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Implication of Quorum Sensing and Biofilm Formation in Medicine, Agriculture and Food Industry

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Contents

Quorum Sensing-Controlled Gene Expression Systems in Gram-Positive and Gram-Negative Bacteria

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Meghanath Prabhu, Milind Naik, and Veda Manerikar

Abstract

In this chapter, quorum sensing (QS)-controlled gene expression systems in Gram-positive and Gram-negative bacteria is particularly emphasized. Acyl homoserine lactone (AHL) autoinducer (AI)-mediated signalling is a communication system in Gram-negative bacteria that control specific genes expression imparting physiological characteristics such as biofilm formation, bioluminescence, antibiotic synthesis, plasmid transfer, virulence factor, metal resistance and hydrocarbon degradation. AI concentrations reach a threshold level when adequate bacterial density is present that allows sensing a critical cell mass and in response they activate or repress target genes expression. Strikingly, AI binds the LuxR-type proteins, triggering them bind DNA and activate transcription of target genes. Synthesis of the AHL is dependent on a *luxI* homologue and a *luxR* homologue encoding a transcriptional activator protein, which is accountable for recognition of the cognate AHL and expression of correct gene. Gram-positive bacterial QS systems typically use secreted small oligopeptides via a dedicated ABC (ATP-binding cassette) exporter protein and two-component systems, which involve membrane-bound sensor kinase receptors and transcription factors present in cytoplasm which is responsible for alterations in gene expression. The process of signal transduction takes place as a phosphorelay cascade.

Keywords

Quorum sensing (QS) · Acyl homoserine lactone (AHL) · Autoinducer (AI) · ABC (ATP-binding cassette) · Controlled gene expression

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2.1 Introduction

Quorum sensing (QS) is a mechanism by which bacteria 'talk' with one another in response to population density through signalling molecules by controlling gene expression, thereby coordinating their behaviour. A process of bacterial QS depends on the production of extracellular chemical signalling molecules known as 'autoinducers' (AIs) (Nealson et al. 1970; Rutherford and Bassler 2012; LaSarre and Federle 2013; Naik et al. 2017; Mukherjee et al. 2017; Syal 2017). It is well documented that QS is used to coordinate global pattern of gene expression and regulation in bacteria (Turovskiy et al. 2007). It is used by both Gram-positive and Gram-negative bacteria to regulate expression of characters that permit bacteria to exploit particular niche. Such collective gene expression helps pathogenic bacteria to save energy during its host attack process which is otherwise energetically very expensive when taken up by individual cell (LaSarre and Federle 2013). QS is used to coordinate gene expression and regulation that promote invasion, defence and spread among local populations and is well documented particularly in human bacterial pathogens (LaSarre and Federle 2013; Papenfort and Bassler 2016).

In order to tolerate environmental changes, bacterial population have evolved QS mechanism to sense the adjacent environment, assimilate these signals and acclimatize their physiology to survive under changing conditions. The bacterial population in community perceive, respond and collectively modify behaviour through AIs, the concentration of which increases as bacterial population increases (Fuqua et al. 2001; Camilli and Bassler 2006; Papenfort and Bassler 2016). Through QS molecules, a species-specific cell-to-cell communication is achieved which plays important role in effective pathogenic or symbiotic interactions of diversity of bacteria with plant and animal hosts (Rutherford and Bassler 2012). Noteworthy that, AI relay mechanisms and target genes regulated by bacterial signalling systems vary in each case that allow bacteria to synchronize the gene expression and behaviour of the complete bacterial community. Bacterial community shows distinct characteristics due to QS such as biofilm formation, exopolysaccharide (EPS) production, bioluminescence, pigment and siderophores production, secretion of the virulence factor (toxin, hemolysin, enzymes, antibiotic resistance), metal resistance and aromatic hydrocarbon degradation (Fuqua et al. 2001; Rutherford and Bassler 2012; LaSarre and Federle 2013; Papenfort and Bassler 2016).

In a nutshell, all of the identified QS systems rely on three principles:

1. The members of the bacterial population synthesize AIs (signalling molecules).
2. AIs are sensed by the receptors that are present inside the bacterial cytoplasm or on the membrane.
3. Expression of genes essential for cooperative behaviours are triggered as well as detection of AIs results in activation of AI synthesis. Autoinduction loop apparently endorses synchrony in the population.

In this chapter, we describe the QS-controlled gene expression systems in Gram-negative and Gram-positive bacteria.

2.2 Gram-Negative and Gram-Positive Bacterial Quorum Sensing

2.2.1 AHL-Based Gene Expression Controlling System in Gram-Negative Bacteria

Different types of signalling systems are present in Gram-positive and Gram-negative bacteria. In the most described cases, *N*-acyl homoserine lactones (AHLs) (also referred as autoinducer-1, i.e. AI-1) signalling system is exclusively used by Gram-negative bacteria and is one of the best-investigated signalling mechanisms. The *V. fischeri* LuxR/LuxI bioluminescence system (R/I system) was first ever bacterial communication system investigated, after which many QS systems were studied in different Gram-negative bacteria (Lazdunski et al. 2004). The LuxI-like AHL synthases synthesize a specific AHL by joining the acyl side chain of a particular acyl–acyl carrier protein (acyl-ACP) from the fatty acid biosynthetic apparatus to the homocysteine moiety of *S*-adenosylmethionine (SAM) (Papenfort and Bassler 2016). These moieties are made up of homoserine lactone (HSL) ring attached to an acyl chain. The acyl side chain can vary in length from 4 to 16 (or up to18) carbons atoms, can be completely saturated and possess hydroxyls or carbonyls on the third carbon (Fuqua et al. 2001; LaSarre and Federle 2013). Some AHLs are also reported to be detected by membrane-bound sensor kinases, e.g. LuxN of *V. harveyi*, that start phosphorelay signalling cascades after ligand binding. After a threshold level of the AHL concentration is achieved in the surrounding, there is interaction between the AHL and a LuxR-type receptor in the cytosol of the bacteria. LuxR receptors are important transcriptional regulators whose DNA-binding properties initiate upon interaction with the AHL, resulting in target gene expression regulation in response to the AHL accumulation. A well known example of LuxI/R signalling is *Chromobacterium violaceum*, which utilizes CviI, CviR and AHL (C6HSL) to control violacein production (Stauff and Bassler 2011).

2.2.1.1 *Pseudomonas aeruginosa*

P. aeruginosa is a Gram-negative, opportunistic bacterial human pathogen associated with various kinds of serious illnesses such as respiratory infections, gastrointestinal infection, urinary tract infection, septic shock, etc. (Gupta et al. 2011; Prabhu et al. 2014). *P. aeruginosa* secrete various kinds of siderophores such as pyocyanin, pyoverdine, pyochelin and phenazine derivatives as well as pyorubin, pyomelanin, chloraphin or various combinations of these molecules (Prabhu et al. 2014). These siderophores are secreted as secondary metabolites when populations reach threshold level and also regulate growth of virulence factors in *P. aeruginosa* (Lamont et al. 2002). *P. aeruginosa* regulates several gene expressions via QS and employs three interconnected QS systems – LasRl, RhlRl and PQS – that each produces unique signalling molecules. *P. aeruginosa* possesses two recognized QS systems: LuxI/R-type QS systems produce and recognize N-3-oxododecanoyl-L-homoserine lactone (3OC12-HSL), whereas LasI/R and RhlI/R synthesize and detect C4-homoserine lactone. These dictate synchronous

synthesis of virulence factors and production of biofilms that are crucial in infections by *P. aeruginosa* (Mukherjee et al. 2017). The LasR:3OC12–HSL complex triggers transcription of numerous genes including RhlR. RhlR attaches to the autoinducer N-butanoyl-L-homoserine lactone (C4-HSL), the product of the RhlI synthase. RhlR:C4-HSL regulates a large genes cluster as well as those encoding virulence factors, viz. pyocyanin, elastases and rhamnolipids. RhlR is dependent on C4-HSL, but in the absence of C4-HSL, it is also able to work as a transcriptional regulator. QS-activated genes encoding products, viz. Pel and Psl exopolysaccharides, rhamnolipids and phenazines play important role in biofilms (Mukherjee et al. 2017). Biofilm enables horizontal gene transfer (HGT) between bacteria and thereby conferring resistance and metabolic benefit to the whole biofilm community (Syal 2017).

2.2.1.2 *Vibrio cholerae*

In *V. cholerae*, QS regulates genes accountable for the development of over 70 virulence factors such as cholera toxin. QS also regulates pilus formation and the expression of genes responsible for biofilm formation. QS activates type VI secretion, resulting in lysis of neighbouring non-kin cells which carry out the scavenging of DNA from lysed cells and HGT. Molecule (S)-3-hydroxytriecan-4-one was identified as an AI in *V. cholerae*, which is similar to (Z)-3-aminoundec-2-en-4-one as in *V. harveyi* (Papenfort and Bassler 2016). These molecules collectively are referred as cholera AI-1 (CAI-1). In *V. cholerae*, the CAI-1 AI synthase (CqsA) acts on SAM and decanoyl-CoA to produce amino-CAI-1 that may be spontaneously converted into CAI-1. Both amino-CAI-1 and CAI-1 are biologically active. Amino-CAI-1 is more stable than CAI-1 which increases the possibility that CAI-1 promotes a rapid response to fluctuations of AI (LaSarre and Federle 2013). The uncharacterized CAI-1 is made by CqsA (cholerae quorum sensing) and sensed by its similar sensor CqsS. AI-2 and CAI-1 are responsible for downregulation of several genes while upregulating the expression of Hap protease, the enzyme enabling the removal of *V. cholerae* from the intestine (Federle and Bassler 2003; Turovskiy et al. 2007).

2.2.2 Peptide-Based Gene Regulation System in Gram-Positive Bacteria

Peptide signals or oligopeptide-two-component-type QS system is used by Gram-positive bacteria which are comprised of membrane-bound sensor kinase receptors and cytoplasmic transcription factors that regulate alterations in gene expression (Papenfort and Bassler 2016). Many peptide AIs known till today are sensed by a membrane-bound sensor kinase, which changes its kinase/phosphatase activity in reply to communication with peptide, which changes the phosphorylation state of the response regulator. The final outcome is activation or repression of QS target genes. The *agr* QS system of *S. aureus* and the *fsr* system of *Enterococcus faecalis* both involve utilizing extracellular detection and both control virulence factor production like hemolysins (hly), Panton–Valentine leukocidin (*pvl*), enterotoxin A

(*entA*), coagulase (*coa*) and immune-modulatory factors encoding genes (Qazi et al. 2006; Oogai et al. 2011; Rutherford and Bassler 2012).

2.2.2.1 *S. aureus*

S. aureus is the normal flora of the human skin but is a foremost reason of nosocomial infections globally and leads to diseases from minor skin infections to fatal systemic disorders which include pneumonia, bacteraemia and sepsis (David and Daum 2010). Ability to cause disease by *S. aureus* based on expression of various adhesion molecules, toxins and compounds that hamper the immune system (Qazi et al. 2006). *Staphylococcus aureus* and various *Streptococci* have peptide-mediated QS systems (Qazi et al. 2006). Peptide signals in *S. aureus* are detected at the surface of the cell or intracellularly. Expression of genes encoding virulence factors are regulated by peptide-based QS (Garmyn et al. 2011; Oogai et al. 2011; Rutherford and Bassler 2012). Free-living *S. aureus* does not cause infection, for instance, endocarditis, osteomyelitis and foreign body-related infections, but are triggered by biofilms. Surface-associated adhesins, hemolysin, toxins and autolysins, the virulence factors important for staphylococcal infections, are regulated via the accessory gene regulator (agr) system (Oogai et al. 2011). The transcription of two different transcription units present on the agr locus in *S. aureus* is controlled by P2 and P3 promotors. *agr*BDCA is a P2 promotor which encodes four proteins that establish the *Agr*-sensing mechanism. In *S. aureus*, *agr* QS centres around cyclic autoinducing peptides (AIPs) belonging to four distinct groups that cooperate with cognate AgrC sensor kinases of the same group and control exotoxin production and biofilm production (Li and Tian 2016). Octapeptide is an AIP molecule in *S. aureus* with an exceptional thioester ring structure. As levels of AIP rises in extracellular atmosphere, it binds to the histidine kinase receptor (AgrC), which results in its autophosphorylation. The response regulator AgrA is further activated due to autophosphorylation, which along with SarA regulates the transcription at promotors (P2 and P3), resulting in increased intracellular concentration of RNAII (QS amplification) and RNAIII (exoproteins). Fascinatingly, Kaufmann et al. (2008) reported that AIP from *S. aureus* has the capacity for activating the *agr* regulon on its own and is also capable of inhibiting the *agr* activation of other strains. Such cross-strain inhibition of the *agr* response has been used to cure staphylococcal skin infections in animals. The peptide-based *agr* QS system is crucial for the progress of aggressive infections and disease, viz. subcutaneous abscesses, pneumonia, rabbit osteomyelitits and endocarditis (Kaufmann et al. 2008; Li and Tian 2016).

2.2.2.2 *Listeria monocytogenes (Lm)*

Gram-positive *Lm* is well-recognized bacterial pathogen causing listeriosis both in humans and animals (McGann et al. 2007). Sources of *Lm* infection are very diverse and range from contaminated foods, such as raw meat, raw milk, milking utensils, vegetables, dairy products, sausages, fruit juices, to ready-to-eat, packed foods and various environmental sources (Rieu et al. 2007). *Lm* is placed first in the list of emerging pathogens of concern for the public health and, therefore, for the food industry (Rantsiou et al. 2012). *Lm* is known to synthesize several virulence factors

such as invasion-associated proteins, internalin A, listeriolysin O (LLO), biofilm formation (Rieu et al. 2007; Naik et al. 2017) and various transcription factors (Rantsiou et al. 2012). Virulence factors encoding genes are under the control of the only QS mechanism involving *agr* peptide-sensing system as a complex controlling network for directing gene expression (Garmyn et al. 2009; Garmyn et al. 2011; Zetzmann et al. 2016). The virulence ability of an *agrD* deletion mutant was studied by Riedel et al. (2009), which approves the role played by *agr* QS system during the virulence of *Lm*. This report confirms that AgrD-dependent QS affects biofilm development, invasion, virulence and universal gene expression in *Lm* (Riedel et al. 2009). Production of AI-2 by Pfs and LuxS pathways in *Lm* has only been hypothesized, as genes *pfs (lmo1494)* and *luxS (lmo1288)* are existing in the genome of *Lm.* The *Lm*'s *agr* operon is similar to the *S. aureus* that comprises the four-gene operon *agr*BDCA system. Despite the resemblances at protein level, genetic organization and phenotypic characteristics regulation, *agr* systems vary about their mechanisms of target gene controlling in *Lm* (Zetzmann et al. 2016).

2.2.2.3 *Bacillus cereus*

B. cereus causes intestinal and non-intestinal infections in humans and is generally linked to food poisoning. QS regulates the ability of this bacteria to cause acute diarrheal disease through controlling the gene expression for the synthesis and secretion of a diversity of hemolysins, toxins, degradative enzymes and phospholipases (Rutherford and Bassler 2012). *B. cereus* members show the PlcR/PapR signalling system. PlcRa is a quorum sensing regulator with a signalling heptapeptide for PlcRa activity. 3D structural paralog of PlcR is PlcRa and bound explicitly to the abrB2 promoter. Inside the cells, PapR cooperates with PlcR, this results in complex formation which binds PlcR target spot on DNA leading to the stimulation of the PlcR regulon, which consists of 48 genes (Huillet et al. 2012).

2.3 Factors Affecting Quorum Sensing

The characteristics of surrounding physical environment of bacteria could influence QS (Decho et al. 2010). Similarly, diffusion of the signal through a specified environment will impact signal concentrations, with low flow rates encouragement and high flow rates controlling the AHL molecule build-up, respectively. In alkaline conditions generally, the AHL molecules are chemically unstable, thus accelerating the signal degradation under high pH environment (Fuqua et al. 2001). This effectively upsurge the concentration of quorum needed to trigger the associated quorum sensor. Interactions of the AHLs with extracellular reactants that weaken or sequester the signal molecules may also affect quorum build up. Expression of the AHLs synthase genes are directly affected and regulated by diverse environmental and physiological conditions, therefore directly affecting the production of signal.

2.4 Cross-Talk Between Different Bacterial Species

Gram-positive and Gram-negative microorganisms produce the AHL signal molecules and peptide signal molecules, respectively (LaSarre and Federle 2013; Papenfort and Bassler 2016; Naik et al. 2017). Signalling pathways from various bacterial communities collide resulting in interspecies communication (Qazi et al. 2006; Biswa and Doble 2013; Naik et al. 2017). *LuxS*-encoded autoinducer-2 (AI-2) system were reported to be used by both Gram-negative and Gram-positive bacteria that is major QS signalling systems involved in gene regulation. Also, there are QS signals which go beyond these classes, including *Pseudomonas* quinolone signal (PQS), diffusible signal factor (DSF) and autoinducer-3 (AI-3) (Lazdunski et al. 2004; Walters et al. 2006; Papenfort and Bassler 2016). Gram-negative bacterium *Salmonella enteritidis* was never reported to produce the AHL, but lately de Almeida et al. (2017) reported exogenous AHL stimulates biofilm formation in *Salmonella enteritidis*. Gram-negative bacteria producing peptide signal molecules has previously been reported (Han et al. 2011). Gram-negative bacteria such as *Proteus mirabilis*, *Pseudomonas aeruginosa, Citrobacter freundii* and *Enterobacter agglomerans* were reported to produce cyclic dipeptides which are capable of activating the AHL biosensor (Holden et al. 1999). Holden et al. (1999) confirmed that the Gram-negative bacteria were also capable of producing cyclic peptide molecules for quorum sensing cross-talk apart from the AHL. The AHL molecules produced by other bacteria are also believed to cross the bacterial cell envelope through diffusion, and existence of Gram-positive bacteria producing and responding to the AHL molecule has also been reported in marine *Exiguobacterium* sp. (Biswa and Doble 2013). *Chromobacterium violaceum* showed inhibition in the presence of C3-oxo-octanoyl homoserine lactone (OOHL) molecule produced by *Exiguobacterium* sp. (Biswa and Doble 2013); however, *Exiguobacterium* sp. was not inhibited by even at 100 μM of standard OOHL suggesting that the AHL molecules might be well recognized in the system of Gram-positive bacteria. This strain possesses a LuxR homolog designated as ExgR and also has LuxI homolog downstream to ExgR. Thus, suggesting a probability that bacteria might respond to the cross signal produced by another bacterium. The general observation was that the LuxR-type proteins can be activated by exogenous addition of the AHL molecules in heterologous hosts (Fuqua et al. 2001). *S. aureus* was reported to respond negatively to external AHL molecules. It has never been reported to harbour the AHL quorum sensing system. External *N*-acyl homoserine lactone was reported to antagonise virulence gene expression and QS in *S. aureus*. Also 3-oxo-C12-HSL was reported to inhibit *agr* QS expression in *S. aureus* (Qazi et al. 2006). In a very recent study by Naik et al. (2017), it was shown that Gram-positive *Lm* does not produce the AHL but responds to the AHL-forming biofilm. Naik et al. (2017) also observed the increase in biofilm formation by *Lm* with increasing concentration of the AHL molecule. The numbers of QS molecules will undoubtedly increase due to discovery of new QS molecules in novel bacteria. This will further reveal cross-talk between Gram-positive and Gram-negative bacteria.

2.5 Concluding Remarks

QS enables bacteria to coordinate communal behaviours. It is a very important gene expression and controlling mechanism used by various bacteria to regulate collective traits that permit bacteria to successfully exploit particular niches such as human gut and also in causing chronic infections in humans. Although through explosive research data in biochemistry, genetics, genomics and signal diversity of QS, we know the mechanism of QS systems and how it functions at the molecular level, but the correct biological function of many QS systems remains as a great scope. There are surely numerous QS systems to be discovered and there is a chance to separate out important differences between these QS systems. We are just starting to understand the cross-talk and bacterial sociality between various bacterial species via QS. The regulations of QS system open up a new area for treating infectious diseases and also use bacteria to realize the biology of sociality (Whiteley et al. 2017).

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