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Bacterial quorum sensing role as a virulence factor and its applications in modern medicine

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Abstract

Some bacterial species engage in two well-documented social behaviors: the formation of surface-associated communities known as biofilms, and intercellular signaling, or quorum sensing. The bacterial species employ various types of molecular communication systems recognized as quorum sensing for the synchronization of differential gene expression to regulate virulence traits and biofilm formation. Recent studies have begun to reveal how these two social behaviors are related in different species and the role of quorum sensing inhibitors; molecules that interfere with quorum sensing among bacteria in blocking the action of autoinducers. This review highlights the role of quorum sensing in biofilm formation for different species and multispecies, in addition to various enzymes used for their quorum quenching activity resulting in the degradation of signaling molecules or blocking of gene expression. The effectiveness of these strategies has been validated in different animal models and it seems that these practices will be transformed in near future to develop the medical devices including catheters, implants, and dressings for the prevention of bacterial infections.

Key words: quorum sensing, bacterial virulence factor, modern medicine

Introduction

Communication is known as an essential element of structured social activity, a means of sharing or interaction between people. Different species have various contact types, depending on their lifestyles. One such phenomenon of communication, unique to bacteria, is called Quorum Sensing (QS) (Waters *et al.*, 2005).

Quorum sensing (QS) is a communication mechanism that regulates gene expression in response to fluctuations in cell-population density. In QS, bacteria and fungi produce signal molecules, terms auto-inducers (AI), that increase in concentration as function of cell density (Waters *et al.*, 2005).

The Researchers have thought of bacteria as individual cells for several years, engineered to proliferate under different circumstances, but unable to communicate and interact with each other, reacting collectively to environmental stimuli, as typical of multicellular species. (Duan *et al*., 2003; Greenberg, 2003; Ben Jacob *et al*., 2004; Eberl and Tümmler, 2004).

This view began to change few decades ago with the discovery of the cooperative regulation of luminescence in the Gram-negative marine bacterium *Vibrio fischeri* (Nealson *et al*., 1970) and regulation of the genetic competence in the Gram-positive bacterium *Streptococcus pneumonia* (Tomasz *et al*., 1965).

These bacteria were shown to coordinate their behavior via the secretion of specific signaling molecules in a population density-dependent manner. During growth, the bacteria secrete these molecules, which accumulate in the surrounding environment as the population density

increases until a critical threshold concentration is reached, which then triggers expression of certain sets of genes (Fuqua *et al.*, 1994).

This type of cell-to-cell communication was termed ‘quorum sensing’ in order to emphasize the fact that a sufficient number of bacteria, the bacterial ‘quorum’, is needed to induce or repress expression of target genes. (Fuqua *et al*., 1994).

The signaling molecules utilized by quorum sensing systems are often acylated homoserine lactones (AHL) in the case of Gram-negative bacteria, small peptides in the case of Gram-positive bacteria or autoinducer-2 (AI-2), which has been found in both Gram negative as well as Gram-positive bacteria and therefore considered to be a universal bacterial language, the ‘bacterial esperanto’ (Winans, 2002).

Quorum sensing is also involved in the regulation of a wide variety of different physiological processes, including antibiotic biosynthesis, swarming, swimming and twitching motility, plasmid conjugal transfer, biofilm development or the production of bacterial virulence factors in plant, animal or human pathogens (Miller *et al.,* 2001; Whitehead *et al*., 2001; Camara *et al*., 2002; Fuqua and Greenberg, 2002; Lazdunski *et al*., 2004; Pappas *et al*., 2004).

Apart from regulatory functions, there are also many non-signalling properties of autoinducers, such as iron chelation, membrane modification and antibiotic activity. (Schertzer *et al.*, 2009).

Engineered QS systems can also be used for the production of valuable biochemicals, pathogen diagnostics and therapeutics, cancer detection and biocontrol (via quorum quenching). Hence, it is necessary to understand the functioning of autoinducers and their diverse signaling and

non-signaling aspects in view of potential applications in biotechnology (Mangwani, *et al*., 2012)

So based on the foregoing, we will highlight the meaning of quorum sensing system**,** understanding the components and the effect of the system in the colony, the difference in mechanism in the positive and negative gram stained bacteria and the modern application of this phenomenon in the modern biotechnology and medicine.

Quorum sensing system mechanisms

The mechanism in gram-negative bacteria

In Gram negative bacteria, the signal molecules are N-(AHLs), which are also called auto-inducer 1 (AI-1) (Moré *et al.*, 1996). They consist of a conserved homoserine lactone ring, which is connected to an acyl side chain of variable length (4 to 18 carbon atoms) and variable extra modification.

AHLs with a short acyl side chain can diffuse passively in and out the bacterial cell. This is in contrast with AHLs with a long acyl side chain and the Autoinducer peptides , which need active transport mechanisms to cross the bacterial cell membrane. (Novick *et al.*, 2008; Moré *et al.*, 1996]

LuxI homologous proteins (which is a quorum sensing regulators) play a major role in the synthesis of the AHLs, which increase in concentration as the cell density increases. ((Fuqua *et al.*, 2001; Waters *et al.*, 2005)

At a critical concentration, LuxR homologues bind the signal molecules and subsequently control gene transcription. It is becoming more and more clear, however, that there is a considerable diversity in the

way in which the LuxI and LuxR homologues from different bacterial species operate. (Smith *et al.*, 2006)

This QS system is primarily used for intraspecies communication since LuxR type proteins only detect particular AHLs. Nevertheless, proteins of the LuxR type have been identified that are able to detect several AHLs. For example, *Salmonella* SdiA is believed to be primarily involved in bacterial communication between organisms (boyen F *et al.*, 2009).

The mechanism in gram-positive bacteria

Within Gram-positive bacteria, target gene expression is controlled via signaling peptides, also known as pheromones, at the population level. (Siepka *et al.*, 2012). AIs are actively transported by molecules synthesized by Gram-positive bacteria. Using the two-component detection system, Gram-positive bacteria interact with each other and respond to the presence of autoinducers (Kleerebezem *et al*., 1997).

Inside the bacterial cell, the oligopeptides are generated and then transported to the outside environment via the ABC (ATP-binding cassette transporter) transport protein (Li, Tian, 2012).

The mechanism of signal transmission occurs on a basis of cascade of phosphorylation and dephosphorylation (Li *et al.*, 2012).

The signal oligopeptides released outside after reaching a threshold concentration are detected by transmembrane protein kinase that acts as a receptor protein.

Protein kinase interaction with the ligand contributes to its autophosphorylation, thereby triggering a cascade of reactions that result in regulatory protein phosphorylation. The phosphorylated form of the

regulatory protein will recognize and bind to the appropriate promoters of the target genes involved in QS, thus initiating their expression (Vijayalakshmi, 2013).

The QS mechanism plays a different biological function in different Gram-positive bacteria species (Cook *et al.,* 2014). This mechanism controls the acquisition of competence in *Bacillus subtilis* and *Streptococcus pneumoniae* cells, while it regulates virulence in *Staphylococcus aureus* cells and the conjugation process in *Enterococcus faecilis* cells (Ziemichód *et al.,* 2017).

The homogenous and heterogeneous effect on bacteria

The communication of bacteria is carried out with the help of AI.

AI produced by one cell can interact with the receptor protein of another bacteria and induce in it the expression of particular genes (Khmel, 2008). As a consequence, organized expression of these genes takes place in the entire bacterial population (Gintsburg, 2003).

Therefore, bacteria regulate the expression of genes at the population level due to contact triggered by the operation of signal systems. In the case of systems using AHLs as signal molecules, contact of bacteria with the participation of QS systems was studied. Since receptor proteins can interact with a variety of AHLs, including those that aren't part of their own QS system, contact between bacteria of different taxonomic groups is possible (Khmel, 2008).

Heterogeneous communication between *Pseudomonas aeruginosa* and another pathogenic bacterium *Burkholderia cepacia* was one of the first examples of interspecies communication (in this case, even intergenus communication) (Lewenza, 2002).

The QS system contained two types of AHL, which are synthesized in small amounts, functioning in the cells of *B. cepacia*; this system takes part in regulation of the synthesis of pathogenicity factors (Conway, 2002).

In the case of associated infection with *P. aeruginosa* and *B. cepacia*, the pathogenicity of *B. cepacia* increases at the expense of AHL of *P. aeruginosa*. For example, bacterium of one genus can increase the synthesis of pathogenicity factors at the expense of AHLs of bacteria from another genus (de Kievit, 2000).

These findings indicate that using QS control to examine bacterial contact in natural communities opens up new important possibilities for epidemiology. Situations in which nonpathogenic bacteria producing autoinducers interact with slightly pathogenic (or basically nonpathogenic under some conditions) bacteria may result in infection are very likely. (Lewenza, 2002).

QS and the biofilms formation

To protect themselves from hard environment, stress and starvation, bacteria may form biofilms, a lifestyle that is characteristically more stress-resistant. Most biofilm systems have demonstrated enhanced resistance to external insults such as antibiotics, shear force, and the host immune system (Gilbert, 1997).

One can envisage different ways in which QS might influence biofilm formation. For example, QS-regulated functions might serve to initiate biofilm formation. Inducing concentrations of QS signals might precede starvation and other types of stress associated with crowded planktonic bacterial populations (lewis, 2001; Daives, 2003).

QS may also function to control the population size in a biofilm. QS may serve as the checkpoint for reinitiating the cycle by promoting dispersion or dissolution of a subpopulation of cells. In this case, dispersing cells might escape the nutritional stress that accompanies or follows inducing concentrations of QS signal (Steinmoen *et al.*, 2002)

For nonmotile species, QS might serve to regulate population density in a biofilm using a different mechanism. Some Gram-positive bacteria initiate autolysis in response to reaching a quorum. (Steinmoen *et al.*, 2002)

QS can induce behaviors in biofilm cells (as they transition from a QS-uninduced to a QS-induced state), such as the production of secreted factors like exopolysaccharides or other adhesins, that alter the course of biofilm growth. Alternatively, QS could trigger or inhibit community behaviors such as surface motility, which could in turn have a profound effect on the structure of biofilm. (Irie, 2008).

Role of the QS system in the pathogenesis of bacteria

It has believed that the Quorum sensing system play a major role in the pathogenesis of certain species which can utilize the system. We will discuss briefly the role of QS in some common human-infecting bacteria.

Vibrio cholera

Vibrio cholera is the culprit of cholera disease by producing exotoxins, irritant to the intestinal wall and causes acute watery diarrhea. It has about 20 genes involved in the pathogenicity of the bacteria and Regulon, which encodes for production and secretion of toxins, and genes required for survival in host cells. These genes regulate transcription Regolon toxT, tcpP /I, toxR a cascade controlled, the adjustment to external

factors such as temperature, pH, osmotic pressure, and so respond. It is now clear that QS is involved in the regulation of these genes (saghi, 2015).

Pseudomonas aeruginosa

Gram-negative bacillus that causes serious nosocomial infections in the hospital due to the high resistance of biofilms to antibiotics and variation in nature. According to certain studies, the bacterium is an opportunistic pathogen with over 600 genes dominated by QS. In bacteria with high drug resistance, QS and biofilm formation are important. Biofilm inhibition can be a chronic infection and drug resistance in the bacteria solution of the above if QS and its antagonists are used (Preston *et al.*, 1997; Wu H ,2001).

Pseudomonas aeruginosa has at least two QS systems named (RhlR / I) and (LasR / I). System LasR / I, controls the formation of Regolon rhl and pathogenicity genes toxA, apr, lasA, lasB. System RhlR / I, is processing the production of elastase (has a breaking strength on IL-2).

The bacteria with the help of the system, the ability to survive and multiply within cells are found (Wu H ,2001).

Staphylococcus aureus

Several extra cellular protein toxins are linked to *Staphylococcus aureus* QS. These proteins are developed at various growth stages and can be regulated by the early stage of infection in QS that has spread to neighboring tissues (saghi, 2015).

The *S. aureus* quorum-sensing system is encoded by the accessory gene regulator (*agr*) locus. The *agr* system contributes to virulence in model biofilm-associated infections, including endocarditis and osteomyelitis. Although, the precise role of the *agr* system varies with the

type of infection model used, The *agr* locus consists of two divergent operons driven by the P2 and P3 promoters. The P2 operon contains *agrBDCA* and codes for the RNAII transcript. P3 drives transcription of RNAIII, the effector molecule of the *agr* locus. (Yarwood, 2004).

AgrD and agrB genes encoded a small peptide (QS). The production of these molecules was dependent on cell density and RNAII and RNAIII helps control gene expression (Yang, 2003).

The importance of the QS system in the modern medicine

After the latest studies that proved the essential and vital role of the quorum sensing system in the pathogenesis and survival of certain pathogenic bacterial species, there is a modern promising trend in treating the QS system as a new antibiotic target, especially for the resistant strains of *pseudomonas species*, that their treatment considered challenging.

Given that QS deficient mutants of bacterial pathogens are avirulent and lack virulence gene expression, it may be possible to monitor bacterial infections by inhibiting microbial pathogen QS signaling. In addition to quorum sensing inhibitors, the discovery of quorum quenching enzymes has provided crucial tools for assessing the feasibility of this novel strategy. (Yi-Hu, 2005).

Quorum quenching

Quorum quenching is one of the most effective techniques to inhibit the expression of virulence and disrupt the infection of host cells. the host cells produce the quorum quenching enzymes as a defense against the infecting bacteria by manipulating the quorum-sensing signals (Uroz, 2009; Dong, 2000) .

Many AHL-degrading enzymes have been cloned from various microorganisms and studied for their applications in the control of infectious diseases. AHL-degrading enzymes have been divided into two functional groups—AHL lactonase and AHL acylase. AHL lactonase catalyzes AHL ring-opening by hydrolyzing lactones, whereas AHL-acylase hydrolyzes the amide bond of AHL (Dong, 2000).

AHL lactonase gene, (aiiA) was first identified from *Bacillus* sp. 240B1, is the most-studied AHL degrading enzyme. It belongs to the metallo-β-lactamase superfamily and has been identified and characterized in various bacteria such as AhlS from *Solibacillus silvestris*, AttM from *Agrobacterium tumefaciens*, AhlD from *Arthrobacter* sp, and AidC from *Chryseobacterium* sp.(Dong, 2000; Zhang, 2002).

AHL signal analogues and compounds targeting the AHL receptors

Several studies have focused on creating native AHL signal molecule analogues in which the acyl side chain or lactone moiety has been changed. Several compounds have been shown to impact the formation of biofilms (Schaefer,1996).

AHL analogues in which the lactone ring was replaced by a cyclopentyl or a cyclohexanone ring significantly affected biofilm formation of *Serratia marcescens* and *P. aeruginosa*. In addition, AHL in which the amide function was replaced by a triazolyldihydrofuranone showed biofilm eradicating as well as biofilm inhibitory activity against *B. cenocepacia* and *P. aeruginosa* (Ni N, 2009).

Furthermore, phenylpropionyl homoserine lactones and phenoxyacetyl homoserine lactones, analogues with aromatic groups on

the acyl-side chain, inhibited *P. aeruginosa* biofilm formation (Brakman, 2012).

Next to compounds resembling AHL, several unrelated compounds are shown to block AHL QS and thereby affect biofilm formation of AHL producing strains. Some of these compounds originated from natural extracts. For example, bergamottin and dihydroxybergamottin isolated from grapefruit juice and extracts from South Florida plants inhibited AHL QS and affect biofilm formation of *P. aeruginosa* (Geske 2005; Brakman,2012).

Certain compounds such as allicin , ajoene, a cyclic thioacetal and cyclic disulfide were identified to be responsible for the QS inhibitory effect of the garlic extract (Jakobson, 2012). Patulin, ajoene and garlic extracts increased biofilm susceptibility of *P. aeruginosa* biofilms toward tobramycin treatment and resulted in an increased clearance of *P. aeruginosa* in an *in vivo* pulmonary infection model. (Rusmussen, 2005; Jakobson, 2012).

Conclusion:

The Quorum sensing system is essential for both of the survival and the pathogenesis of the utilizing bacteria. This fact opens a lot of doors and raising hopes for using the system as a" Target" for the modern antibacterial therapy and get rid of the resistance problem.

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