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CONFERENCE PROCEEDINGS

Quorum-Sensing Regulation of Gene Expression: Fundamental and Applied Aspects and the Role in Bacterial Communication

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Abstract—Quorum sensing (QS) is a specific type of regulation of gene expression in bacteria; it is dependent on the population density. QS systems include two obligate components: a low-molecular-weight regulator (autoinducer), readily diffusible through the cytoplasmic membrane, and a regulatory receptor protein, which interacts with the regulator. As the bacterial population reaches a critical level of density, autoinducers accumulate to a necessary threshold value and abrupt activation (induction) of certain genes and operons occurs. By means of low-molecular-weight regulators, bacteria accomplish communication between cells belonging to the same or different species, genera, and even families. QS systems have been shown to play a key role in the regulation of various metabolic processes in bacteria and to function as global regulators of the expression of bacterial genes. Data are presented on different types of QS systems present in bacteria of various taxonomic groups, on the species specificity of these systems, and on communication of bacteria by means of QS systems. The possibility is considered of using QS regulation systems as targets while combating bacterial infections; other applied aspects of QS investigation are discussed.

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Key words: quorum-sensing regulation, bacteria, autoinducers, *N*-acyl-homoserine lactones, bacterial communication

The phenomenon termed quorum sensing (QS), a specific type of regulation of bacterial gene expression operating under conditions of high density of the bacterial population, has attracted the keen interest of numerous researchers engaged in microbiology, microbial genetics, medicine, and agriculture. QS systems include two obligatory components: low-molecular-weight regulators (autoinducers, AIs), readily diffusible through the cytoplasmic membrane; and receptor proteins, which interact with the regulators. The concentration of autoinducers in the medium is proportional to the number of the bacterial cells present. At a low population density, bacteria produce a basal level of AIs. As the population density increases, autoinducers accumulate in the medium. When their concentration reaches a certain threshold value, the AIs begin to interact with the corresponding receptor proteins; the receptor-protein–autoinducer complexes bind to promoter regions of genes/operons, which results in the induction of expression of certain bacterial genes. By means of AIs, bacteria accomplish communication between cells belonging to the same or different species, genera, and even families. Through cell-to-cell communication, bacteria can achieve coordinated expression of genes in cells of the entire population consisting of bacteria of the same or different species; this phenomenon promotes the survival of bacteria under alternating environmental conditions. This "social" behavior of bacteria suggests an analogy between bacterial populations and multicellular organisms [1–11].

QS regulation was first discovered about 30 years ago in the luminescent marine bacterium *Vibrio fischeri*, and for a long time it was considered to be peculiar to this particular bacterium. However, in recent years, regulation of this type has been found to be widespread among bacteria of various taxonomic groups [3, 5, 10–12]. QS regulation plays a key role in many processes, such as the interaction of bacteria with higher organisms (plants and animals), regulation of bacterial virulence, biofilm formation, conjugation, and regulation of the expression of genes related to the biosynthesis of enzymes, toxins, antibiotics, and other secondary metabolites. With the use of methods of transcriptome and proteomic analysis, it was shown that QS systems function as global regulation factors. Research into QS regulation systems and bacterial communication opens new prospects of investigation of bacterial behavior in natural environments.

Bacterial QS systems employ a wide range of signal molecules as autoinducers (Table 1). The number of autoinducers recognized by researchers is constantly growing. Interestingly, a bacterial species may use

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Different types of autoinducers involved in quorum-sensing regulation systems

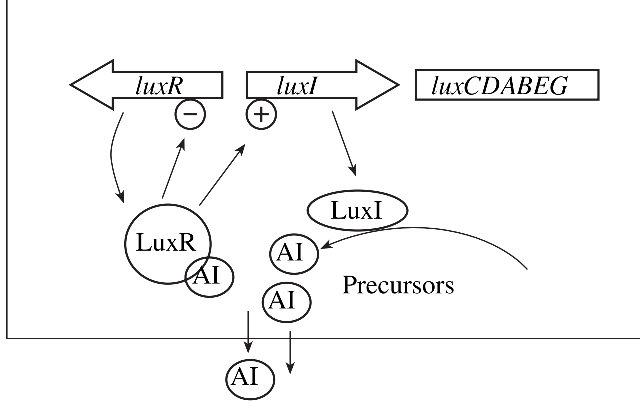
AI type	AI structure	Bacterium/AI
AHL	(structure)	*P. chlororaphis*/*N*-hexanoyl-homoserine lactone
	(structure)	*V. fischeri*/*N*-3-oxohexanoyl-homoserine lactone
	(structure)	*P. aeruginosa*/*N*-3-oxododecanoyl-homoserine lactone
AIP	ADPITRQWGD	*B. subtilis*/ComX
	ERGMT	*B. subtilis*/CSF
	YSTCYFIM (S–C=O thiolactone)	*S. aureus*/AIP-I
	INCDFLL (S–C=O thiolactone)	*S. aureus*/AIP-III
AI-2	(structure)	*S. typhimurium*
	(structure)	*V. harveyi*
Butyrolactones	(structure)	*S. griseus*/butyrolactone (A-factor)

more than one type of signal molecule. Below, the bacterial QS systems presently known will be considered.

Types of QS Systems

QS systems of gram-negative bacteria (LuxI–LuxR-type systems). In gram-negative bacteria, the QS systems that employ *N*-acyl-homoserine lactones (AHLs, or AI-1s) as an autoinducer are the best studied. The AHL molecule consists of a homoserine lactone ring and an acyl side chain (table). More than 40 AHL species are known, which differ in the acyl chain length (from C4 to C18) and the substituents in the acyl chains; these distinctive features determine the specificity of the effect of AHLs. AHLs are produced by gram-negative bacteria only. The receptor proteins with which AHLs interact, and AHL synthases, are homologous to the *Vibrio fischeri* proteins LuxR and LuxI, respectively, and constitute the LuxR- and LuxI-like protein families [1, 3, 4]. QS systems involving AHLs have been described in a large number of gram-negative bacteria, including pathogenic and phytopathogenic ones [2, 3, 5, 6].

The QS regulation of the *lux* operon of *V. fischeri* (Fig. 1) has been studied in the greatest detail. Protein LuxI (autoinducer synthase) is responsible for the production of *N*-3-oxohexanoyl-homoserine lactone



Quorum-sensing regulation of the *lux* operon of *Vibrio fischeri.* AI, autoinducer; *lux*I, LuxI synthase gene; *luxR*, LuxR receptor protein gene; *lux*CDABEG, *lux* operon genes.

(3OC6-HSL). The complex of the receptor protein LuxR and 3OC6-HSL binds to the promoter of the *lux* operon and activates its transcription, which results in luciferase synthesis and light emission. With the increase in the density of the *V. fischeri* cell population, 3-OC6-HSL accumulates in the medium, and its concentration reaches the threshold value (ca. 1–10 μg/ml) sufficient for the activation of LuxR and its binding to the promoter region of the *lux* operon, resulting in the induction of this operon. Importantly, the *luxI* gene, encoding the synthase of the autoinducer, is a member of the *lux* operon; therefore, upon the induction of the operon, the amount of AI increases abruptly [1, 3, 4].

LuxR-like proteins consist of two domains. The N-terminal domain is responsible for binding AHL, and the C-terminal domain is necessary for binding to DNA. The receptor protein is amenable to proteolytic degradation; however, in the complex with AHL, it is resistant to proteolysis. The interaction with AHL promotes dimerization of the LuxR–AHL complex; the dimers formed bind to the promoter region, usually to the specific 20-bp-long *lux* site, which contains inverted repeats [1, 3, 4]. The receptor protein preferably interacts with its native AHL (a component of the same QS system), and exhibits lower affinity to alien AHLs, differing in molecule structure. The preference for a particular AHL is determined by the size of the binding pocket of the receptor protein [6]. However, the species specificity of AHLs is not rigorous, and one and the same AHL types may be produced and recognized by bacteria of different species and genera.

QS regulation has been studied in detail in the pathogenic bacterium *Pseudomonas aeruginosa.* In this bacterium, which causes severe infections of respiratory tracts, a large number of genes, including those responsible for the synthesis of virulence factors, are activated by two QS systems, LasI LasR and RhlI RhlR. The former system includes synthase LasI, responsible for the production of autoinducer *N*-3-oxododecanoyl-homoserine lactone (3OC12-HSL), and receptor protein LasR. This system regulates the synthesis of secreted virulence factors, responsible for the destruction of host organism tissues infected by *P. aeruginosa*; these factors include elastase, protease, and alkaline phosphatase. The system also activates the expression of genes of the second QS system of *P. aeruginosa.* Protein RhlI is the synthase of the second AHL of this bacterium, *N*-butyryl-homoserine lactone (C4-HSL). The complex of protein RhlR with C4-HSL is involved in the regulation of the expression of several genes important for the virulence of this bacterium and its survival under natural conditions: the elastase and alkaline phosphatase genes (which are at the same time subject to regulation by the QS system of the first type); the *rpoS* gene, which codes for the RNA polymerase σ^S subunit (the key factor in the regulation of transcription of most genes expressed during the transition to the stationary growth phase); genes involved in pyocyanine synthesis, etc. It has been shown that the expression of more than 600 genes of *P. aeruginosa* is regulated by QS systems [2, 13, 14].

Of considerable interest are data suggesting that the autoinducer 3OC12-HSL may exert direct influence on the eukaryotic organism in the absence of the bacterium *P. aeruginosa*. 3OC12-HSL molecules interact with immune system components such as interleukins, and inhibit lymphocyte proliferation and cytokinin production. Injection of this compound induced inflammatory process in mice [15, 16].

QS regulation in gram-positive bacteria. In gram-positive bacteria, the best studied are the QS systems involved in virulence control in *Staphylococcus aureus*, regulation of competence (i.e., of the ability to accept exogenous DNA in the process of transformation) in *Staphylococcus aureus* and regulation of competence and sporulation in *Bacillus subtilis.* These systems employ autoinducers of a different nature, namely, secreted peptides (AIPs), which include linear peptides and peptides containing a thiolactone ring (table). The functioning of these QS systems occurs as follows. AIPs interact with specific receptors, two-component sensor histidine kinases; peptide processing and modification occur in most cases. The phosphorylation–dephosphorylation cascade is switched on. The sensor kinase is phosphorylated; then, the phosphate group is transferred to a specific protein, a response regulator, after which the phosphorylated regulator binds to DNA and activates transcription of the target gene [3, 6, 9, 11, 17, 18].

The QS system of *S. aureus* has been most thoroughly studied. This system is involved in the regulation of the synthesis of protein factors promoting bacterial adhesion (and thus colonization), toxins, proteases, and other virulence factors. It has been shown that, in *S. aureus*, QS regulation is accomplished by a complex multicomponent mechanism which includes a large number of specific proteins, regulatory RNA III, and

inhibitory peptide RIP. Within the species *S. aureus*, four clinically important groups are recognized which synthesize AIPs with different amino acid sequences. Each AIP type activates its own receptor protein and inhibits the activation of the receptor proteins of the remaining three *S. aureus* groups, thereby suppressing their virulence [11, 17–19]. Thus, the specificity of the AIP-involving signalling systems is very high, at least in staphylococci; it is determined by the precision of the AIP–receptor protein interaction.

Interestingly, streptomycetes, which represent another group of gram-positive bacteria, use quite different compounds—γ-butyrolactones—as QS system autoinducers (table). In streptomycetes, QS was shown to be involved in the regulation of morphological differentiation and of secondary metabolite production [11]. The signal molecules of streptomycetes are structurally similar to AHLs of gram-negative bacteria; it is therefore tempting to assume the possibility of communication between these phylogenetically remote groups of bacteria in natural environments.

QS systems that include the AI-2 autoinducer. The AI-2 autoinducer was first discovered in cells of *Vibrio harveyi*. AI-2 is a compound of unusual structure, its molecule containing a boron atom (see table) [20]. The autoinducer accumulates in the second half of the exponential growth phase; upon the transition to the stationary phase, its content decreases abruptly. The *luxS* genes and the LuxS proteins (AI-2 synthases) which they encode occur in various bacteria, both gram-negative and gram-positive. The *luxS* gene has been found in a half of the bacterial genomes sequenced [3, 5, 6, 8, 11]. Proceeding from the homology of LuxS proteins in bacteria of different taxonomic groups, it has been speculated that different bacteria produce one and the same AI-2 autoinducer, which is thus a universal autoregulator. However, when the structure of one more AI-2 molecule was determined (that produced by *Salmonella typhimurium*), it turned out to be different from the structure of 2 *V. harveyi* AI-2: for example, the *S. typhimurium* AI-2 does not contain a boron atom (table). It was shown that, under natural conditions, these two AI-2 and their precursors may occur in equilibrium and undergo mutual interconversion [11, 21].

Among the QS systems that employ AI-2, the *V. harveyi* system involved in the *lux* operon regulation has been studied in sufficient detail. A peculiarity of this system is that it employs, in addition to AI-2, two more autoinducers that interact with each other. This highly complicated regulation system also employs synthases of the autoinducers and a large number of other proteins (including the AI-2 receptor protein LuxP, three sensor kinases, etc.), as well as five small regulatory RNAs. The functioning of this QS system involves a phosphorylation–dephosphorylation cascade [11].

On the whole, little is known about the functions of AI-2 and the roles of these autoinducers in the regulation of cellular processes. It has been shown that a QS system that employs AI-2 is involved in the regulation of the transcription of 242 *Escherichia coli* genes, making up 5.6% of the genome of this bacterium. Such systems are involved in the control of virulence in *Vibrio cholerae, Streptococcus pyogenes*, and pathogenic strains of *E. coli*, as well as in the regulation of sporulation in *Bacillus subtilis* [8, 11, 22].

Applied Aspects of the Investigation of QS Regulation Systems

The research into QS regulation carried out in recent years has opened prospects of possible practical applications, one of which is a new approach to the design of therapeutics against pathogenic bacteria, based on the inhibition of their QS systems [9, 23]. This approach is currently being pursued in many research laboratories and biotechnological companies.

Since QS systems play an important role in the regulation of bacterial virulence, QS inhibition suppresses the synthesis of bacterial virulence factors. It has been suggested that the drugs that inhibit QS systems be termed antipathogenic drugs, as opposed to antimicrobial drugs [23], since it is just pathogenicity that they are meant to suppress. As distinct from classical antimicrobial drugs, antibiotics first of all, they do not exhibit bactericidic or bacteriostatic action on the pathogenic bacteria; consequently, they do not produce selective pressure that results in the rapid emergence of resistant pathogenic strains, whose formation and spread are among the most urgent problems of modern medicine.

One more serious problem of antimicrobial therapy is the ability of pathogenic bacteria to form biofilms, which are structures with unique characteristics formed by microbial communities attached to surfaces. The ability of bacteria to develop in the form of biofilms causes great difficulties in medicinal practice because in biofilms, bacteria are much more resistant to antibacterial drugs, disinfectants, and the immune system of the host organism. QS regulation has been shown to play the key role in the formation of biofilms [24–26]. Therefore, drugs inhibiting QS are promising agents for suppressing bacterial biofilm formation [9, 23].

The inhibition of QS can be achieved via several mechanisms [9, 23].

1. Suppression of the synthesis of autoinducers employed by QS systems. *S*-adenosylmethionine (SAM) is known to be the precursor of QS system autoinducers AHL and AI-2. Most of the works on the suppression of AHL synthesis have employed various SAM analogues. For example, such SAM analogues as *S*-adenosylhomocysteine and *S*-adenosylcysteine have been shown to be potent inhibitors of AHL synthesis by *P. aeruginosa* [23, 27, 28].

2. Inhibition of autoinducer binding to receptor proteins. The functioning of QS systems can be suppressed by autoinducer antagonists which hinder AI binding to receptor proteins. The greatest attention has

been paid to competitor inhibitors of AHLs, which are structurally similar to them. Such compounds interact with the AHL binding site in the receptor proteins but do not activate them.

Recently, much attention has been given to natural antagonists of QS autoinducers, specifically, to furanone derivatives. The first such antagonists to be recognized were halogenated furanones produced by the Australian alga *Delisea pulchra*; they inhibited QS in *P. aeruginosa* [23, 29, 30]. Subsequently, it was found that furanone derivatives are produced by various organisms: algae, fungi, actinomycetes, etc. Numerous QS-inhibiting furanone derivatives have been chemically synthesized [9, 23].

Investigation of the mechanism of action of these compounds has shown that furanone compounds compete with AHL for the binding sites of the receptor proteins. Furanone binding with the receptor protein affects the stability of the protein–ligand complex and results in rapid degradation of the receptor protein [30, 31]. Recently, a furanone derivative was shown to inhibit the AI-2-involving QS in *E. coli* and to suppress biofilm formation [32]. Furanone derivatives are promising as a base for the design of QS-inhibiting therapeutics. However, the furanone compounds that have been tested so far have proved too toxic to be used in medicine, and their modification and search for new, nontoxic, compounds are pertinent tasks.

3. Degradation of autoinducers employed by QS systems under the action of specific enzymes is a new promising approach to obtaining antibacterial therapeutics. AHL-degrading enzymes are intensely screened for, in the first place, lactonases cleaving the homoserine lactone ring in AHL molecules. Such lactonases have been found in bacilli [33, 34]. It was shown that the introduction of a cloned gene encoding AHL lactonase into cells of the phytopathogenic bacterium *Erwinia carotovora* decreased the production of AHL and, consequently, the production of virulence factors, including pectinolytic enzymes, and, hence, infectivity. The introduction of a cloned lactonase gene into the genomes of transgenic plants made them much less sensitive to the *E. carotovora* infection [10, 34, 35]. Another line of research that may yield practically valuable results is the degradation of AHLs by bacterial enzymes with a different type of catalytic activity, namely, by AHL acylases, which detach the AHL acyl chains [10, 36, 37]. Bacteria have been found that utilize AHLs as the sole source of carbon and nitrogen. Possibly, the suppression of QS systems is a widespread mechanism of competition between bacteria [6].

Higher organisms have also been found to possess specific mechanisms of AHL degradation. It was shown that the epithelial cells of human respiratory tracts are able to inactivate the *P. aeruginosa* AHLs (3OC12-HSL) and other AHLs (e.g., C6-HSL), apparently by means of enzymatic activity [38].

4. Suppression of the QS systems of gram-positive bacteria. To suppress *S. aureus* virulence, whose regulation involves QS systems, natural RIP peptides or their chemically synthesized analogues can be used [19, 39–42]. The efficiency of using peptides has been demonstrated in experiments with different animals infected with *S. aureus.* Other approaches take advantage of the inhibitory effect of AIP on *S. aureus* (see above) or employ vaccination with component proteins of the QS system.

Therapeutics suppressing QS may be included in the material used for production of implanted devices (e.g., cardiac valves, contact lenses), catheters, etc. to prevent formation on them of biofilms, which often cause severe chronic diseases.

The above-described strategy of antibacterial therapy based on QS inhibition may also be applied to counter the development of phytopathogenic bacteria causing various plant diseases. QS inhibitors can be used to cope with pipe biofouling. On the other hand, activation of QS systems may be used to increase the efficiency of biological treatment of wastewater by enhancing biofilm formation.

QS and Bacterial Communication under Natural Conditions

Currently, it has become commonplace to consider QS as a phenomenon similar to language-based communication and to view low-molecular-weight autoinducers as “words.” As we have seen, the bacterial language based on autoinducers is rather rich; the number of AIs discovered is constantly increasing. Below, several examples of bacterial communication under natural conditions are presented.

One of the first studied examples of interspecies communication was the interaction between *P. aeruginosa* and another pathogenic bacterium, *Burkholderia cepacia* (in this case, it was even an intergeneric communication). *Burkholderia cepacia* possesses an AHL-involving CepI–CepR QS system, which participates in the regulation of the synthesis pathogenicity factors. The AHL synthesis by this bacterium is quite weak. It was shown that, upon complex infection of lungs by *P. aeruginosa* and *B. cepacia* resulting in cystic fibrosis, the pathogenicity of *B. cepacia* is enhanced due to the *P. aeruginosa* AHL [2, 43, 44]. AHLs were directly detected in lung tissue infected by *P. aeruginosa.* Thus, *B. cepacia* can regulate the production of its pathogenicity factors in response to an AI produced by a bacterium of another genus. This finding vividly demonstrates that investigation of bacterial communication under natural conditions may discover its new aspects important for epidemiology. It is quite possible that the interaction of nonpathogenic bacteria that produce autoinducers with other bacteria that are otherwise weakly pathogenic or nonpathogenic may result in the development of an infection.

Several papers have reported that bacteria inhabiting the plant rhizosphere (various *Pseudomonas* species, *Serratia liquefaciens*) produce therein AHLs and, by means of signal molecules, exchange information that is important in the competition between microorganisms in the rhizosphere [45–47].

The above-described data demonstrate that QS regulation is widespread among bacteria of various taxonomic groups. QS systems are involved in the global regulation of a large number of processes occurring in bacterial cells. Undoubtedly, the phenomenon of QS regulation requires further profound study. By now, QS systems have been studied in a rather restricted range of bacteria; the molecular mechanisms of various types of QS regulation have been insufficiently studied. In many cases, it is still unclear what bacterial properties are controlled by QS systems.

Of great interest are the data showing that the autoregulators employed by QS systems may be involved in the regulation of cellular processes not only in bacteria but also in eukaryotes—mammals and plants. In particular, it was shown that plants can respond to the AHLs produced by the pathogenic bacterium *P. aeruginosa* and the symbiotic bacterium *Sinorhizobium meliloti.* By using proteomics methods, global changes were shown to occur under the action of AHLs in the production of more than 150 plant proteins. In addition, AHLs were shown to induce the secretion by plants of compounds that inhibited or stimulated QS in bacteria [48–50].

In the course of their evolution, eukaryotic organisms may have acquired the capacity to recognize QS signals and to respond by the production of compounds that are their competitors and of enzymes degrading the signal molecules. Recently, data have been published that allow one to assume that certain signal mechanisms of bacteria and eukaryotes are of a common evolutionary origin and that communication between the organisms of these domains may have a much larger scale than is currently thought [11].

All the above said leads to the conclusion that investigation of the QS regulation systems is a new vast field of activity for researchers engaged in biology and medicine, and that it opens wide prospects of practical applications.

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