Research Article

Quorum Sensing

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Abstract

Quorum sensing is the regulation of gene expression in response to fluctuations in cell population density. Quorum sensing bacteria produce and release chemical signal molecules called autoinducers that increase in concentration as a function of cell density. The detection of a minimal threshold stimulatory concentration of an autoinducer leads to an alteration in gene expression. Quorum sensing allows bacteria to monitor the environment for other bacteria and to alter behavior on a population-wide scale in response to changes in the number and/or species present in a community. Most quorum sensing controlled processes are unproductive when undertaken by an individual bacterium acting alone but become beneficial when carried out simultaneously by a large number of cells. Thus, quorum sensing confuses the distinction between prokaryotes and eukaryotes because it enables bacteria to act as multicellular organisms. These processes include symbiosis, virulence, competence, conjugation, antibiotic production, motility, sporulation, and biofilm formation. Recent advances in the field indicate that cell-cell communication via autoinducers occurs both within and between bacterial species. Furthermore, bacterial autoinducers elicit specific responses from host organisms. Although the nature of the chemical signals, the signal relay mechanisms, and the target genes controlled by bacterial quorum sensing systems differ, in every case the ability to communicate with one another allows bacteria to coordinate the gene expression, and therefore the behavior, of the entire community. Presumably, this process bestows upon bacteria some of the qualities of higher organisms. Quorum sensing and its inhibition (quorum quenching) have significant clinical implications in terms of antimicrobial therapy.

Key Words: Quorum sensing, virulence, autoinducer, quorum quenching, bacteria, therapy.

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INTRODUCTION

Quorum sensing (QS) is the regulation of gene expression in response to fluctuations in cell population density Quorum sensing was discovered and described over 25 years ago in two luminous marine bacterial species, *Vibrio fischeri* and *Vibrio harveyi*.[1] In both species, the enzymes responsible for light production are encoded by the luciferase structural operon *lux CDABE*[2,3], and light emission was determined to occur only at high cell-population density in response to the accumulation of secreted auto inducer signaling molecules.[1] Until recently, only a few other cases of bacterial regulation of gene expression in response to cell-cell signaling were known. For example, antibiotic production by *Streptomyces spp.*[4], conjugation in *Enterococcus faecalis*[5], and fruiting body development in *Myxococcus xanthus*[6] were also recognized to be controlled by intercellular signaling. These bacterial communication systems were considered anomalous, and in general, bacteria as a whole were not believed to use cell-cell communication. Rather, the exchange of chemical signals between cells/organisms was assumed to be a trait highly characteristic of eukaryotes. The recent explosion of advances in the field of cell-cell communication in bacteria has now shown that many or most bacteria probably communicate using secreted chemical molecules to coordinate the behavior of the group. Furthermore, it is known that a vast assortment of different classes of chemical signals are employed, that individual species of bacteria use more than one chemical signal and/or more than one type of signal to communicate, that complex hierarchical regulatory circuits have evolved to integrate and process the sensory information, and that the signals can be used to differentiate between species in consortia. It seems clear now that the ability to communicate both within and between species is critical for bacterial survival and interaction in natural habitats.[7]

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AUTO INDUCERS

QS is a bacterial cell-cell communication process that involves the production, detection, and response to extracellular signaling molecules called autoinducers (AIs).[8] From a historical perspective, the most commonly studied autoinducers belong to one of the following three categories: acylated homoserine lactones (AHLs), used by Gram-negative bacteria (also sometimes referred to as autoinducer-1 [AI-1]); peptide signals, used by Gram-positive bacteria; and autoinducer-2 (AI-2), used by both Gram-negative and Gram-positive bacteria. There are also other QS signals that go beyond these classes, including Pseudomonas quinolone signal (PQS), diffusible signal factor (DSF), and autoinducer-3 (AI-3), and new molecules will undoubtedly be discovered as the study of quorum sensing expands to species of bacteria yet to be investigated.[9] AIs accumulate in the environment as the bacterial population density increases, and bacteria monitor this information to track changes in their cell numbers and collectively alter gene expression. QS controls genes that direct activities that are beneficial when performed by groups of bacteria acting in synchrony. Processes controlled by QS are highlighted in (Table 1).[10-12]

Table 1. Processes controlled by QS

- Bioluminescence
- Sporulation
- Competence
- Antibiotic production
- Biofilm formation
- Virulence factor secretion

Despite differences in regulatory components and molecular mechanisms, all known QS systems depend on three basic principles. First, the members of the community produce AIs, which are the signaling molecules. At low cell density (LCD), AIs diffuse away, and, therefore, are present at concentrations below the threshold required for detection. At high cell density (HCD), the cumulative production of AIs leads to a local high concentration, enabling detection and response.[13] Second, AIs are detected by receptors that exist in the cytoplasm or in the membrane. Third, in addition to activating expression of genes necessary for cooperative behaviors, detection of AIs results in activation of AI production.[14,15] This feed-forward auto induction loop presumably promotes synchrony in the population. Gram-positive and Gram-negative bacteria use different types of QS systems (Figure 1). Gram-positive bacteria use peptides, called auto inducing peptides (AIPs), as signaling molecules. Once produced in the cell, AIPs are processed and secreted. When the extracellular concentration of the AIP is high, which occurs at HCD, it binds to a cognate membrane-bound two-component histidine kinase receptor. Usually, binding activates the receptor's kinase activity, it autophosphorylates, and passes phosphate to a cognate cytoplasmic response regulator. The phosphorylated response regulator activates transcription of the genes in the QS regulon. In some cases of Gram-positive bacterial QS, AIPs are transported back into the cell cytoplasm where they interact with transcription factors to modulate the transcription factor's activity and, in turn, modulate gene expression changes. Gram-negative bacteria communicate using small molecules as AIs. These are either acylhomoserine lactones (AHLs) or other molecules whose production depends on S-adenosylmethionine (SAM) as a substrate.[16] AIs are produced in the cell and freely diffuse across the inner and outer membranes. When the concentration of AIs is sufficiently high, which occurs at HCD, they bind cytoplasmic receptors that are transcription factors. The AI-bound receptors regulate expression of the genes in the QS regulon. In some cases of Gram-negative bacterial QS, AIs are detected by two-component histidine kinase receptors that function analogously to those described in the preceding paragraph for Gram-positive QS bacteria. Dozens of clinically-relevant bacteria use QS to regulate the collective production of virulence factors.[8]

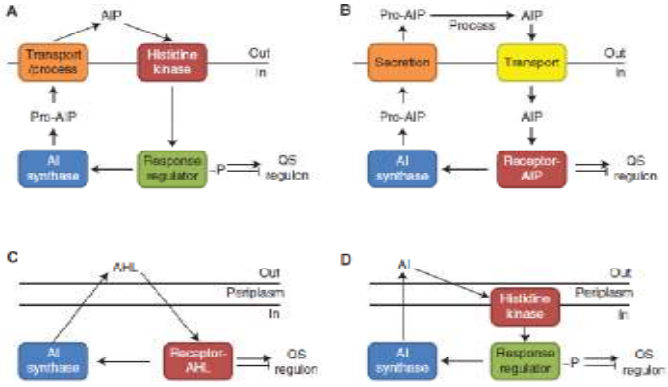

Figure 1: Bacterial QS circuits. Autoinducing peptide (AIP) QS in Gram-positive bacteria by (A) two-component signaling, or (B) an AIP-binding transcription factor. Small molecule QS in Gram-negative bacteria by (C) a LuxI/LuxR-type system, or (D) two-component signaling[8]

QUORUM SENSING AND "ANTIVIRULENCE" THERAPIES

Blocking communication of one's adversaries serves as an effective tactic to disrupt cooperative actions among individuals or groups. The knowledge gained over the last 40 years that bacteria commonly benefit from social interactions and intercellular signaling presents an opportunity to interfere with their ability to coordinate efforts to invade their hosts, whether human, animal, or plant. In fact, it is now realized that communication interference naturally exists in the microbial world, and it stands to reason that this ploy to gain an advantage over competitors was originally invented by bacteria. In many cases, the responses elicited by QS signals are ones that contribute directly to pathogenesis through the synchronized production of virulence determinants, such as toxins, proteases, and other immune-evasive factors. Additionally, QS can contribute to behaviors that enable bacteria to resist antimicrobial compounds or drugs, such as biofilm development. If these efforts to coordinate were blocked, it is theorized that bacteria would lose their ability to mount an organized assault on the host's defense or immune system or would be less able to form organized community structures that promote pathogenesis, such as biofilms. For some bacteria, working together as a group provides a means to build a defense or to surmount a barrier that individual bacterial cells find impossible to achieve. Blocking interactions between bacteria would effectively force bacteria to live as individuals fending for themselves. One key advantage proposed in targeting QS is based on the premise that a treatment that does not suppress growth of a cell will not exert a selective pressure to develop resistance to that treatment. QS is not an essential process, and QS mutants in general have not displayed growth defects. Granted, interfering with the regulation of virulence factor production will likely reduce fitness for survival in certain situations, but if maintaining a delicate control over QS-regulated genes is critical to the cell (and the exquisite layers of complexity found in many quorum-sensing pathways bolster this assumption), then developing resistance mechanisms against quorum-inhibiting therapies may be a difficult proposition for bacteria, which could help promote long-term efficacy of anti-QS therapies.[9]

CHEMICAL COMPLEXITY IN BACTERIAL AUTOINDUCERS

Recent research shows that a rich diversity of chemical molecules is used for communication in the bacterial world. New genetic, biochemical, and imaging techniques have enhanced our ability to identify and measure the readouts of cell-cell communication. These tools have led to the identification of several novel molecules and classes of molecules that are clearly bona fide autoinducers mediating cell-cell communication (Article1). A few examples are given in Table 2.[17-19]

Table 2. Examples of autoinducers

1. PQS. The molecule 3,4-dihydroxy-2-heptylquinoline, termed PQS, is a signal that is integral to the *P. aeruginosa* quorum-sensing cascade. This signal acts as an additional regulatory link between the Las and Rhl QS circuits.

2. 3OH PAME. 3OH palmitic acid methyl ester (3OH PAME) transmits information via the two-component sensor histidine kinase-response regulator pair, PhcS-PhcR, to cause the plant pathogen *Ralstonia solanacearum* to switch from a motile to an infective state.

3. CYCLIC DIPEPTIDES. Newly described in a number of gram-negative bacteria, at high concentrations, cyclic dipeptides antagonize AHL binding to cognate receptors.

BIOFILM FORMATION

Biofilms are now considered ubiquitous in the natural world.[20] In nature, bacteria are frequently found encased in polysaccharide matrix attached to a solid surface. This mode of growth, referred to as a biofilm, offers protection from environmental agents that would otherwise threaten their plank tonic counterparts. Bacterial biofilms have been observed to be extremely heterogeneous, both structurally and with regard to the physiology of the bacterial cells within them. The prevailing conceptual model depicts bacterial biofilms as being made up of micro colonies, which serve as the basic unit of the greater biofilm structure. Micro colonies are hydrated structures consisting of bacterial cells enmeshed in a matrix of exopolymeric substances (EPSs). Bacteria may proliferate on the attachment surface, leading to micro colony expansion. Eventually, community growth becomes limited by substrate availability due to increased diffusion distances, and the biofilm reaches a steady state. Such mature biofilms often consist of "towers" and "mushrooms" of cells in an EPS matrix. Interstitial voids and channels separate the biofilm structures and facilitate a convective flow in order to transport nutrients to interior parts of the biofilm and remove waste products. Biofilms have become evident in many, if not most, environmental, industrial, and medical bacteria related problems. A recent public announcement from the NIH stated that more than 60% of all microbial infections involve biofilms.[21] *P. aeruginosa* is an example of an organism

frequently found growing in biofilms. Microscopic analysis of *P. aeruginosa* biofilm communities reveals that they are not just sugar-encased masses of cells, but rather distinct mushroom and stalk-like structures that contain intervening water channels to allow nutrients to flow in and waste products to flow out. In clinical setting, biofilms formed on medical devices and in bacterial infections can wreak havoc, largely because bacteria growing as biofilm are refractile to host defenses including phagocytes, antibodies, and complement.[22] Moreover, these organisms are highly resistant to antibodies making eradication by using conventional chemotherapy virtually ineffective. Thus, novel ways of preventing biofilm formation and eradicating those already established must be found. Recently, a link between biofilm formation and QS was discovered in *P. aeruginosa*. Analysis of biofilms formed by a *P. aeruginosa* mutant deficient in the production of the las signal molecule, 3-oxo-C12-HSL, revealed a biofilm that was much thinner and lacked the three-dimensional architecture observed in that of the parent. Even more noteworthy was the fact that, while the parental biofilm was resistant to the detergent sodium dodecyl sulfate (SDS), the mutant biofilm rapidly dispersed from the underlying surface after SDS exposure. When grown in the presence of exogenous 3-oxo-C12-HSL, the mutant biofilm resembled that of the parent and was resistant to SDS. Thus, it appears that QS plays a critical role in the formation of mature, differentiated biofilm structures. It is not known at this time whether other bacteria use QS during biofilm formation. However, at least in case of *P. aeruginosa*, strategies designed to block QS may be an effective means of preventing biofilm formation.[23] The process of biofilm formation by *Candida albicans* involves three main steps: the initial colonization of the substratum by the yeast cells, growth and hypha formation and the production of an extracellular matrix, primarily composed of β-1,3-glucan. The mature biofilm consists of yeasts, hyphae, and pseudohyphae; however, eventually, the yeast cells leave the biofilm. In *C. albicans* also the QS can modulate all stages of biofilm formation, i.e. attachment, maturation, and dispersal.[24] The best characterized QS molecule produced by *C. albicans* is "Farnesol,"[25] which regulates the inter-conversion between its yeast and filamentous form. In *in vitro* experiments, farnesol has been shown to reduce the size of biofilms. The other QS molecule that may also alter biofilm development in *C. albicans* is "tyrosol."[26] In experiments, farnesol has been shown to repress hyphal growth by inhibiting the Ras1-adenylate cyclase-protein kinase A signaling pathway. However, the role of farnesol in multicellular population can be better understood by discovering mutants with altered farnesol response and farnesol production.[27]

APPLICATIONS OF QS

QS is a novel target for antimicrobial therapy. The continuing emergence of multiple drug-resistant strains of bacteria has necessitated finding novel strategies for treating bacterial infections. The discovery that wide spectrums of organisms use QS to control virulence factor production makes it an attractive target for discovery of new anti-virulence therapeutics. The pathogenic organisms can be rendered a virulent if the QS mechanisms that control virulence factors can be targeted. The scientific research has focused on the synthesis and characterization of AI analogs, mostly focusing on AHL-based QS systems. By virtue of the intrinsic cytotoxic activity of AHLs, they can aptly now be regarded as "small molecule toxins".[28] The QS pathways can be disrupted at various levels; for example at AIs and R protein levels, which have a unique specificity for one another. Non-cognate AIs typically only weakly activate or may inhibit R protein activation altogether. Therefore, analogs that bind to but do not activate R proteins could act as antagonists to prevent AI binding, which in turn would shut down the QS cascade. The ability of AI analogs to inhibit activation of R proteins has already been demonstrated in a number of bacteria, including *V. fischeri, A. tumefaciens, Chromobacterium violaceum,* and *Aeromonas salmonicida.*[29] Recently, an enzyme from an isolate of Bacillus that is capable of degrading AHLs was discovered. This enzyme is encoded by the *aiiA* gene (AI inactivation) and contains two domains that are homologous to the active sites of the following metalloenzymes: glyoxalase II, metallo-B lactamase and arylsulfatase. Expression of *aiiA* in E. carotovora decreased generation of proteolytic enzymes and significantly reduced AI production.[30] For finding another way of interfering with QS, the biosynthetic pathways of some AHL molecules have been elucidated. Interrupting the AHL biosynthetic pathway and shutting down AHL synthesis, perhaps through the use of analogs of AHL precursors, would be a highly effective means of blocking the QS cascade.[29]

QUORUM QUENCHING

The fundamental role of quorum sensing appears to be global control of the physiology of bacterial populations. This control is often exerted at the interface of different bacterial populations or at the bacterial-host margin. In niches in which bacterial populations compete for limited resources, the ability to disrupt quorum sensing may give one bacterial species an advantage over another that relies on quorum sensing. Likewise, a host's ability to interfere

with bacterial cell-cell communication may be crucial in preventing colonization by pathogenic bacteria that use quorum sensing to coordinate virulence. Thus, it is not surprising that mechanisms have evolved to interfere with bacterial cell-cell communication in processes termed quorum quenching (QQ). Analogous mechanisms presumably exist for promoting QS-controlled behaviors when such behaviors provide benefits to organisms cohabitating with QS bacteria.[31] Recently, an immunotherapeutic approach for QQ was pioneered by generation of the anti-AHL monoclonal Ab (mAb), RS2-1G9, elicited against a synthetic 3-oxo-C12-HSL analog. The RS2-1G9 was found to efficiently suppress QS signaling in *P. aeruginosa* and conferred protection upon mammalian cells via neutralization of 3-oxo-C12-HSL *in vitro*. The monoclonal antibodies against staphylococcal AIPs have been developed by using a hapten in which the hydrolytically labile thiolactone was replaced with a more stable lactone moiety. The mAbs thus developed were evaluated both *in vitro* and *in vivo* and were shown to possess potent QQ abilities, including the protection of mice from an otherwise lethal *S. aureus* infection.[28,32,33] Naturally occurring QQ processes are being tested as novel antimicrobial therapies. Overexpression of aiiA in tobacco and potato plants confers resistance to *E. carotovora,* which requires AHL-controlled virulence factor expression to cause disease [34]. Likewise, coculture of Bacillus thuringiensis decreased *E. carotovora*-mediated plant disease in an aiiA-dependent manner.[35] Mice treated with synthetic antagonists of *S. aureus* AIP show resistance to infection.[36] Similarly, purified halogenated furanones appear to attenuate virulence of bacteria in mouse models.[37,38] These and other examples predict that inhibition of QS offers an attractive alternative to traditional antibiotics because these strategies are not bactericidal and the occurrence of bacterial resistance therefore could be reduced. Likewise, approaches aimed at promoting beneficial QS associations may enhance industrial scale production of natural or engineered bacterial products.

CONCLUSIONS AND FUTURE PERSPECTIVES

The ability to coordinate behavior in a cell-density-dependent fashion has several obvious advantages (Table 3).

Table 3. Advantages of QS.

1. To optimize and regulate a variety of activities.
2. To communicate and to alter behavior in response to the presence of other bacteria.
3. Allow a population of bacteria to coordinate global behavior and thus act as a multi-cellular unit.
4. Enhance pathogenicity.
5. Evade host defense.
6. Improve overall survival.

Although the study of QS is only at its beginning, we are now in a position to gain fundamental insight into how bacteria build community networks. Novel antimicrobial strategies could be designed based on information garnered from studies of QS/QQ, which suggests that research on QS/QQ could have enormous practical applications. QS inhibitory compounds might constitute a new generation of antimicrobial agents with applications in many fields, including medicine (human and veterinary), agriculture, and aquaculture, and the associated commercial interests are substantial.

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