article is in oceans *V. fischeri* to explain that realizes its bioluminescence with the QS system, and most importantly, to emphasize that this QS system is also used by other pathogenic bacteria, causing disease by managing virulence factors.

QUORUM SENSING (QS)

Do bacteria talk? The answer to this question is yes. So how does this work? It's happening with QS (Figure 1). QS was first discovered in *V. fischeri*, it is interbacterial communication that ties gene expression to bacterial cell density. QS involves the selfproduction of a diffusible pheromone called an AI, which serves as an extra cellular signal molecule that accumulates in the medium and evokes a characteristic response from cells [5]. Bacterial processes such as biofilm [14], virulence factors, secretion, secretion systems (T1SS, T2SS, T3SS etc.), bioluminescence, sporulation, gene transfer, antibiotic production and competence for DNA uptake are often critical for survival. However, these behaviors are seemingly futile if performed by a single bacteria acting alone. Yet, we know that bacteria perform these tasks effectively. How do bacteria manage? We now understand that, through a

process called QS, bacteria synchronously control gene expression in response to changes in cell density and species complexity. QS allows bacteria to switch between two distinct gene expression programs: one that is favored at low-cell-density (LCD) for individual, asocial behaviors (act), and another that is favored at high-cell-density (HCD) for social, group behaviors (act) [15]. This movement of bacteria in groups with a social behavior are socio-bacteriological aspects.

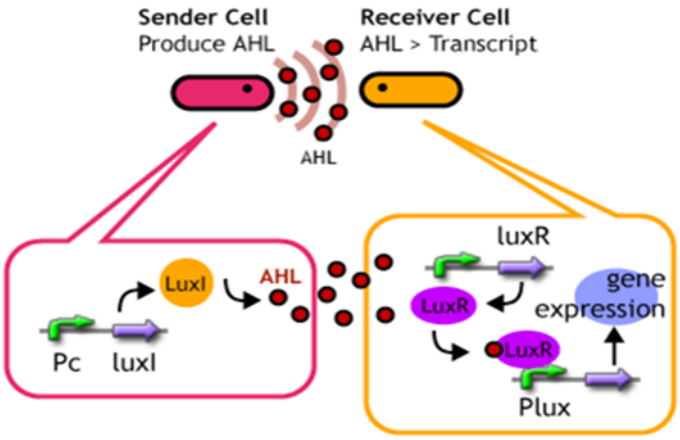

Figure 1. Bacterial QS [5]

One primary system that controls bioluminescence through regulation of the *lux* operon is QS, a conserved system across many microbial species that regulates gene expression in response to bacterial concentration. QS functions through the production of an AIs, usually a small organic molecule, by individual cells. As cell populations increase, levels of AIs increase, and specific proteins that regulate transcription of genes bind to these AIs and alter gene expression. This system allows microbial cells to communicate amongst each other and coordinate behaviors, which require large amounts of cells to produce an effect [16].

In *V. fischeri*, there are two primary QS, each of which respond to slightly different environments. The first system is commonly referred to as the lux system, as it is encoded within the lux operon, and uses the AHL. The protein LuxI synthesizes this signal, which is subsequently released from the cell. This signal, AHL, then binds to the protein LuxR, which regulates the expression of many different genes [17]. The second system, commonly referred to as the ain system, uses the (one of the AHL molecules) C8-HSL, which is produced by the protein AinS. Similar to the lux system, the C8-HSL increases activation of LuxR [18].

The different genetic targets of the *ain* and *lux* systems are essential, because these two systems respond to different cellular environments. The ain system regulates transcription in response to intermediate cell density cell environments, producing lower levels of luminescence [19]. On the other hand, the lux QS occurs in response to high cell density, producing high levels of luminescence and regulating the transcription of other genes, including QsrP, RibB, and AcfA [20]. Both of the ain and lux QS are essential for colonization of the squid and regulate multiple colonization factors in the bacteria [17]. If the situation is evaluated in terms of a pathogenic bacteria, *Aeromonas hydrophila* synthesizes the AHL molecule with the *ahyI* gene and detects the AHL molecule with the *ahyR* gene. Thus, interbacterial communication occurs, triggering virulence and starting the disease [21].

BIOLUMINESCENCE

Bioluminescence is luciferase enzyme. Initially, it was proposed that one molecule of reduced flavin mononucleotide ($FMNH_2$) was utilized to reduce luciferase. These conclusions were modified a year later, when two reduced flavin molecules instead of one were found to be involved [22]. Another research group [23] suggested that during bioluminescence one molecule of $FMNH_2$ combined with oxygen to form a highly reactive organic peroxide while the other combined with an aldehyde molecule to form an aldehyde-$FMNH_2$ compound. These reactions were believed to account for the energetics, but it was difficult to reconcile this with its spectral requirements. Currently, it is known that the blue-green light emission of bioluminescence, arises from the reaction of molecular oxygen

with $FMNH_2$ and a long-chain aldehyde to give FMN, water and a corresponding fatty acid. The luciferase enzyme catalyzes a mixed function oxidation of the long-chain aldehyde and $FMNH_2$. The reaction is highly specific for $FMNH_2$, which is protected against autooxidation once bound to the enzyme [24]. The reaction is summarized as:

$FMNH_2 + O_2 + RCHO \rightarrow FMN + RCOOH + H_2O + light.$

Bioluminescence in bacteria can also be regulated through a phenomenon known as autoinduction [25]. In bioluminescence, once the concentration of the AI reaches a specific threshold (above 10^7 cells mL^{-1}), it triggers the energetically costly synthesis of luciferase and other enzymes involved in luminescence. Thus, by sensing the level of AI, the cells are able to estimate their density and ensure that the luminescent product will be sufficiently high to cause an impact in the environment [26]. The AI for *V. fischeri*, AHL, was once thought to be species-specific [27], however studies have established that AHL can use as a signal molecule for Gram-negative bacteria. This suggests that the AI protein can facilitate interspecies communication [28], allowing QS bacteria to monitor the population of other species (cross talk) as well as their own [29, 24].

BIOLUMINESCENCE WITH QS MANAGEMENT IN *V. FISCHERI*

It begins with an interesting animal that lives deep in the Pacific Ocean, called the Hawaiian short-tailed squid (*Euprymna scolopes*), which belongs to the Sepiolidae family of octopuses. What makes this creature interesting is the light-emitting organ it carries in its abdomen. In the 1960s, a group of scientists tried to understand how squid produced light and found that a bacteria called *V. fischeri* had settled in the organ that produces the light. Bacterial cells live inside this organ in the squid's abdomen, and the squid produces light in return. It has been observed that *V. fischeri* living in a free do not produce light. The reason for this was thought to be because light production takes more than half of the total energy of the cell, so that the bacterium does not produce free light without an adequate food source. Towards the end of the 1960s, an interesting feature of *V. fischeri* was observed, which was reproduced in liquid culture media; they produced light when there was a certain density of bacterial cells in the environment. It has been determined that bacteria produce signal molecules and when there is enough of this molecule in the environment, bacteria produce light. In addition, it has been observed that bacteria produce light even though there are few bacterial cells in the environment with plenty of autoinducing molecules. In other words, *V. fischeri* understands how many bacterial cells are in the environment and produces light accordingly. In order for the produced light to work, bacteria must move in sync. This was the first proof of the idea that bacteria are also social creatures, and that they should be referred to as multicellular organisms, not as single-celled organisms. Thus, for the first time, the mechanism of detecting the number of siblings in the environment of bacteria was called QS. The autoinducing molecule produced by *V. fischeri* was first isolated by Eberhard *et al*. in 1981 and this signal molecule was shown to be in the AHL structure [30, 31, 32].

VIRULENCE FACTORS

Disease mechanisms are toxins, virulence, immune response inhibitors, adhesion, invasion and colonization. Virulence is the pathogenicity of a microbe, that is, its ability to cause disease [33, 34]. Virulence describes the degree of virulence (pathogenicity) within a group or species of microorganisms. In general, it covers two features: the ability of the microorganism to initiate disease (infectivity) and the severity (grade) of the resulting disease. Considering these features, few, moderate and highly virulent strains can be found in a pathogenic species. Virulence can be evaluated quantitatively. For example, the number of bacteria required to kill half of the experimental animals is lethal dose $(LD)_{50}$; The number of bacteria required to infect half of the experimental animals is called the infectious dose $(ID)_{50}$. These values vary considerably among microorganisms. The main reason for this variability is the virulence factors contained in the microorganism [35].

Biofilm, dermonecrotic factors, conjugation, antibiotic production, hemolysis, virulence during infection, ımmune response, elastase, pigment production, mass escape, cell division, bioluminescence, extracellular protease, transfer of plasmids, phenotypes, cytotoxin enterotoxin (Act) such as by QS system are some of the virulence factors managed [21].

VIRULENCE FACTORS WITH QS MANAGEMENT IN PATHOGENIC BACTERIA

Many Gram-negative bacteria and Gram-positive bacteria utilize peptide QS systems to control gene expression [36]. It has been proven that bacteria communicate with social behavior via signaling molecules, monitor whether they reach a certain majority and trigger critical gene expressions such as virulence factors as soon as they reach a sufficient number. Thus, by not stimulating the immune system of the host before time, it creates a successful disease process [37].

QS refers to the phenomenon that bacteria can sense their population density and regulate gene expression using chemical signaling molecules, thereby promoting cell-to-cell communication to synchronize the behaviors of bacteria, such as bioluminescence, biofilm formation and maturation, virulence-factor expression, motility, and so on [38, 39, 40, 41].

Biofilm [42], pigment, rhamnolipid [34], elastase, hemolysis [21], sporulation, antibiotic resistance, conjugation, transfer of plasmids, cytotoxin enterotoxin (Act), dermonecrotic factors and immune response are just some of the virulence factors responsible for the disease. And these virulences are carried out under the management of the QS system.

N-butanoyl-L-homoserine lactone (BHL) with 4-8 carbons in the Acyl side chain and *N*-(3-oxododecanoyl)-L- with 6-12 carbons in the Acyl side chain in the bacterial fish pathogen clinical *Yersinia ruckeri* (12 strains). Investigated the production of homoserine lactone (OdDHL) signaling molecules through *Chromobacterium violaceum* CV026 and *Agrobacterium tumafeciens* NT1 microbiological monitor systems (with biosensor strains). He determined that *Y. ruckeri* strains produced BHL molecule through *C. violaceum* CV026 and OdDHL molecule through *A. tumafeciens* NT1 by tests using *Pseudomonas aeruginosa* PAO1 strain as a positive control. Elastase was investigated by spectrophotometer, rhamnolipid with 0.2 g of CTAB (Cethyltrimethylammoniumbromide), 5mg/l methylene blue and M9-glutamate minimal medium agar. Hemolysis was investigated by bacteria inoculation on 5% blood agar, protease on 2% skimmed milk powder agar, and amylase on 2% starch agar. As a result, *Y. ruckeri* communicates through the signal molecules they produce, and as soon as they reach the desired majority, they trigger critical gene expressions for fish and produce virulence factors. In addition, it was determined that these strains did not produce virulence factors such as rhamnolipid, protease, amylase and hemolysis activities. Determined that *Y. ruckeri* uses the QS molecules BHL and OdDHL. Reported that *Y. ruckeri* produces elastase, a virulence specific to the human pathogen of *P. aeruginosa*, to a small extent, and this is valuable in terms of the pathogenicity of *Y. ruckeri* [43].

DISCUSSION AND CONCLUSION

Of *V. fischeri* bacteria the QS model starting with, and after that investigation of the specific of the QS model of all bacteria are important scientific literatures that reveal the bacterial world, the ocean environment and the virulence management of pathogenic bacteria.

[34] reported some Gram-negative bacteria (*Vibrio alginolyticus*, *Vibrio anguillarum*, *Pseudomonas fluorescens*, *A. hydrophila*, *Y. ruckeri*) have with QS system and with this system virulence factors managed. *V. anguillarum*, *V. alginolyticus* and *P. fluorescens* bacteria establish bacterial communication by producing the OdDHL signal molecule. *A. hydrophila* and *Y. ruckeri* bacteria use both BHL and OdDHL signal molecules in bacterial communication [34]. [42] reported some Gram-negative bacteria (*Staphylococcus warneri*, *Aeromonas sobria*, *Y. ruckeri*, *Flavobacterium psychrophilum*, *V. anguillarum*) have with QS system their biofilm managed. [21] determined the virulence of elastase, hemolysis and biofilm of *A. hydrophila* pathogen have managemented by QS system and determined this system inhibited with gallic acid, rosmarinic acid, vanillic acid phenolic compounds.

Bacteria have evolved diverse strategies to compete for limited space and resources. Because these mechanisms can be costly to use, their expression and function are often restricted to specific environments where the benefits outweigh the costs. However, little is known about the specific cues that modulate competitive mechanisms as bacterial symbionts transition between free-living and host habitats. Here, we explained the bioluminescent squid and fish symbiont *V. fischeri* to probe for host and environmental conditions that control interbacterial competition via the Secretion System (SS) [44]. The ability of bacteria to take up DNA and incorporate foreign DNA into their genomes permits them to rapidly evolve and gain new traits and acquire antibiotic resistances. It also facilitates laboratory-based investigations into mechanisms of specific phenotypes, such as those involved in host

colonization. *V. fischeri* has long been a model for symbiotic bacteria-host interactions as well as for other aspects of its physiology, such as bioluminescence and biofilm [45].

As can be seen, QS proves that bacteria are in communication and that they solve many vital issues thanks to this communication between them. The discovery that bacteria are able to communicate with each other changed our general perception of many single, simple organisms in our world. Understanding how bacterial cells communicate with each other has a number of important practical implications for the control of pathogen bacteria, fully understanding nature and for the screening of bacteria that produce other high value products.

Bioluminescence is very important for the discovery of the QS and for revealing the perfection of nature. It is also crucial in uncovering the discovery and control of disease-causing virulence of QS through bioluminescence. The only strength of a creature as small as bacteria is its genes. Since there is a system that dominates the expression of QS genes, increasing studies in this area, investigating every problem related to QS in detail, reducing the infectious power in the bacterial world can be suggested as an alternative method of protection from disease.

Learning the QS, which is responsible for the formation of virulence factors that play a leading role in the pathogenesis of bacteria and manages this situation, and as a result brings the issue of interruption of interbacterial communication, highlights the breakthrough in prophylaxis.

Thanks to the QS system, they act together with the power of communication, removing the bacteria from the microscopic dimension and making them socio-bacteriological. Detection of their socio-bacteriological aspects is of drug value in stopping bacteria acting together and preventing diseases.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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