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# Bacteria-Host Crosstalk: Sensing of the Quorum in the Context of *Pseudomonas aeruginosa* Infections

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**Keywords**

Host-pathogen interactions · Bacteria · Cell-to-cell signaling · Quorum sensing · *Pseudomonas aeruginosa* · *N*-acyl homoserine lactones · Biofilms · Innate immunity · Mucosal surfaces · Proteogenomics

**Abstract**

Cell-to-cell signaling via small molecules is an essential process to coordinate behavior in single species within a community, and also across kingdoms. In this review, we discuss the quorum sensing (QS) systems used by the opportunistic pathogen *Pseudomonas aeruginosa* to sense bacterial population density and fitness, and regulate virulence, biofilm development, metabolite acquisition, and mammalian host defense. We also focus on the role of *N*-acylhomoserine lactone-dependent QS signaling in the modulation of innate immune responses connected together via calcium signaling, homeostasis, mitochondrial and cytoskeletal dynamics, and governing transcriptional and proteomic responses of host cells. A future perspective emphasizes the need for multidisciplinary efforts to bring current knowledge of QS into a more detailed understanding of the communication between bacteria and host, as well as into strategies to prevent and treat *P. aeruginosa* infections and reduce the rate of antibiotic resistance.



## Introduction

Quorum sensing (QS) is a cell-to-cell communication that allows bacteria to recognize the population density by producing and sensing small diffusible signaling molecules. This form of bacterial intercellular signaling coordinates gene regulation and controls numerous cooperative behaviors, including biofilm formation, virulence traits, metabolic demands, and host-microbe interactions [1]. Multicellular eukaryotic organisms have coexisted with bacteria for approximately 2 billion years under evolutionary pressure and both represent remarkable examples of adaptive evolution. Our body meets numerous potential pathogens daily, and during the first critical hours and days, the outcome of infections and development of disease depend on the properties of both bacterial community and our innate immune system [2]. Epithelial surface linings of the mucosa, e.g., in the gut and lung, provide physical and immune barriers between the host and pathogens and external environment. Tight junctions (TJ) and adherens junctions (AJ) are specialized transmembrane protein complexes located between neighboring epithelial cells and associated with the cytoskeleton and regulatory proteins [3]. The apical surface of the epithelial cells in the intestine and lung is equipped with two types of projections, microvilli versus cilia, and covered

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with a mucus layer made of glycoproteins that protects against mechanical, chemical, and microbial agents. The lumen of the gut and the lung is also largely inhospitable for microbes because of the presence of antimicrobial factors, such as lysozyme, α-defensin, and lactoferrin. Moreover, macrophages and neutrophils are activated by bacterial products (e.g., cell wall components, formylated peptides, flagellin) or immune stimuli (e.g., complement components, cytokines, antibodies) can quickly phagocyte and kill bacterial pathogens at the early onset of infection, and dendritic cells in mucosa activate the adaptive immune response, including T and B cells [3]. Using QS communication, bacteria can coordinate their social behavior, influencing host cell activities in a noninvasive manner. The early events in the communication between bacteria and host cells may happen even before the bacteria bind to and enter host cells and then spread further. Research over the past 2 decades has greatly increased our understanding of how bacterial QS communication orchestrate cooperative behaviors of bacteria during host-microbe interactive coexistence. These advances open up new frontiers of the sociomicrobiology research field aiming to find new strategies for the prevention and treatment of bacterial infections.

## *Pseudomonas aeruginosa*

*Pseudomonas aeruginosa* is a social, nonfermentative opportunistic Gram-negative bacterium that inhabits diverse environments. Normally considered to be commensals on the host body, bacteria can establish themselves as opportunistic pathogens. Being highly adaptable, invasive, toxigenic, and able to colonize various surfaces and tissues, *P. aeruginosa* can cause severe nosocomial outbreaks and also threaten local and systemic infections in patients with compromised underlying health conditions, particularly in those with ventilator-associated pneumonia, burn wounds, cystic fibrosis, and bloodstream infections [4]. As other members in a large group of so-called ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumonia, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* species), it is capable of escaping from the action of multiple drugs and represents a new paradigm of a "superbug" in pathogenesis, transmission, and antibiotic resistance [5]. Therefore, traditional therapeutic options for *P. aeruginosa* have become limited and finding novel alternative prevention and treatment strategies is an urgent priority.

## QS Signaling Networks in *P. aeruginosa*

### *Concept of QS*

The general concept of QS is that small-signal molecules broadcast the information about cell density in the bacterial population and allow collective coordinated production of costly extracellular items. This gives beneficial cooperation with each other, behavior as a powerful multicellular community, and performance of tasks, which would be impossible for single cells [1]. Sophisticated QS networks exist in both Gram-negative and Gram-positive bacteria, and they communicate via many different circuits and various signal molecules. Despite the diversity of QS mechanisms, there are common items among these networks. Many of the QS-controlled social factors and cooperative behaviors are conserved and include biofilm formation, virulence traits, and metabolic demands [6].

### P. aeruginosa *QS Systems*

*P. aeruginosa* harbors one of the most complex QS systems (Fig. 1), equipped with at least four distinct but deeply intertwined and subordinated circuits [6]. There are two *N*-acylhomoserine lactone (AHL) circuits, LasI/LasR and RhlI/RhlR; both are homologs of LuxI/LuxR type, and both are activated by an increased cell density within a bacterial population (Fig. 1). Each AHL-dependent system is composed of a LuxI-type synthase and a LuxR-type receptor [6]. LasI produces a molecule, *N*-3-oxo-dodecanoyl-L-homoserine lactone (3O-$C_{12}$-HSL), which is detected by the cytoplasmic receptor LasR. RhlI produces *N*-butyryl-L-homoserine lactone ($C_4$-HSL), which is recognized by the cytoplasmic receptor RhlR. LasR and RhlR are transcriptional regulators and together control the activation of more than 300 genes in the *P. aeruginosa* genome [7]. In addition, there is a 3O-$C_{12}$-HSL-binding receptor QscR, a LuxR homolog which not only controls its own set of genes but also inactivates LasR and RhlR and thereby represses many Las- and Rhl-dependent genes resulting in prevention of QS responses before the bacteria reach a quorum in a population [8].

An additional level of complexity is added by the third QS circuit, the *P. aeruginosa* quinolone signal (PQS) system (Fig. 1), which is interconnected to the AHL-dependent signaling and can be triggered by iron limitation within bacterial population [9]. Here, PqsABCDE produces the precursor 2-heptyl-4-quinolone (HHQ), and PqsH catalyzes conversion of HHQ to 2-heptyl-3-hydroxy-4-quinolone (PQS), detected by the receptor PqsR [10]. Phosphate starvation can activate the production of

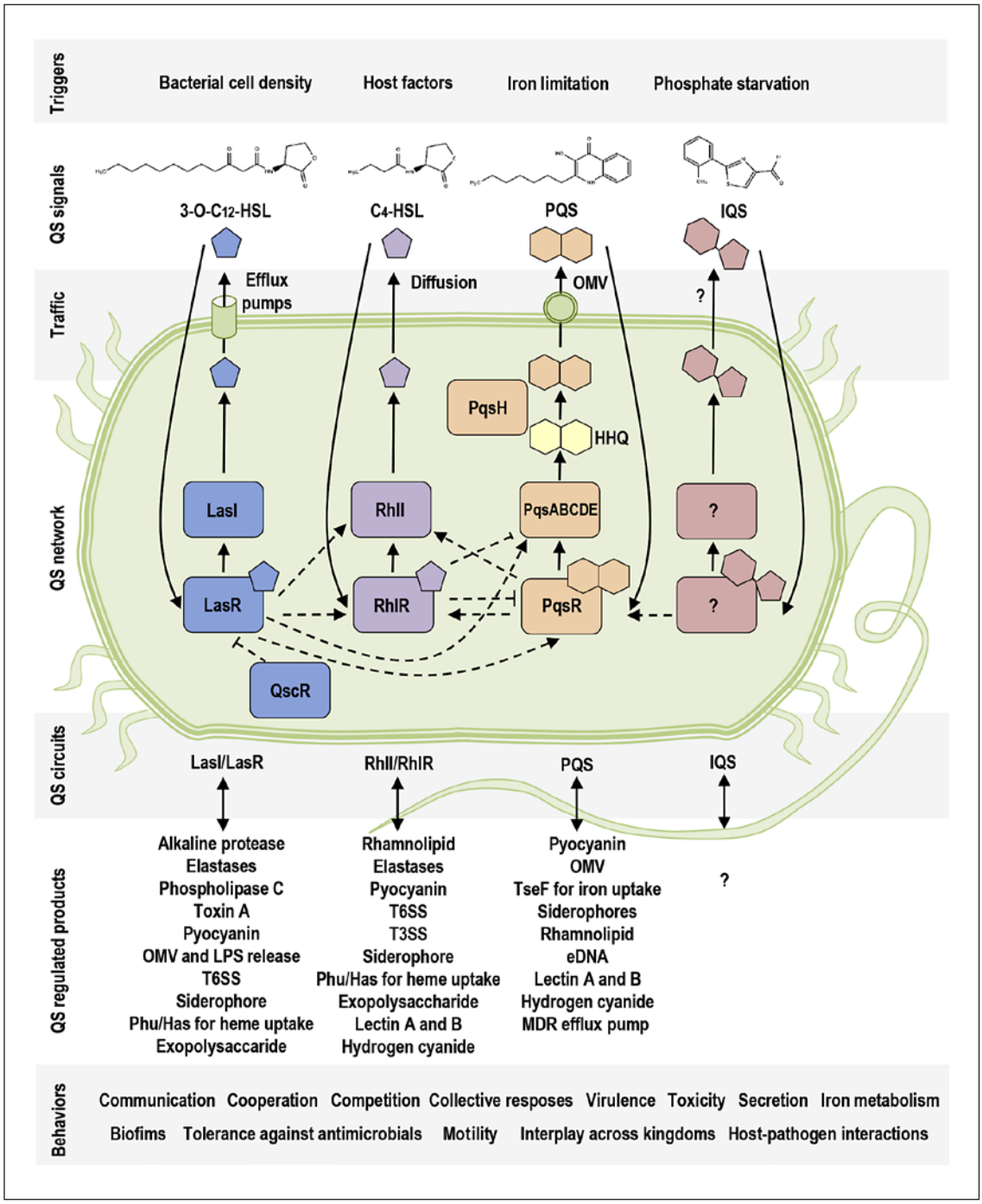


**Fig. 1.** The QS system in *P. aeruginosa*. The scheme illustrates (in different colors) four main circuits of the QS system: AHL-dependent circuits, Las and Rhl, which are interconnected to the PQS circuit, and IQS. They can be triggered by certain stimuli, such as bacterial cell density or iron limitation, etc. Chemical structures are shown for four main QS signal molecules, 3-O-$C_{12}$-HSL, $C_4$-HSL, PQS, and IQS. Furthermore, the scheme shows QS-regulated products and cooperative behaviors.

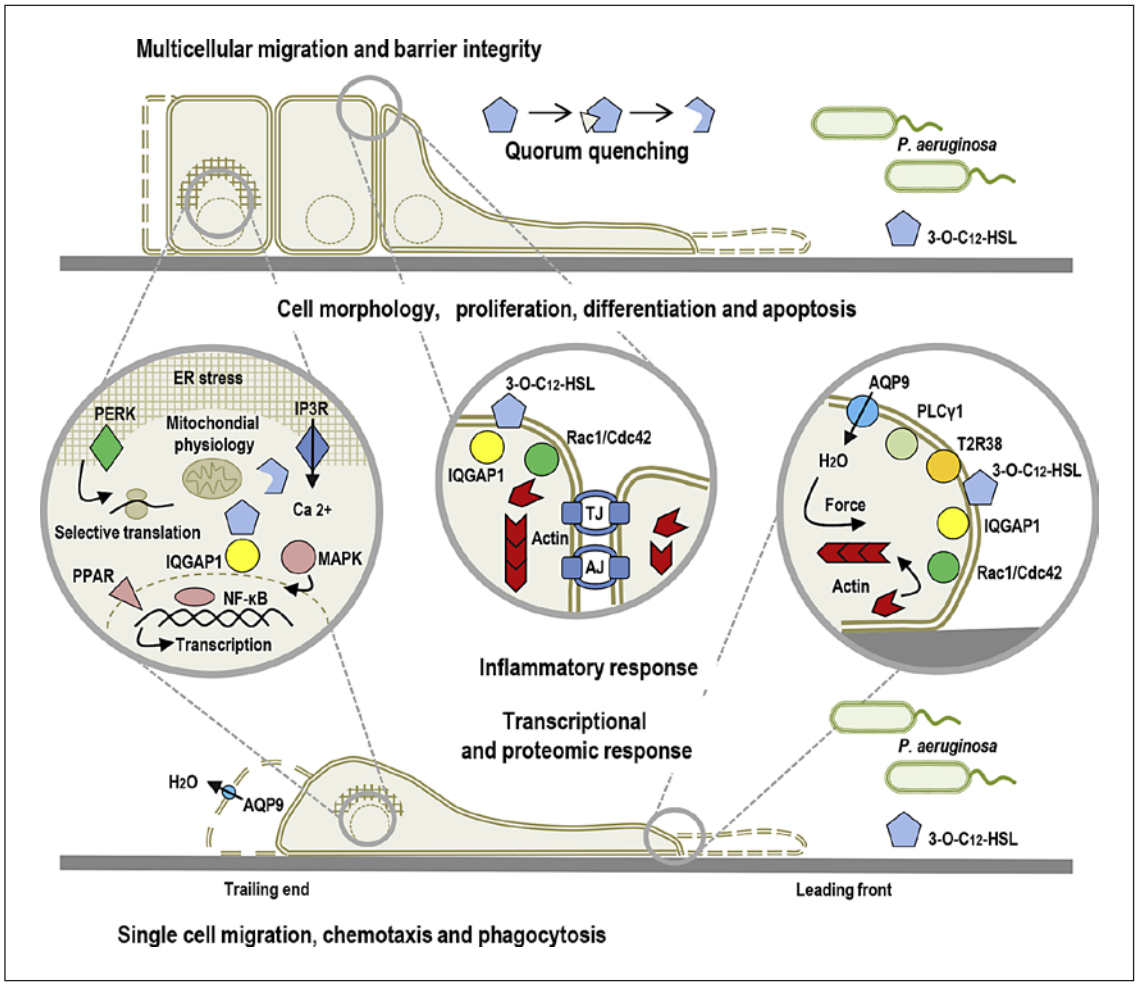


**Fig. 2.** QS communication during host-microbe interaction. The scheme illustrates the impact of *P. aeruginosa* 3O-$C_{12}$-HSL on the mammalian host at cellular and molecular levels. The model also shows that 3O-$C_{12}$-HSL can associate and target several membrane-associated proteins, e.g., scaffold IQGAP1, sensory T2R38, and nuclear PPAR, which promote interaction with signaling cascades and cellular processes. These are connected together by calcium signaling, homeostasis, and mitochondrial and cytoskeletal dynamics, for example, and govern transcriptional and proteomic responses.

yet another QS molecule, 2-(2-hydroxyphenyl)-thiasole-4-carbaldehyde, involved in the integrated QS (IQS) system, which in turn activates the expression of *pqs* genes [11]. It has been proposed that the IQS signal molecule is synthesized by AmbBCDE [11], but recent results imply that IQS is a byproduct in the synthesis of siderophore pyochelin [12]. The bacterial receptor for IQS still remains elusive. In addition, in biofilm communities, bacteria can communicate using long-range electrical signals via ion channels [13]. Host factors can crosstalk with microbiota via QS [14] and trigger AHL- and PQS-dependent QS communication (Fig. 1), for example neurotransmitter serotonin, estrogen steroid, and stress hormones [15, 16].

The profile of QS molecules formed by *P. aeruginosa* when growing in vitro as a planktonic culture is dominated by a high concentration of $C_4$-HSL (30 μM), an intermediate amount of PQS-family molecules and 3O-$C_{12}$-HSL (1.5–10 μM), and smaller concentrations of other AHL-family members (0.1–1 μM), which differ in the length of the fatty acid chain from C4 to C14 [17]. In biofilms growing in vitro, the concentration of QS signals can be much higher, for example, 3-O-$C_{12}$-HSL accumulates at up to 300–600 μM [18]. The functional QS system has a high impact on the pathogenesis of bacteria. Thus, in experimental models of *P. aeruginosa* infections in mice, such as burn wounds and pneumonia, bacterial

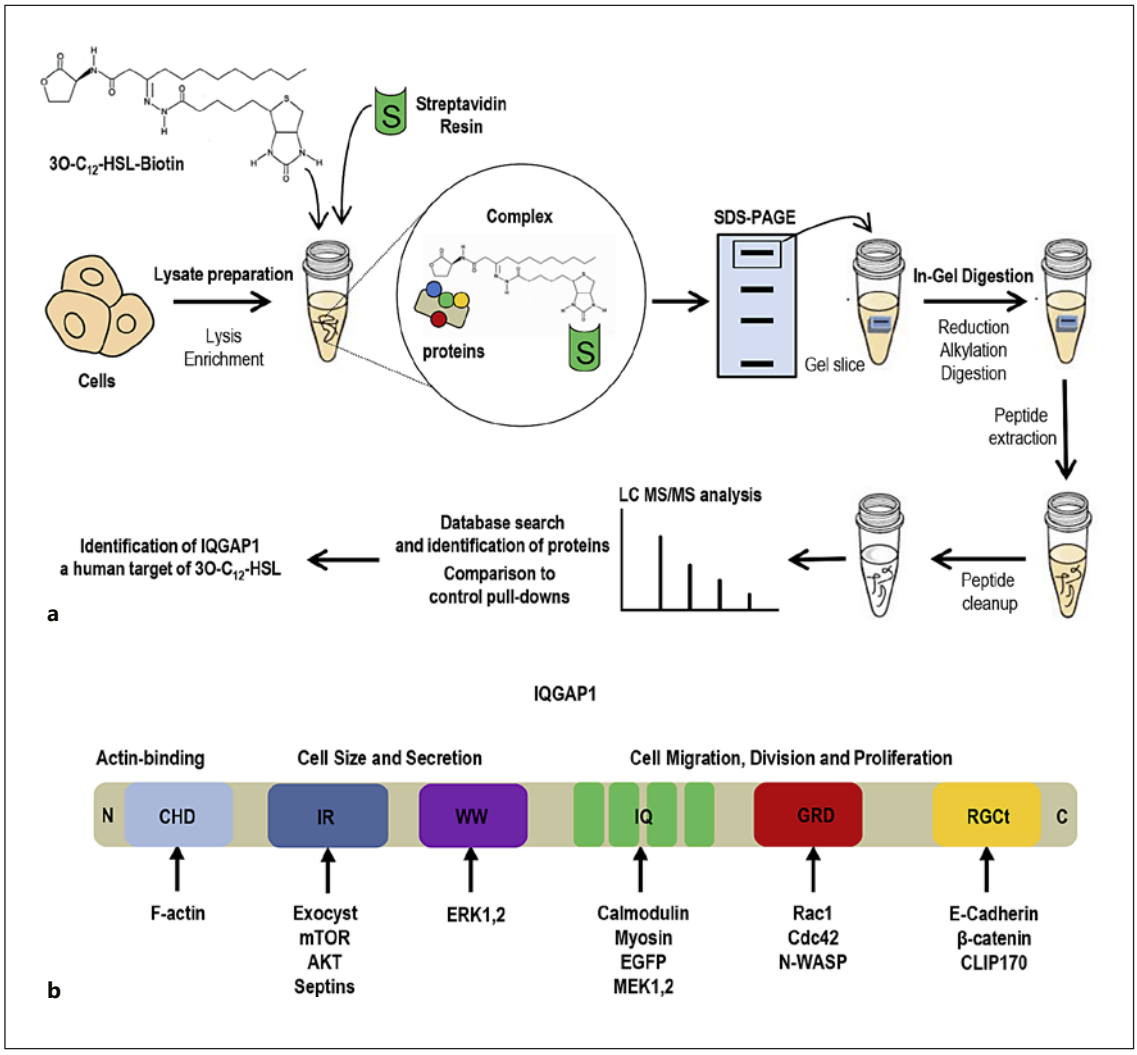


**Fig. 3.** IQGAP1 as a human target of 3O-$C_{12}$-HSL. **a** A pull-down approach with a biotin-conjugated 3O-$C_{12}$-HSL probe and mass spectrometry-based proteomic analysis used to identify the target IQGAP1. For more details on methods, refer to Karlsson et al. [25]. **b** Schematic structure of IQGAP1 with several domains that interact with many different proteins and thereby regulate diverse cytoskeletal reorganization and cell signaling events.

strains containing mutations or deletions in one or several of the QS genes were obviously less virulent than wild-type bacteria [19–21]. These observations have led to further studies with focus on fundamental insights into the molecular basis of QS, bacterial pathogenesis, host-pathogen interactions, and novel strategies to combat bacterial infections. The nature of QS communication was also assessed using chemically synthetized small molecules that are structurally and functionally identical to natural AHL and PQS existing in *P. aeruginosa* cultures. These were used both in in vitro and in vivo studies in a variety of models and systems (Fig. 2), and mainly at around 1- to 300-μM concentrations [20, 22–24], thereby relating to different scenarios of communication between microorganisms and hosts in environments inhabited by planktonic bacteria and in biofilms. Chemical tools were designed and applied to find out and visualize human targets for QS molecules (Fig. 3, 4) and study the effects and pathways of QS signaling on host cells [25]. Novel inhibitors and activators of QS receptors and synthases were developed and included different classes, such as agonists, antagonists, partial agonists, and those that mimic native QS compounds, many of which have been reviewed recently [26]. Indeed, QS blockers can target cer-

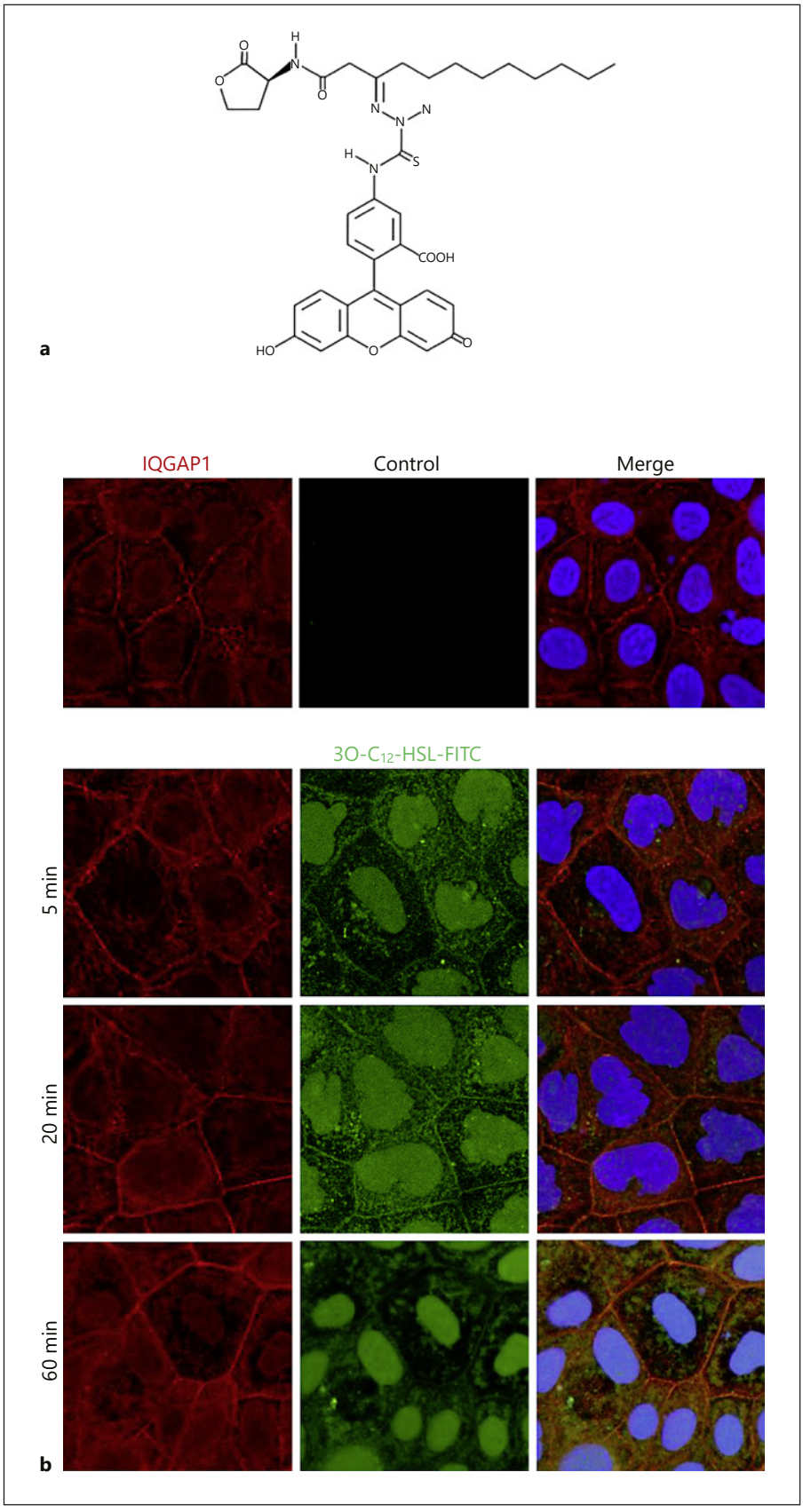


**Fig. 4.** Imaging of IQGAP1 and 3O-$C_{12}$-HSL in human intestinal epithelial cells. **a** Synthetic fluorescently tagged 3O-$C_{12}$-HSL-FITC used for imaging. **b** Caco-2 human intestinal epithelial cells were treated with 1 μM of 3O-$C_{12}$-HSL-FITC (green) or 0.018% DMSO as a diluent control for 5, 20, or 60 min. Samples were fixed, and then the IQGAP1 was immunolabelled (Atto-647N; red) and the nucleus stained with DAPI (blue), as described previously [25]. The samples were visualized by confocal imaging. The image size is 67.6 × 67.6 μm and pixel size is 0.13 μm.


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tain points of QS circuits and thereby inhibit bacterial virulence. It is proposed that resistance to QS inhibitors will develop slowly [27], making them promising anti-virulence agents and potential alternatives to traditional antibiotics [28, 29].

## QS-Regulated Factors That Impact *P. aeruginosa* Communities and Pathogenicity

### *Motility and Adhesion*

*P. aeruginosa* can exist either as free-swimming planktonic organisms or in biofilm communities associated to surfaces or tissues. Planktonic bacteria differ from those living within the early or confluent biofilm stages in terms of their transcriptome [30] and proteome profiles [31, 32]. When planktonic, *P. aeruginosa* moves using a single polar flagellum, an essential part of its swimming motility in aqueous environments and its direction is driven by chemotaxis towards or away from the gradient of concentration of environmental stimuli. Bacterial adhesion is mediated by both specific and nonspecific interactions. Nonspecific forces, including hydrophobicity and electrostatic charge, for example, are influenced by the cell surface and milieu composition. Specific interaction and adhesion are mediated by proteins, lipids, and sugars in the cell membrane. Bacteria possess polar type 4 pili, which are the main adhesins but also mediate a flagellum-independent surface translocation, called twitching motility. QS molecules produced by LuxS-family synthase are involved in biogenesis and function of pili and flagella in *Salmonella*, *Vibrio*, and *Escherichia coli*, but not in *P. aeruginosa* [33, 34]. However, QS system controls social cellular motility in *P. aeruginosa*, known as swarming, mostly via the rhamnolipid (RHL) production (Fig. 1). Both flagella and pili are potent virulence factors enabling the bacteria to move to and bind to host cells or mucus layers, sense mechanical features of their environment and facilitate the early stage of biofilm development at the surface [35]. *Pseudomonas* adhesins recognize different components of the host extracellular matrix, i.e., collagen, fibrinogen, elastin, and laminin. Bacterial adhesins can interact with host transmembrane proteins, called cell adhesion molecules, such as integrins, selectins, cadherins, and immunoglobulins for binding and sometimes for cell entry.

### *Lipopolysaccharide*

Adhesion initiates a closer physical contact between tissue surfaces and bacterial traits, such as lipopolysaccharide (LPS), a dominant complex glycolipid of the outer membrane in Gram-negative bacteria, a highly potent activator of the innate immune system and a key player in pathogenesis. The classical LPS molecule has a three-domain structure: the conservative lipid A, the hydrophobic moiety that anchors LPS to the outer membrane; the more variable core oligosaccharide, which together with lipid A maintains the integrity of the outer membrane; and the hypervariable O-antigen polysaccharide, which is a polymer of repeating oligosaccharides connected to the core with direct contact to external milieu [36]. Various modifications in LPS biosynthesis and structure, such as loss of O-antigen and lipid A modifications, occur during adaptation of pathogens to chronic infections in respiratory and gastrointestinal tracts, which results in alteration of host immune responses and promotes bacterial persistence [37]. Typically, LPS is anchored to the bacterial outer membrane via lipid A, but it can also be released from the cells to external milieu during normal growth and AHL-dependent QS system is involved in this release (Fig. 1) [38]. The LPS provides an effective permeability barrier against antibiotics and antimicrobial peptides. The last-resort antibiotic colistin, also known as polymyxin E, binds to LPS with high affinity; LPS modifications lead to the development of antibiotic resistance and changes in bacterial fitness and virulence potential [39]. LPS is able to enhance bacterial cell surface hydrophobicity, and therefore increase *P. aeruginosa* motility and impact adhesion and biofilm formation [40]. Flagellin and LPS of *P. aeruginosa* can associate with host pattern recognition receptors, e.g., Toll-like receptors (TLR5 and TLR4) expressed on different host cells, and thereby initiate an inflammatory response via the NF-κB signaling pathway [4].

### *Enzymes and Exotoxins*

*P. aeruginosa* is able to secrete a large variety of enzymes and exotoxins, which have established roles as virulence factors that damage tissue, provide nutrition supply for the bacteria, increase bacterial survival, actively subvert immune responses, and promote the development of an infection and further spreading of bacteria to underlying tissues and the circulatory system.

In particular, proteases possess proteolytic activity against many different types of substrate in host tissues, e.g., complement components, mucins, fibrin, cytokines, immunoglobulins (Ig), and epithelial junctions [4]. *Pseudomonas* produces several extracellular proteases that serve for these purposes and are often associated with in vivo and in vitro infections [41, 42]. Three of them – al-

kaline protease (APR), elastase LasA and LasB – are produced by *P. aeruginosa* under the control of the Las and Rhl circuits in the QS system (Fig. 1) [43]. APR and elastases are exported via the type 1 and type 2 secretion systems (T1SS and T2SS, respectively), the general secretory mechanism in Gram-negative bacteria [44]. These enzymes are zinc metalloproteases and require calcium for proteolytic activity against various types of substrates and to combat host immune responses. Thus, APR degrades the C2 component of the complement system, preventing its activation via the classical and lectin pathways and thereby inhibiting phagocytosis and bacterial clearance [45]. Similarly, elastases cleave complement components and also elastin, collagen, IgG, mucin, and surfactant proteins to escape from phagocytosis and clearance [46]. *Pseudomonas* proteases can mimic the activity of neutrophil elastase by cleaving peptides from host thrombin that inhibits inflammatory responses [47].

Three extracellular phospholipases C (PLC), PLC-H, PLC-N, and PLC-B, hydrolyze lipids in host cell membranes, e.g., sphingomyelin and phosphatidylcholine, and pulmonary surfactant. The production of one of them, PLC-B, but not two others, is under control by AHL-dependent QS-system (Fig. 1) [48, 49]. PLC are secreted via twin arginine translocase pathway and T2SS [44]. The activity of this single virulence factor in *P. aeruginosa* was directly linked with effects on lung function during infection [50]. PLC-B has one more specific function: it is required for the directed twitching motility of *P. aeruginosa* towards a gradient of certain phospholipids, such as phosphatidylcholine and phosphatidylethanolamine, which are strong chemoattractants for prokaryotes [51, 52].

*Pseudomonas* exotoxin A (ETA) belongs to the two-component AB family, where the B subunit has cell binding activity and the A subunit has enzymatic activity [53]. ETA is secreted from cytoplasm into the extracellular space through T2SS [54]. Once secreted, ETA specifically binds its B subunit to lipoprotein receptor-related CD91 and gets into the host cell via clathrin-coated regions of the plasma membrane [55]. Once in endosomes, ETA has two pathways open to reach the endoplasmic reticulum (ER): lipid-dependent sorting and the KDEL receptor-mediated pathway, both of which go through the Golgi apparatus [56, 57]. Then, ETA goes from the ER into the cytosol, ADP-ribosylates the eukaryotic elongation factor-2 (eEF-2) on the ribosomes, inactivate it, and thereby block the translocation of mRNA and protein synthesis in the host cell. The regulation of ETA is complex and related to glucose and iron metabolism and the Las/Rhl circuits of the QS system (Fig. 1) [58].

*P. aeruginosa* secretes a number of virulence factors known as phenazines, and one of them is pyocyanine (PYO). It is an aromatic compound that contributes to the green color of *P. aeruginosa* cultures. PYO is toxic due its ability to increase intracellular levels of reactive oxygen species, in particular superoxide, which leads to oxidative stress, NAD(P)H depletion and enzyme inhibition, DNA damage, and cell death. Numerous studies have disclosed the importance of PYO in the pathophysiology of *P. aeruginosa* infection in different tissues and biological systems [59]. All three QS systems, Las, Rhl, and PQS, play a role in the regulation of PYO production (Fig. 1) [48], and a recent study uncovered a higher level of its complexity [60].

*Protein Secretion Systems*

Secreted proteins and enzymes are large hydrophilic molecules which need to be transported via either spherical 50- to 250-nm outer membrane vesicles (OMV), or assemblies of specialized macromolecular complexes, called protein secretion systems. OMV are multifunctional structures that bleb from the outer membrane of bacteria and typically include proteins, phospholipids, nucleic acids, LPS, QS signals, ions, and metabolites. These extracellular structures are considered as a type zero secretion system (T0SS), an additional and independent traffic system [61]. Six classical types of protein secretion systems have been identified in *Pseudomonas*, termed T1SS to T6SS, and they are conserved in Gram-negative bacteria. [44]. Both secretion modes, T1SS-T6SS and T0SS, are essential for the interaction between bacteria and their environments, used to deliver virulence factors, and linked to QS signaling in *P. aeruginosa* (Fig. 1) [44, 62]. Furthermore, PQS in a strong interaction with LPS is required for OMV formation [63] and the Las circuit controls the release of OMV in extracellular milieu [38]. Moreover, PQS signal molecules in OMV can hijack iron ions from the extracellular medium via the OMV-associated metal-binding protein TseF, secreted by the type 6 secretion system (T6SS). The delivery of PQS-iron complexes into recipient bacterial cells goes through interaction between the TseF (T6SS effector for iron uptake), ferric pyochelin receptor FtpA, and porin OprF [62, 64]. In parallel, QS enables differential regulation of the expression of genes at the loci of T6SS [65]. The expression of T6SS in *P. aeruginosa* is positively regulated by the AHL-dependent Las and Rhl circuits of the QS system during transition from exponential to stationary phase growth, and modulates bacteria entry into epithelial cells [66]. Furthermore, the expression of exoensyme S regu-

lon *exoS*, which comprises genes for T3SS and four effector proteins, ExoS, T, U, and Y, is coordinated by the Rhl circuit of the QS system [67]. They are GTPase-activating proteins and ADP-ribosyltransferase, and able to induce cell death, inhibit phagocytosis during pneumonia, and lead to disruption of the pulmonary-vascular barrier, allowing bacterial dissemination into the bloodstream [68].

*Iron Uptake*

Efficient uptake of iron by bacteria is another important factor, along with virulence, which allows colonization of the host and establishment of infection [69]. Like the majority of organisms, *P. aeruginosa* needs iron to grow. However, it is confronted with a problem of iron availability in a mammalian host because iron is sequestered in host proteins. Here, the largest part of iron is present in the heme molecules found in intracellular hemoproteins, such as hemoglobin, myoglobin, and cytochromes. Also, iron can be reversible when bound to extracellular glycoproteins, such as lactoferrin, ferritin, and transferrin. *P. aeruginosa* uses multiple iron uptake strategies [70], and at least three of them – the siderophore system (pyoverdine and pyochelin), heme uptake system, and Feo system – are controlled via different QS circuits (Fig. 1) and triggered by bacterial cell density and iron limitation [71–73]. Pyoverdine (PVD) binds iron and displaces it from transferrin, and it can also act as a signaling molecule: when iron-bound, it causes the upregulation of exotoxin A, proteases, and PVD itself [4]. PVD is essential to *P. aeruginosa* to cause infections [74] and involved in the establishment of biofilms [69]. The heme uptake system, represented by Phu- and Has-components and positively regulated by Las and Rhl circuits of QS, allows *P. aeruginosa* to take up heme from hemoglobin and utilize it as a source of iron [71]. Uptake of $Fe^{2+}$ through Feo system demands the involvement of QS-controlled phenazines, such as PYO, which are able to reduce $Fe^{3+}$ bound to host proteins to $Fe^{2+}$ [73]. The uptake of $Fe^{2+}$ is important when bacteria grow not as planktonic but rather as biofilms in microaerobic or aerobic conditions and lower pH, which is a common situation during lung infections.

*Biofilms*

Higher organisms, including humans, are colonized by microorganisms, either as free-living bacterial cells or biofilms, which can be associated with normal microflora, persistent infections, and with the contamination of medical devices [75]. Biofilms are robust, organized social communities of microorganisms connected to each other and to a surface and encased by extracellular polymeric substances (EPS), as a matrix. The biofilm lifestyle is very distinct from that of planktonic bacterial cells as this ecosystem includes a completely new, higher level of physical and social interactions between community members and the matrix, and can be viewed as a biogenic habitat on the microscale [76]. Typically, biofilms have a high cell density, ranging between $10^8$ and $10^{11}$ cells/g wet weight [77], and a heterogenic community, comprising many species with different gene expressions and metabolic and physiological activities that fluctuate over time [76]. EPS comprises most of the biomass of the biofilm rather than cells, and is mainly composed of polysaccharides, lipids, proteins, and extracellular DNA (eDNA) [78]. Matrix components provide structural stability, facilitate liquid and nutrient transport, and support robust integrity to a biofilm, including tolerance against antimicrobials [79], stress factors, and immune cells [75, 80]. The environment of biofilms provide a perfect milieu for intercellular communication. Indeed, the concentration of QS signals can be up to 1,000-fold higher in biofilms existing in the lung or gut than in environments inhabited by planktonic bacteria. Thus, 3-O-$C_{12}$-HSL accumulates at 300–600 μM in biofilms growing in vitro [18]. Moreover, the QS system, together with other signaling systems, is involved and required for biofilm development in *P. aeruginosa* [76, 81].

The process of bacterial biofilm development consists of three key stages: attachment and transition from planktonic to sessile lifestyle; growth of microcolonies, biofilm maturation and differentiation; and detachment and dispersal of cells to inhabit new sites [82]. For microcolony and early biofilm formation, bacterial twitching motility and the ability to produce RHL and iron chelating siderophores are required, which are elements controlled by AHL and PQS circuits of the QS system (Fig. 1) [83, 84]. RHL is a glycolipid surfactant, which is essential for optimal interactions between the substratum and bacterial cells, and therefore also for the swarming motility [83] and early biofilm formation [84]. This biosurfactant maintains the pores and channels between microcolonies to facilitate liquid and nutrient transport within mature biofilm [85]. It has furthermore been reported to have antimicrobial properties against other bacteria, viruses, and fungi, and thereby give an advantage for *P. aeruginosa* in the competition and niche colonization in the tissues. RHL is a potent virulence factor since it is able to disrupt epithelial junctions, kill neutrophils, and inhibit phagocytosis [4].

The PQS system is also responsible for increased synthesis of eDNA, which interacts with EPS and is needed

for its stability and resistance. *P. aeruginosa* requires nucleic acids mostly during early biofilm formation, while taking advantage of capsular and aggregative polysaccharides at several development stages [86]. One of them, aggregative glucose-rich PEL exopolysaccharide, facilitates stability, adherence, and compactness of the biofilm and cell-to-cell associations, and is controlled by the AHL-dependent QS system [87]. In the matrix, PEL can also serve a protective role, which relies on its ability to bound with and inhibit antibiotics [88]. Moreover, two QS-dependent carbohydrate-binding proteins, lectin A and B, are located in the outer membrane and important for cell recognition, adhesion, and proper biofilm formation [89, 90]. There are several accessory matrix components that support biofilm life: iron siderophores, cyclic glucans, LPS, and OMV [69]. Thus, many QS-regulated factors have an impact on biofilm formation and development at all stages of an infectious process (Fig. 1).

Phenotypic and genotypic alterations can occur in *P. aeruginosa* over time during acute and chronic infections and environmental changes. Thus, bacteria isolated from patients with an established chronic infection are usually nonmotile, nonadhesive, less cytotoxic, and less inflammatory than the strains isolated from the patients with acute infection. Other common changes include some mutations in the circuits of the QS system, downregulated T3SS and structural changes in LPS which results in alteration of host immune responses and promote bacterial persistence. However, strains from chronic infections more readily form colonies and biofilms, as they are usually more mucoid and overexpress exopolysaccharides [4].

## Traffic and Human Targets for *P. aeruginosa* 3O-$C_{12}$-HSL

### *Diffusion and Active Transport in Bacterial and Host Cells*

QS molecules differ in their ability to diffuse across the plasma membrane or the membrane of subcellular organelles. For instance, *P. aeruginosa* AHL with a short fatty acid chain containing 4–6 carbons are freely diffusible across the membrane, in contrast to those with a long acyl chain, 3O-$C_{12}$-HSL, and PQS, due to the larger size and hydrophobic nature of the latter [91]. The PQS transport across the bacterial membrane is facilitated by membrane transporters and bacterial OMV that also contain other bacterial products [64]. The active traffic of 3O-$C_{12}$-HSL across cell membranes is driven by members of a large family of proteins, called the ATP binding cassette (ABC) transporter. For example, multidrug-resistant (MDR) efflux pumps, such as MexAB-OprM and MexGHI-OpmD, are involved in the active traffic of 3O-$C_{12}$-HSL and PQS, respectively [91, 92]. MDR efflux pumps can furthermore extrude a wide range of substrates, not just antibiotics and toxic compounds, but also bacterial endogenous QS signal molecules, indicating that these membrane transporters are essential in bacterial pathogenesis and host-pathogen interactions. In human cells, the ABC transporter, ABCA1, was proposed to be involved in the active efflux of 3O-$C_{12}$-HSL. Thus, microarray analysis of the transcriptional response of human lung epithelial cells revealed that mRNA levels for several genes involved in xenobiotic metabolism and drug transport were increased after exposure to 3O-$C_{12}$-HSL [93].

### *IQGAP1 Is a Human Target for 3O-$C_{12}$-HSL*

In mammalian cells, long acyl chain AHL with an intact lactone ring are able to interact with phospholipids and diffuse across membrane systems, where membrane microdomains, such as caveolae and lipid rafts, may facilitate this process [94] via interactions with a sub-membrane organization of filamentous actin, actin-binding proteins, and anchoring membrane proteins. The overall plasma membrane fitness and the dynamic of these interactions, including those of the actin cytoskeleton, can influence the shape of microdomain compartments and the capacity of transport and receptor signaling [95]. The entry of 3O-$C_{12}$-HSL into the host cell across the plasma membrane is followed by interaction and colocalization with the IQ-motif-containing GTPase-activation protein (IQGAP1) and paralleled by phosphorylation of Rac1 and Cdc42 and essential changes in the actin cytoskeleton network (Fig. 2); these events also trigger alterations in human epithelial cell migration and wound healing [25]. IQGAP1 was identified as a human target for bacterial 3O-$C_{12}$-HSL using a pull-down approach with the biotin-conjugated 3O-$C_{12}$-HSL probe and mass spectrometry-based proteomic analysis [25] (Fig. 3a). IQGAP1 is a 189-kDa multidomain signaling protein involved in many important cellular processes and functions (Fig. 3b). It orchestrates diverse cytoskeletal rearrangements and cell signaling events for cell cycle, polarization, migration, and adhesion, for example [96]. IQGAP1 localizes at the plasma membrane in the leading edge of migrating cells, in the cytoplasm and also at the cytoplasmic face of the nuclear envelope [97]. IQGAP1 interacts with a variety of proteins, including actin, calmodulin, Rac1, Cdc42, β-catenin, E-cadherin, myo-

sin, exocyst, ERK, MAPK, and mTOR [96, 97]. Using a fluorescent dye-conjugated 3O-$C_{12}$-HSL probe (Fig. 4a) and nanoscale super-resolution microscopy (Fig. 4b), it was demonstrated that 3O-$C_{12}$-HSL colocalizes with and targets IQGAP1 to modulate the migration of human epithelial cells [25].

*Recognition of 3O-$C_{12}$-HSL by Sensory and Nuclear Receptors*

The *P. aeruginosa* 3O-$C_{12}$-HSL activates and associates with the chemosensory G-protein-coupled receptor T2R38 (Fig. 2) on leukocytes of different origins [98, 99]. Still, the role of sensory receptors in innate immunity processes and others beyond the taste is not fully resolved. *P. aeruginosa* 3O-$C_{12}$-HSL may also bind to nuclear peroxisome proliferator-activated receptors (PPAR) to modulate DNA binding activity and transcription of NF-κB-dependent genes (Fig. 2) [100].

Thus, by passing through the plasma membrane in host cells, 3O-$C_{12}$-HSL can associate and target several membrane-associated proteins, which promote interactions with intracellular molecules and signaling cascades, and further with RNA and DNA processes in eukaryotic cells.

## *P. aeruginosa* 3O-$C_{12}$-HSL Regulates an Ensemble of Host Functions

During the last 2 decades, many investigators have indeed shown that *P. aeruginosa* 3O-$C_{12}$-HSL has multiple effects on mammalian cells and acts via different signaling pathways (Fig. 2), and the recent advances have been reviewed [101, 102].

*Inflammatory Response*

Earlier studies were focused on the role of *P. aeruginosa* 3O-$C_{12}$-HSL in modulation of innate and adaptive immune responses and inflammatory signaling. It affects both pro- and anti-inflammatory responses, inhibiting the production of cytokine TNF-α, IL-12 [20, 103–105], and increasing the secretion of interleukins, e.g. IL-6, IL-8 [106–109], IL-10 [103, 104, 109], and IL-1β [109]. In addition, 3O-$C_{12}$-HSL interferes with T cell proliferation [105] and blocks the differentiation of the Th1 and Th2 cells [110], which play important roles in the regulation of immune responses (Fig. 2). Transcriptome, systems biology, and network analyses revealed activation of multiple innate immune pathways in lung epithelial cells by 3O-$C_{12}$-HSL [93, 107].

*Host Transcription*

Moreover, 3O-$C_{12}$-HSL has been shown to be a strong activator of inflammatory response via the phosphorylation of MAPK (Fig. 2) and induction of transcriptional factor NF-κB signaling [106]. NF-κB is a major transcription factor that controls many genes, regulating both the innate and adaptive immune response during infections, and incorrect regulation of NF-κB may lead to the development of cancer, inflammatory, and autoimmune diseases. In the classical pathway, bacterial compounds (LPS, flagellin, lipoteichoic acid, RNA, or DNA) are recognized by TLR as specific membrane-bound pattern recognition receptors, which leads to NF-κB activation and targeted gene expression. However, 3O-$C_{12}$-HSL does not interact with TLR expressed on immune cells and thus likely activates host cells via the mechanism distinct from the TLR pathway [111]. It was later shown that 3O-$C_{12}$-HSL activates the ER stress transducer protein kinase RNA-like ER kinase (PERK), increases phosphorylation of the eukaryotic translation elongation factor eI-F2α leading to the selective translation and thereby affecting protein synthesis, particularly IL-8 [108]. 3O-$C_{12}$-HSL triggers the unfolded protein response and increases the expression of its certain target genes, being negatively correlated with LPS-induced NF-κB activation [112].

*Mitochondrial Physiology, Pro-Apoptosis, and Quorum Quenching*

The *P. aeruginosa* 3O-$C_{12}$-HSL also influences mitochondrial physiology [113, 114] by depolarizing the membrane potential and releasing mitochondrial cytochrome C into the cytosol; it was concluded that 3O-$C_{12}$-HSL has a pro-apoptotic effect via activating caspases 3/7 and 8 without the involvement of Bak/Bax [114]. Indeed, it appears to trigger apoptosis in certain types of cells, such as mouse and human fibroblasts, monocyte-, and neutrophil-like tumor cell lines [115]. Still, polarized human epithelial cells [25, 116] and human primary macrophages and neutrophils [101, 117] did not reveal any apoptosis-like changes after 3O-$C_{12}$-HSL-treatment. Maturity and polarization of epithelial sheets seem to protect them against the pro-apoptotic effect of 3O-$C_{12}$-HSL [116], but do not prevent loss of barrier integrity and repair capacity [25, 101]. Polarized epithelial monolayers, in contrast to nonpolarized cells, are also able to degrade 3O-$C_{12}$-HSL using membrane-associated paraoxonase 2 [116] that catalyzes the opening of the lactone ring but also has antioxidant activity and benefits mitochondrial function in the response to oxidative stress and facilitates the responses of the innate immune system. Inactivation

of AHL, or so-called quorum quenching by enzymes (Fig. 2), has also been described in cells of other origins, for example in bacteria, fungi, plants, and various mammalian cells. Different quorum-quenching strategies have been applied as promising tools in the areas of medicine, agriculture, and anti-biofouling [29].

*Calcium Signaling*

*P. aeruginosa* 3O-$C_{12}$-HSL initiates strong and rapid calcium signaling in neutrophils, fibroblasts, and epithelial cells [22, 24, 107, 118] (Fig. 2). $Ca^{2+}$ is a second messenger regulating many processes, being as diverse as gene transcription, muscle contraction, epithelial integrity, immune defense, cell motility, and phagocytosis. The calcium signaling proteome is tissue- and cell-specific and suited to a particular demand and function. In neutrophils and epithelial cells, 3O-$C_{12}$-HSL can induce calcium influx from intracellular stores such as ER and actin cytoskeleton relying on the inositol 1,4,5-triphosphate receptors (IP3R) [22, 24] (Fig. 2).

*Directional Cell Migration: Chemotaxis*

As a response to external cues, such as a soluble gradient of cytokines, growth factors, and bacterial traits, the host cell can initiate directional migration, also defined as chemotaxis, where a cellular steering system will guide the cell towards the higher concentration. Host cells can utilize different migratory patterns depending on cell morphology, cytoskeletal organization, cell-extracellular matrix interaction, and extracellular stimuli [119]. During migration, the cell is polarized in the direction of motion, possessing leading and trailing edges, blebbing, wide and thin membrane protrusions, the lamellipodium and small finger-like projections, the filopodia. Within the human body, we can define single cell and multicellular, collective migration (Fig. 2); both can be modulated by *P. aeruginosa* 3O-$C_{12}$-HSL [25, 101], which we will discuss more below.

*Single Cell Migration*

Rapidly moving cells, such as neutrophils, macrophages, and fibroblasts, utilize the pattern of single cell migration. They can either crawl in the amoeba manner (neutrophils) or move in the mesenchymal mode, utilizing a multistep cycle of protrusion, adhesion, and retraction (fibroblasts, macrophages) [119]. Human neutrophils and macrophages are fast-migrating phagocytes controlling inflammation and infection at the very early contact with bacteria. Thus, *P. aeruginosa* 3O-$C_{12}$-HSL and 3O-$C_{10}$-HSL, but not $C_4$-HSL, strongly promote their chemotaxis [24, 101, 120] and increase phagocytic capacity in a dose-dependent manner [101, 121]. Moreover, *P. aeruginosa* with a complete QS system elicits a more intensive phagocytosis in macrophages than the *lasI/rhlI* mutant lacking both 3O-$C_{12}$-HSL and $C_4$-HSL [23]. Both chemotaxis and phagocytosis require rapid changes in cell size and morphology driven by homeostasis and the transport of ions and water across the membrane via water channels called aquaporins (AQP). Thus, 3O-$C_{12}$-HSL enhances the cell area, volume, protrusive activity, and AQP9 expression and structural dynamics in moving macrophages [117]. Furthermore, AQP, together with ion channels and other transporters, mediate the influx of ions and water across the cell membrane (Fig. 2); water creates an increased local intracellular hydrostatic pressure [122], which forces the membrane to extend, allowing the polymerizing actin cytoskeleton to fill the protrusion and promotes cell migration [117, 123, 124]. AHL causes filamentous actin accumulation in the leading edge of migrating phagocytes, as regulated by calcium signaling, activation of phospholipase Cγ1, and the Rho family of small GTPases, such as Rac1 and Cdc42 [24, 101], which also control the formation of membrane protrusion activity. Through these mechanisms, leukocytes can quickly migrate to the site of AHL and mount a more effective phagocytosis of bacteria. However, in contrast to the stimulatory effect on macrophages and neutrophils, 3O-$C_{12}$-HSL has been shown to suppress chemotaxis, degranulation, and cytokinesis in mast cells [125], key effectors of allergic processes. Thus, the interactions between QS signals and innate immune cells are rather complex, and while 3O-$C_{12}$-HSL is recognized as a stimuli for macrophages and neutrophils, mast cells are likely targets for its suppressive action and may contribute to the pathogenicity of *P. aeruginosa* and its ability to avoid host defense.

*Multicellular Migration*

Multicellular migration, like epithelial sheet migration, occurs in the processes such as wound healing and renewal of epithelial cell monolayers in the skin and the gut (Fig. 2). This type of directional locomotion is highly influenced by the fitness of the whole epithelial sheet: differences in morphology, dynamics of cellular junctions, and abilities to respond to the external cues surrounding cells [119]. *P. aeruginosa* 3O-$C_{12}$-HSL, but not $C_4$-HSL, induces loss of barrier integrity and disruption of TJ and AJ complexes associated with actin cytoskeleton (Fig. 2) in polarized intestinal [101, 126] and airway epithelial cells [116]. These processes are being affected by calcium-dependent signaling [22], the MAPK cascade [127], and

activation of metalloproteases via protease-activated receptor (PAR) and lipid rafts [126]. TJ and AJ are multiprotein complexes composed of many transmembrane and cytoplasmic proteins associated with cytoskeleton, transport proteins, and a variety of regulatory and signaling proteins. TJ and AJ complexes include, for example, occludin-zonula occludens (ZO), cadherin-catenin, claudin-ZO, and occludin-tricellulin. 3O-$C_{12}$-HSL-induced perturbation in barrier integrity was associated with changes in the phosphorylation status of TJ and AJ proteins [22, 128]. Being highly dynamic structures, cell junctions can alter barrier integrity and permeability upon a broad variety of stimuli, including immune cells, bacteria, cytokines, toxins, and oxidative stress. Normally and after an injury, the epithelial sheets undergo a process of renewal and wound healing, which are dependent on the balance of collective cell migration, proliferation, and differentiation [3]. *P. aeruginosa* 3O-$C_{12}$-HSL, encoded by the *lasI* gene, modulates wound healing in a dose-dependent manner in an in vitro model of polarized human epithelial cells [25] and rat in vivo model of skin sheets [129]. Low doses of short fatty acid molecule $C_4$-HSL, encoded by the *rhlI* gene, also promote wound healing, which was paralleled with cyclooxygenase-driven neutrophils infiltration [130]. As in cases of phagocyte activity, 3O-$C_{12}$-HSL induced an increase in epithelial sheet migration that was also associated with activation of the Rho family of small GTPases and actin cytoskeleton reorganization [25].

In summary, research over recent decades has suggested that *P. aeruginosa* 3O-$C_{12}$-HSL signals, through different mechanisms, can interfere with RNA and DNA processes, protein synthesis, calcium signaling, homeostasis, and mitochondrial and cytoskeletal dynamics in host cells (Fig. 2). In these ways, *P. aeruginosa* communication via 3O-$C_{12}$-HSL can perturb an ensemble of important cellular processes in the host, such as cell morphology, proliferation, differentiation, and apoptosis, and thereby many biological activities and functions.

## Conclusion and Outlook

Our knowledge about the cellular and molecular mechanisms involved in bacteria-host crosstalk is constantly expanding. In this review, we have discussed how *P. aeruginosa* use QS systems to regulate its virulence, biofilms, and metabolic demands, and thereby promote infection in a host (Fig. 1). We have also addressed the role of *P. aeruginosa* AHL-dependent QS signaling in the modulation of a diverse array of host functions with a focus on innate immune responses via different targets and mechanisms (Fig. 2). Interference with QS, termed quorum quenching, is a new and promising avenue to combat bacterial pathogenicity and biofilm formation, and thereby enlarge the therapeutic arsenal against bacterial infections and reduce the rate of antibiotic resistance. This naturally occurring strategy has been extensively studied and reviewed by many researches [28, 29]. Further breakthroughs will require multidisciplinary tools to investigate the consequences of host-microbe interactions and insights from both pathogen and host perspectives.


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## Disclosure Statement

The authors have no conflicts of interest to declare.

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