



# Quorum sensing communication between bacteria and human cells: signals, targets, and functions

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Both direct and long-range interactions between pathogenic *Pseudomonas aeruginosa* bacteria and their eukaryotic hosts are important in the outcome of infections. For cell-to-cell communication, these bacteria employ the quorum sensing (QS) system to pass on information of the density of the bacterial population and collectively switch on virulence factor production, biofilm formation, and resistance development. Thus, QS allows bacteria to behave as a community to perform tasks which would be impossible for individual cells, e.g., to overcome defense and immune systems and establish infections in higher organisms. This review highlights these aspects of QS and our own recent research on how *P. aeruginosa* communicates with human cells using the small QS signal molecules *N*-acyl homoserine lactones (AHL). We focus on how this conversation changes the behavior and function of neutrophils, macrophages, and epithelial cells and on how the signaling machinery in human cells responsible for the recognition of AHL. Understanding the bacteria–host relationships at both cellular and molecular levels is essential for the identification of new targets and for the development of novel strategies to fight bacterial infections in the future.

**Keywords:** bacteria–host cell interaction, quorum sensing, *Pseudomonas aeruginosa*, *N*-acyl homoserine lactones, epithelial cells, innate immune cells, neutrophils, macrophages

## INTRODUCTION

*Pseudomonas aeruginosa* is an environmentally highly adaptable Gram-negative bacterium that infects different host species, including higher plants, invertebrates, and vertebrates. In humans, it elicits acute and chronic infections, typically in critically ill patients having compromised epithelial barriers and immune system or the genetic disorder cystic fibrosis. The outcome of infections and establishment of disease depends on both host defence and bacterial capacities. The latter include its autonomic efficiency to grow, divide, and adapt to the environment, and the ability to sense, and communicate with their neighbors in the population to accomplish cooperative activities, e.g., biofilm formation and production of virulence factors. To do this, *P. aeruginosa* uses a mechanisms of cell-to-cell communication called quorum sensing (QS). It allows the bacteria to recognize the population density by sensing and measuring the accumulation of specific small signal molecules that members of the community secrete. When the population density is high, the amount of accumulated signals in the environment is accordingly sufficient to activate signaling pathways that alter bacterial gene expression and activate cooperative responses (Rutherford and Bassler, 2012; Schuster et al., 2013; Fazli et al., 2014).

## *P. aeruginosa* QS CONTROL OF VIRULENCE AND BIOFILM FORMATION

Being equipped with a relatively large genome, *P. aeruginosa* harbors three distinct but subordinated QS systems: two of LuxI/LuxR-type and a third called the *Pseudomonas* quinolone signal (PQS) system. The two LuxI/LuxR-type systems are

*N*-acylhomoserine lactone (AHL) dependent. In the first, the LuxI homolog LasI produces a freely diffusible *N*-3-oxo-dodecanoyl-L-homoserine lactone (3O-C<sub>12</sub>-HSL) that is detected by the LuxR homolog cytoplasmic receptor LasR (More et al., 1996; Parsek et al., 1999). In the second, the LuxI homolog RhlI synthesizes another AHL, *N*-butyryl-L-homoserine lactone (C<sub>4</sub>-HSL) that binds to the cytoplasmic receptor RhlR (Ochsner et al., 1994; Pearson et al., 1995); LasR and RhlR are cognate transcriptional regulators. Together, the AHL–LuxR complexes of both circuits control the activation of more than 300 genes in the *P. aeruginosa* genome. Many of these genes code for production of extracellular products that may be considered as virulence factors, because they can damage host tissues and promote infection, and inflammation. These virulence factors include exotoxin A, elastase, proteases, pyocyanin, lectins, and toxins (Gambello and Iglewski, 1991; Toder et al., 1991; Gambello et al., 1993; Schuster et al., 2003). *P. aeruginosa* uses the third PQS system to control cooperative responses and gene expression of rhamnolipid, a critical biosurfactant in the late stage of biofilm formation (Ochsner et al., 1994; de Kievit, 2009). The signal molecules of this system are bicyclic compounds, 2-alkyl-4(1H)-quinolones (PQS), produced by Pqs-ABCDH and recognized by the receptor PqsR (Deziel et al., 2004; Diggle et al., 2007). Several of PQS can act not only as a QS signals, but also possess antimicrobial, anticancer, or antiallergenic activities. Together with periplasmic components, outer membrane proteins, phospholipids, toxins, lipopolysaccharide (LPS), and DNA, PQS are typically packed into spherical 50–250 nm membrane vesicles that *P. aeruginosa* secrete and deliver to the environment. In this way, vesicles have a role in communication

and competition in microbial communities and with host cells (Heeb et al., 2011; Tashiro et al., 2013). In other cases, *P. aeruginosa* can directly convey its products to other cells using the type VI secretion system. In addition, bacteria possesses an intracellular orphan receptor QscR, a LuxR homolog (Lintz et al., 2011) that can bind to 3O-C<sub>12</sub>-HSL (Oinuma and Greenberg, 2011). This natural target forms dimers with other receptors, i.e., LasR and RhlR, making them inactive and thereby repressing LasRI- and RhlRI-dependent genes leading to prevention of aberrant QS responses before the bacteria reach a quorum in a community (Ledgham et al., 2003). Furthermore, the LasR-3O-C<sub>12</sub>-HSL, RhlR-C<sub>4</sub>-HSL, and PQS-PqsR complexes target the regulation of *lasI*, *rhlI*, *pqsH*, and *pqsR*, which creates an autoinducing feed-forward loop and establishes the tightness and subordination between all three QS systems (Seed et al., 1995; Latifi et al., 1996; Deziel et al., 2004; Xiao et al., 2006; Diggle et al., 2007). Thus, with optimal precision *P. aeruginosa* QS system directly or indirectly controls the expression of more than 10% of genes for multiple virulence factors, secondary metabolites, swarming motility, and biofilm development (Schuster and Greenberg, 2006; Wagner and Iglewski, 2008; Williams and Camara, 2009).

### QS-DRIVEN INTER-KINGDOM SIGNALING

Prokaryotes and eukaryotes have coexisted for many years, during which time they have been exposed to the signals produced and released by the other. The organisms of two kingdoms have also learnt to sense their various molecules including QS signals to influence gene expression and behavior in a process called inter-kingdom signaling (Pacheco and Sperandio, 2009; Gonzalez and Venturi, 2013).

The QS signal molecule AHL affects mammalian host cells and its signaling pathways; this was shown using both *in vivo* and *in vitro* models for immune cells, fibroblasts, and epithelial cells. For the biological activity of AHL, a long acyl chain with more than 10 C-atoms, an intact homoserine lactone ring, and oxo- or hydroxyl substitutions are important. AHL triggers and acts through multiple signaling pathways, e.g., calcium mobilization, activation of Rho GTPases, MAPK, and NFκB that control diverse functions and behaviors in host cells, like cytoskeleton remodeling, chemotaxis, migration, phagocytosis, epithelial barrier function, differentiation, proliferation, apoptosis, and production of immune mediators. This topic has been thoroughly investigated by many research groups during the last decade and extensively reviewed recently (Williams and Camara, 2009; Jarosz et al., 2011; Teplitski et al., 2011).

Many organisms, including bacteria, fungi, plants, and mammalian can disturb and inactivate AHL by enzymes in a way called quorum quenching (Czajkowski and Jafra, 2009; Chen et al., 2013). Humans have also developed an ability to destroy AHL via a class of quorum quenching enzymes called paraoxonases (Amara et al., 2011).

Here, we will further focus on mostly our research on how bacterial QS conversation changes the behavior and function of human neutrophils, macrophages, and epithelial cells, and the signaling responsible for the recognition of AHL.

### EPITHELIAL BARRIER INTEGRITY AND 3O-C<sub>12</sub>-HSL

Epithelial cells are positioned strategically to provide both physical and immune barriers to pathogens and other environmental agents. The physical barrier is created by epithelial cell-to-cell junctions that prevent for instance invasion of pathogens and food constituents. The junctions are multiprotein associations of transmembrane proteins connected to cytoplasmic plaque proteins and the actin cytoskeleton (Van Itallie and Anderson, 2004; Balda and Matter, 2008; Furuse, 2010; Ivanov et al., 2010; Capaldo et al., 2014). In a model of polarized epithelial cells, 3O-C<sub>12</sub>-HSL alters their barrier integrity (**Figure 1**), as evidenced by decreased transepithelial electrical resistance and increased paracellular flux of different-sized dextrans (Vikstrom et al., 2006). The cell junction complexes occludin-ZO-1, JAM-ZO-1 and E-cadherin-β-catenin were disrupted and the expression and distribution of proteins were affected (Vikstrom et al., 2006, 2009, 2010). Some junctional cytoplasmic proteins play a scaffolding role in linking the actin cytoskeleton and helping to recruit an array of signaling pathways, for example the MAPK cascade molecules, protein kinases, and protein phosphatases (Balda and Matter, 2009; Rodgers and Fanning, 2011). Both p38 and p42/44 MAPK are involved in the 3O-C<sub>12</sub>-HSL-induced leaky barrier (Vikstrom et al., 2006). Moreover, the disrupted cell junction associations and enhanced paracellular permeability are paralleled by alterations in the phosphorylation status of TJ and AJ proteins (**Figure 1**; Vikstrom et al., 2009, 2010). Ca<sup>2+</sup> is another important component in the regulating of immune and physical barriers of the epithelium. Mucosal epithelial cells are as other cells, equipped with Ca<sup>2+</sup>-dependent signaling which allows them to initiate immune response to bacteria and their products. The participation of Ca<sup>2+</sup> as a second messenger is thus vital to many physiological processes of the epithelia including response to bacteria (Vandenbroucke et al., 2008; Varani, 2011). 3O-C<sub>12</sub>-HSL can mobilize intracellular calcium through influx from surrounding and release from thapsigargin-sensitive stores via inositol 1,4,5-triphosphate receptors, IP<sub>3</sub>R (**Figure 1**; Vikstrom et al., 2010). These receptors are based in the endoplasmic reticulum (ER) and regulated by their messengers IP<sub>3</sub> (Ivanova et al., 2014). Together with ER, the actin cytoskeleton is also critically involved in Ca<sup>2+</sup> storage and release as well as in the regulation of store-coupled Ca<sup>2+</sup> entry (Lange and Gartzke, 2006).

### 3O-C<sub>12</sub>-HSL-MEDIATED EPITHELIAL MIGRATION AND WOUND HEALING

Establishing and contributing to both physical and immune barriers, the epithelial cells also have to be constantly renewed and prepared to move. After injury, caused by for example oxidative stress, inflammation and infection, the epithelium undergo a wound-healing process. This is dependent on the balance of migration, proliferation, and differentiation of the cells within the wound area (Sturm and Dignass, 2008). Restitution of the epithelium requires extensive reorganization of the cytoskeleton and cellular junctions, regulated by the Rho family of small GTPases, like Rho, Rac, and Cdc42 (Kjoller and Hall, 1999; Evers et al., 2000). 3O-C<sub>12</sub>-HSL modulates epithelial cell migration in a dose- and time-dependent manner



as  $\text{TNF-}\alpha$ ), although higher molar concentrations of AHL were required (**Figure 2A**). Chemotaxis and migration towards AHL are paralleled by cytoskeletal F-actin accumulation in the leading edge of neutrophils, by increased F-actin-to-G-actin ratio and via activation of Rho GTPases Rac1 and Cdc42 (Karlsson et al., 2012a). Rac1 regulates the formation of lamellipodia protrusions and membrane ruffles, and Cdc42 triggers filopodial extensions (Kjoller and Hall, 1999; Evers et al., 2000). Two long acyl chain AHL with 10 and 12 C-atoms activated phospholipase  $\text{C}\gamma 1$  and mobilized intracellular calcium via the  $\text{IP}_3\text{R}$  at

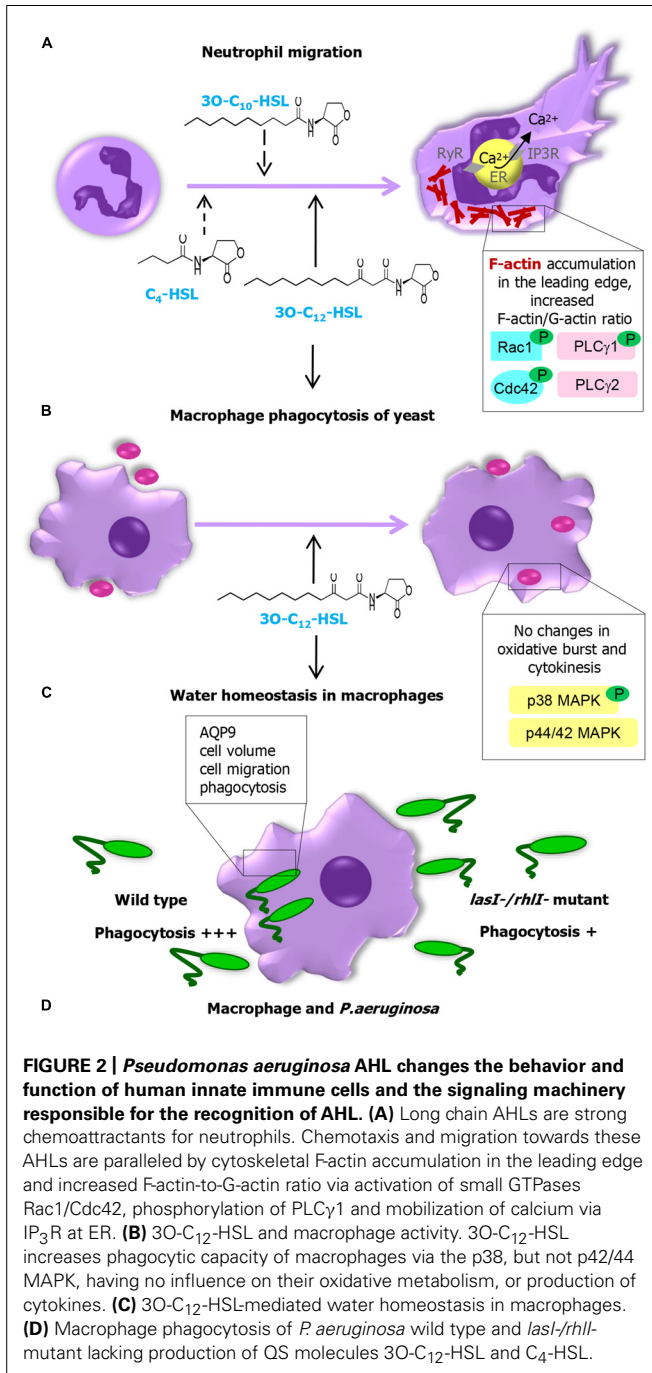
endoplasmic reticulum, whereas an AHL with a short acyl chain failed to do this (Karlsson et al., 2012a; **Figure 2A**). Thus, recognition of AHL QS signals by neutrophils may play a critical role in their recruitment during infections and early stage of biofilm formation.

### AHL AND MACROPHAGE ACTIVITY

Other important players in the innate immune system are macrophages, cells differentiated from monocytes in tissues and stimulated by neutrophils to come to the site of infection after them. Macrophages harbor the characteristics of innate immune cells and traits that initiate mechanisms of adaptive immunity. In response to microbial antigens, they can display strong phagocytic activity, generation of “killer” anti-microbial ROS, NO, “tissue repair” ornithine, pro-inflammatory cytokines stimulating other immune cells to respond to pathogens. In a macrophage phagocytosis model with *Saccharomyces cerevisiae* as preys, 3O-C<sub>12</sub>-HSL increased phagocytic capacity via the p38, but not the p42/44 MAPK signaling pathway (**Figure 2B**). It had no influence on macrophages oxidative metabolism, the level of ROS or production of cytokines (Vikstrom et al., 2005). In *P. aeruginosa*, two functional QS genes, *lasI*, and *rhlI*, which are responsible for synthesis of signal molecules 3O-C<sub>12</sub>-HSL and C<sub>4</sub>-HSL strongly contribute to effective macrophage phagocytosis of this pathogen. AQP9 controls cell migration by accumulation in membrane protrusions and domains preceding their expansions (Karlsson et al., 2011, 2013a,b). This trigger actin cytoskeleton to be remodeled and further regulate macrophage shape, migration, and phagocytosis of microorganisms (**Figure 2D**). 3O-C<sub>12</sub>-HSL caused a rapid and prolonged cell-volume increase controlled by AQP9 in human macrophages (**Figure 2C**), which can be a danger signal and protection mechanism (Hoffmann et al., 2009; Compan et al., 2012). AQP9 is involved in *Escherichia coli* LPS-enhanced brain water content and blood-brain barrier permeability (Wang et al., 2009) and has been identified as a one of markers of chronic inflammation in patients with psoriasis, rheumatoid arthritis, and inflammatory bowel disease (Mesko et al., 2010).

### HUMAN CELL TARGETS FOR 3O-C<sub>12</sub>-HSL

Identifying targets for AHL allows better understanding of QS communication during host–bacteria interactions. The recognition of 3O-C<sub>12</sub>-HSL by mammalian cells probably does not rely on pattern-recognition receptors (PRRs) that usually sense invariant microbial motifs (PAMPs, pathogen-associated molecular patterns) present on or shed from bacteria (LPS, lipoteichoic acid, flagellin, and DNA). The canonical class of PRRs, the membrane-bound toll-like receptors (TLRs) located on immune cells, do not interact with 3O-C<sub>12</sub>-HSL (Kravchenko et al., 2006). Still, as for TLR activation, AHL can trigger and act through multiple signaling pathways, which include calcium signaling, activation of Rho GTPases, MAPK, and transcription factor  $\text{NF}\kappa\text{B}$  that control expression of pro-inflammatory mediators, cytokines, chemokines, enzymes, and interferones (Smith et al., 2002; Shiner et al., 2006; Kravchenko et al., 2008; Mayer et al., 2011; Karlsson et al., 2012a; Glucksam-Galnoy et al., 2013). These



mediators are involved in the coordination of innate immune response and recruit effector cells of the adaptive immune system to the site of the infection to combat the invading bacteria.

During the recognition of 3O-C<sub>12</sub>-HSL by mammalian cells, this lipophilic molecule with a long acyl chain and an intact homoserine lactone ring may interact directly with phospholipids in model membrane systems and in T-cell membranes (Davis et al., 2010). On entering host cells (Shiner et al., 2004; Ritchie et al., 2007), 3O-C<sub>12</sub>-HSL can utilize intracellular nuclear peroxisome proliferator-activated receptors (PPAR) to affect NF- $\kappa$ B signaling (Jahoor et al., 2008; Cooley et al., 2010). The binding of 3O-C<sub>12</sub>-HSL to nuclear PPAR does not exclude the existence of cell surface or membrane-associated receptors, which after binding to 3O-C<sub>12</sub>-HSL likely help phosphorylate phospholipase C and evoke an increase in intracellular calcium (Shiner et al., 2006; Davis et al., 2010; Karlsson et al., 2012a).

Several groups have designed probes and affinity matrixes which could be utilized to detect the mammalian target of 3O-C<sub>12</sub>-HSL (Dubinsky et al., 2009; Garner et al., 2011; Praneenararat et al., 2011; Dubinsky et al., 2013). Using a biotin-based 3O-C<sub>12</sub>-HSL probe, LC-MS/MS, and super-resolution microscopy, the IQ-motif-containing GTPase-activating protein IQGAP1 was identified as a putative human target for 3O-C<sub>12</sub>-HSL in epithelial cells (Figure 1; Karlsson et al., 2012b). IQGAP1 contains multiple domains for binding other proteins and localizes in the leading edge of migrating cells (Briggs and Sacks, 2003; Noritake et al., 2004; Bensenor et al., 2007). It directly interacts with and stabilizes the Rho-family GTPases, Rac1, and Cdc42 in their GTP-bound state (Swart-Mataraza et al., 2002; Briggs and Sacks, 2003), playing an essential role in cell shape, vesicle trafficking, and directional migration (Bensenor et al., 2007). It likely mediates these processes through its other domains, linking it to actin, myosin,  $\beta$ -catenin, E-cadherin, calmodulin, and MAPK (Noritake et al., 2005; Brandt and Grosse, 2007), which allows it to function as a true scaffolding protein (Figure 1). The interaction of 3O-C<sub>12</sub>-HSL with the cell membrane, diffusion and entering into the cytoplasm, targeting of IQGAP1 and PPAR do not exclude each other. It has, for example been shown that different types of lipids, such as chemoattractant leukotriene B<sub>4</sub>, can bind to both the cell surface receptor LTB<sub>4</sub>, and nuclear PPAR.

## CONCLUDING REMARKS

During the last decade of research remarkable insight has been gained into the mechanisms of bacterial QS communication and that *P. aeruginosa* 3O-C<sub>12</sub>-HSL plays at least two distinct roles. Besides regulating bacterial social behavior and offering density-dependent fitness advantages, expression of virulence factors, and biofilm development in bacteria, it also plays a crucial role in the behavior of eukaryotic host cells regulating various vital functions. Moreover, as QS circuits often control virulence and biofilm, there is a high interest in interfering with QS as a new strategy to overcome infectious diseases and biofilm formation (Amara et al., 2011; Heeb et al., 2011; Jakobsen et al., 2013; LaSarre and Federle, 2013).

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