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Quorum sensing is a language of chemical signals and plays an ecological role in algal-bacterial interactions

Jin Zhou[a], **Yihua Lyu**[b,§], **Mindy Richlen**[c], **Donald M. Anderson**[c], and **Zhonghua Cai**[a]

[a]The Division of Ocean Science and Technology, Graduate School at Shenzhen, Tsinghua University, Shenzhen, 518055, P. R. China

[b]South China Sea Environment Monitoring Center, State Oceanic Administration, Guangzhou, 510300, P. R. China

[c]Department of Biology, Woods Hole Oceanographic Institution, 266 Woods Hole Rd., MS 32, Woods Hole, Massachusetts, 02543, USA

Abstract

Algae are ubiquitous in the marine environment, and the ways in which they interact with bacteria are of particular interest in marine ecology field. The interactions between primary producers and bacteria impact the physiology of both partners, alter the chemistry of their environment, and shape microbial diversity. Although algal-bacterial interactions are well known and studied, information regarding the chemical-ecological role of this relationship remains limited, particularly with respect to quorum sensing (QS), which is a system of stimuli and response correlated to population density. In the microbial biosphere, QS is pivotal in driving community structure and regulating behavioral ecology, including biofilm formation, virulence, antibiotic resistance, swarming motility, and secondary metabolite production. Many marine habitats, such as the phycosphere, harbour diverse populations of microorganisms and various signal languages (such as QS-based autoinducers). QS-mediated interactions widely influence algal-bacterial symbiotic relationships, which in turn determine community organization, population structure, and ecosystem functioning. Understanding infochemicals-mediated ecological processes may shed light on the symbiotic interactions between algae host and associated microbes. In this review, we summarize current achievements about how QS modulates microbial behavior, affects symbiotic relationships, and regulates phytoplankton chemical ecological processes. Additionally, we present an overview of QS-modulated co-evolutionary relationships between algae and bacterioplankton, and consider the potential applications and future perspectives of QS.

Keywords

phytoplankton; bacterioplankton; signal language; algal-bacterial relationships; co-evolution; ecological behaviors

Address correspondence to Zhonghua Cai, Graduate School at Shenzhen, Tsinghua University, Shenzhen University Town, Xili Town, Shenzhen City, 518055, Guangdong Province, P. R. China. caizh@sz.tsinghua.edu.cn.

[§]These two authors contributed equally to this work.

I. INTRODUCTION

Microbes comprise around $3.5–5.5\times10^{17}$ g carbon or $4.0–6.0\times10^{30}$ cells, which accounts for approximately half of the total biomass of living organisms on Earth (Whitman *et al.*, 1998). Most microorganisms are found in the ocean, including bacteria, archaea, fungi, and some algae. These organisms drive oceanic energy fluxes process (Falkowski *et al.*, 2008), which in turn influence their diversity and interactions (Strom, 2008). Marine microbes are critical for the biogeochemical cycling of elements due to their abundance, taxonomic diversity, and high potential metabolic activity (Azam and Malfatti, 2007). Marine algae, which are autotrophic and free-living aquatic plants, mediate primary production in the ocean, half of which are transformed into dissolved organic matter that is available for use by heterotrophic prokaryotes (Azam and Malfatti, 2007). Algae consumed by higher eukaryotes supply nourishment to microbial loop through algal exudates/decomposition, thus providing the base of the food web (Carrillo *et al.*, 2006). In addition, algae have high photosynthetic efficiency, and diatoms alone account for approximately 20% of global photosynthesis (Rosenwasser *et al.*, 2014). Consequently, algae play various ecological roles, including the cycling of organic matter (Armbrust, 2009), and help reduce the impact of global warming (Sayre, 2010).

Marine ecosystems are based on multiple interactions among organisms, which may be competitive, mutualistic, parasitic, or symbiotic. Due to the importance and pervasiveness of marine algae, there has been strong scientific interest in elucidating algal-bacterial interactions. Previous studies have focused on the biological, environmental, and physical aspects of these various types of interactions; however, few studies have investigated the role chemical signaling, largely because the field of marine chemical ecology is relatively new (Hay, 2009). Recent evidence shows that the regulation of behavior by chemical signals is not restricted in bacteria, but was also found between microorganisms and their hosts (Freestone, 2013). An example of this activity was proposed by Long *et al.* (2007), who suggested that under symbiotic conditions, small molecules might regulate the colony formation of the phytoplankton *Phaeocystis globosa* by altering energy flow, nutrient release, and carbon sequestration patterns. Hughes and Sperandio (2008) further noted that individual bacteria can alter their behaviour through chemical interactions between organisms in microbial communities, and these communications often occur at scales much bigger than traditionally recognized because of the organisms' ability to respond to surrounding signals. Thus, in addition to affecting the behavior of both individuals and populations, chemical cues might also affect community organization and ecosystem functioning (Hay, 2009).

Quorum sensing (QS) is a common form of chemical signaling receiving increasing attention from marine ecologists. QS occurs within microbial populations in a density-dependent manner (Bassler, 2002), causes downstream changes in gene regulation, and modulates many biological functions such as bioluminescence, virulence factor expression, biofilm formation, sporulation, and bacterial conjugation (Waters and Bassler, 2005; Mangwani *et al.*, 2012). To date, three main QS systems have been described (Table 1): (i) the *LuxR/I*-type system, (ii) the *LuxS*/AI-2 system, and (iii) the AI-3/epinephrine/norepinephrine system. The *LuxR/I*-type system uses acyl-L-homoserine lactone (AHL) as

an autoinducer, and is predominantly used by gram-negative (G^-) bacteria. The *LuxS*/*AI-2* system uses peptide substances as the signal for interspecies communication, and is primarily used by gram-positive (G^+) bacteria. The AI-3/epinephrine/norepinephrine system facilitates signaling among kingdoms. These systems allow bacteria to communicate across species boundaries or involved in interkingdom signaling. Taken G^- bacteria as an example, Figure 1 shows the molecular formation mechanisms of QS and subsequent cascade response process.

In marine microbiological field, previous studies have shown that many bacteria (*Vibrio* sp., *Ochrobactrum* sp., *Shewanella* sp., and *Alteromona*s sp.) possess autoinducer synthases and enable them to produce AHLs (Case *et al.*, 2008; Cuadrado-Silva *et al.*, 2013). These AHL molecules can regulate bacterial behavior and exhibit various ecological functions. Some bacteria belonging to the genera *Vibrio, Shewanella,* and *Sulfitobacter* synthesized or degraded AHLs and modulated the zoospore settlement of their host (*Ulva* sp.) (Tait *et al.*, 2009). In the oligotrophic North Pacific Ocean, blue-green alga (cyanobacterium) *Trichodesmium consortia* regulate alkaline phosphatase activity and control phosphorus acquisition by secrete AI-1 and AI-2 signals (Van Mooy *et al.*, 2012). Hmelo *et al.* (2011) reported that the addition of particulate organic carbon (POC) containing AHLs to bacterial cultures enhanced the functioning of bacterial hydrolytic enzymes involved in POC degradation, and suggested that there might be a link between hydrolytic enzymes and QS. Jatt *et al.* (2015) further identified six AHL signals (i.e. C4-HSL, 3OC6-HSL, C6-HSL, C10-HSL, C12-HSL and C14-HSL) from marine snow, and found that addition of exogenous AHLs enhanced the extracellular hydrolytic enzyme in *Pantoea ananatis* B9. They pointed out that AHL-based QS system could be involved in biosynthesis of extracellular alkaline phosphatase in *P. ananatis* B9. These studies indicated that QS was an important modulator to regulate the ecological functions of marine plankton by affecting related gene or protein expression. Besides these, in recents years, chemical mediators of QS and molecular crosstalk between bacteria and eukaryotes have been described in a wide range of symbiotic organisms (Pacheco and Sperandio, 2009), broadening our understanding about certain multi-species interactions.

In algal-bacterial microenvironments, chemical-mediated processes under natural conditions are not well known. Furthermore, information remains limited about the intercellular signaling that occurs during interactions between algae and associated microbes. In this review, we focus on the recent achievements in QS signals and discuss their ecological functions in symbiotic interactions between algae and bacteria. The aim is to expand current knowledge about algae-bacteria relationships from microsociological prespective.

II. THE PHYCOSPHERE

Bell and Mitchell (1972) coined the term “phycosphere” in microecology to describe the region that extends outward from an algal cell, chain, or colony of cells “in which bacterial growth is stimulated by algal exudates.” The phycosphere is analogous to the rhizosphere (where nutrients pass between the soil and roots), influencing the nutrient fluxes entering and exiting algal cells (Fig. 2). Within this microzone, planktonic bacteria are highly heterogeneous. Furthermore, ingestion, digestion, egestion, excretion, and exudation by

other marine organisms create habitats characterized by the frequent and pervasive occurrence of microscale chemical gradients (Stocker and Seymour, 2012). Marine phytoplankton release substantial amounts of amino acids, simple sugars, complex polysaccharides, organic acids, and lipids into the phycosphere area (Jones and Cannon, 1986); similarly, bacteria generate organic and inorganic substrates that are used by host cells (Doucette, 1995). For example, cobalamin (or vitamin B_{12}) cannot be synthesized by phytoplankton, but is an essential nutrient produced by bacterial communities associated with unicellular algae (Tang *et al.*, 2010). Phytoplankton thus benefit by acquiring micronutrients from bacterial metabolism, which forms the basis of the symbiotic relationship between phytoplankton and bacteria (Geng and Belas, 2010). Positive consequences of this relationship include nutritional contributions, biological matter cycling, and creation of an ecological niche for symbiotic taxa. Conversely, harmful results include competition between taxa, the generation of harmful compounds, and deleterious metabolic impacts. Thus, the phycosphere serves as a hot spot for algal-bacterial communication, in which the diffusive surrounding microzone is a dynamic and fluid environment containing many different types of chemical fluxes (Fig. 2). Notably, some chemical signals, such as those involved in allelopathy and QS, are vital for constructing the heterogeneous and dynamic environment of the phycosphere that creates a harmonious microcommunity.

III. QS COMMUNICATION IN SYMBIOTIC ENVIRONMENTS

Various methods of communication exist within the symbiotic environments of bacteria and algae, including interbacterial and interalgal communication, and interkingdom signaling. Understanding how these two groups of organisms communicate may enhance our understanding about their behavioral ecology within phycospheres.

A. Bacterial intercellular communication

Many marine bacteria, such as proteobacteria, produce QS chemicals and participate in ecological processes. Bacteria from the *Roseobacter* clade (which often co-occur with algae) regulate primary metabolic processes through AHL molecules (Wagner-Dobler and Biebl, 2006). QS-based AHL contributes to the regulation of extracellular hydrolytic alkaline-phosphatase activity and is responsible for the degradation of sinking POC (Jatt *et al.*, 2015); the authors speculated that variability in AHL-triggered POC hydrolysis might have a profound effect on marine food webs. Other chemical compounds (like five or six-membered ring structures with attached lipophilic carbon chains) also exhibit interkingdom signaling activity in prokaryotic and eukaryotic systems (Gerwick *et al.*, 2013). Amin *et al.* (2015) unraveled a bacterial consortium associated with a globally distributed diatom, and showed that one sulfitobacter species promotes diatom cell division via the secretion of the hormone indole-3-acetic acid. This study provided evidence that these interactions are mediated through the production and exchange of infochemicals. Therefore, QS has multiple effects on bacterial behavior, and facilitates communication among bacterial species and with other organisms (Bassler, 2002).

B. Interalgal communication

Eukaryotes use a variety of signaling molecules for different physiological processes; however, compared to bacteria, information about algal cell signaling remains limited. Thus far, molecules identified to be involved in signaling include phosphorlipids, flavonoids, indole-3-acetic acid, and quorum substrates (Van Leeuwen *et al.*, 2004; Sprague and Winans, 2006; Hassan and Mathesius, 2012; Amin *et al.*, 2015). The most commonly used signaling processes by algae are allelochemicals and QS. Allelochemicals are primarily secondary metabolites that influence the survival, reproduction, and/or growth of algae (Graneli and Pavia, 2006). These allelopathic interactions have several critical roles in regulating the concentration and distribution of the target species, cell defense, and in nutrition procurement (Inderjit *et al.*, 2011). Allelopathy also regulates the toxin production in some algal species, including *Alexandrium* spp. and *Prymnesium* spp. (Weissbach *et al.*, 2011), and thus may help improve microalgal cultivation (Mendes and Vermelho, 2013).

Algae, particularly marine diatoms, also use the QS or structural analogues to regulate their own behavior. Among the QS analogues, pheromones were regarded as representative, since homoserine, fucoserratene, and ectocarpene were widely found in *Gomphonema parvulum, Asterionella formosa*, and *Skeletonema costatum*, respectively. These molecules mediate the sexuality and reproductive behavior of algae (Derenbach and Pesando, 1986; Pohnert and Boland, 1996; Hombeck and Boland, 1998). Other representative signaling molecules are hypothesized to function as infochemicals for green algae and diatoms. Examples of such substances include nitric oxide (NO) and 5,6-membered ring molecules (laurenciones, malyngamides, and honaucins). These signals can recruit cells to mount anti-oxidant or anti-inflammatory responses for protection against stress-induced cellular damage (Vardi *et al.*, 2008; Gerwick *et al.*, 2013). Though self-modulation of homeostasis and physiologyical responses via chemical cues in algae are evident, as discussed above, how the different signaling molecules secreted by algae, and their importance in intercellular interactions remain unknown. Futher efforts are of great urgent.

C. Interkingdom signaling

Interkingdom signaling in marine has only recently become an area of scientific interest. To date, research has primarily focused on bacteria, with limited focus on algae (Amin *et al.*, 2012). Crosstalk between bacteria and algae has only been confirmed over the last decade (Bauer *et al.*, 2005; Steinberg *et al.*, 2011; Amin *et al.*, 2015). At present, three types of interkingdom signaling molecules/mechanisms have been reported. First, lipid-based molecules commonly used in bacteria and algae, with poor solubility in aqueous conditions, which allows them to cross cell membranes freely in an energy-independent manner. Second, a certain structureally conserved molecules with related properties between the 3D structures and the functional domains of their regulators (Vannini *et al.*, 2002). Third, bacterial QS molecules and algal pheromones (particularly in diatoms) with similar structures and functionality, which may facilitate their use as crosstalk signals between species. Hughes and Sperandio (2008) reviewed the third form of interkingdom signaling in terrestrial environments, and demonstrated both beneficial and detrimental interactions between eukaryotes and prokaryotes. It speculates that this form of signaling may have similar roles in aquatic environment (Decho *et al.*, 2011).

1. Eukaryotic response to bacteria—Algae have developed the ability to sense bacterial QS signals, and have evolved multiple mechanisms for interpreting these QS signals to initiate physiological responses (Teplitski *et al.*, 2004; Bauer *et al.*, 2005; Joint *et al.*, 2002, 2007). Amin *et al.* (2012) reported that two different bacterial species known to associate with diatoms could secrete different AHLs that enter and accumulate within host-body. It was proposed that once within the cells, these AHLs bind to their molecular targets, lead to different responses depending on whether the bacteria releasing the AHLs are symbiotic or algicidal. In addition to these molecule-dependent signaling regulatory mechanisms, algae also produce AHL mimics that can mislead or "confuse" bacteria (Hughes and Sperandio, 2008). QS signal exchange is required for co-existing hosts and bacteria to interact. The crosstalk of QS between bacteria and algae suggests that interkingdom sensing is widespread in marine environment.

2. Bacterial response to eukaryotes—Accumulating evidence supports the concept that signaling is not limited to intercellular bacterial communication, but is also used by microbes and their hosts. In terrestrial environments, the photosynthetic bacterium *Rhodopseudomonas palustris* uses a plant metabolite (p-coumarate) to produce QS signal molecules (such as p-coumaroyl-homoserine lactone) (Schaefer *et al.*, 2008). This work further suggested that pC-HSL operates as both an intraspecies bacterial signal and as an interkingdom signal to host plants (Schaefer *et al.*, 2008). AHLs that influence the behavior of various algae-associated bacteria have also been detected in marine ecosystem. For example, in the red alga *Gracilaria chilensis*, AHLs produced by the epiphyte *Acrochaetium* sp. control spore release (Weinberger *et al.*, 2007). Subsequent research showed that 12% of *Acrochaetium* sp. strains found on the brown alga *Coplomenia sinuosa* inhibited QS production of the host alga (Kanagasabhapathy *et al.*, 2009). These algal epibiotic bacteria may play an important role in the defensive mechanisms of their host by producing QSI or QSI-like compounds to suppress the settlement of other competitive bacteria. The foregoing examples suggest that bacteria and eukaryotes are able to sense one another's signaling compounds under certain conditions. Identifying these substances and their molecular targets could improve our understanding of QS-based cross-talking in algae-bacteria symbionts (Zhou *et al.*, 2014).

IV. ECOLOGICAL FUNCTIONS OF QS DURING ALGAL-BACTERIAL INTERACTIONS

Interactions between algae and bacteria do not occur in isolation. Specific organisms may be affected at certain times, based on the ratio between different ongoing stimulatory and inhibitory processes (Cole, 1982). Furthermore, the turbulence of marine environment makes life in the phycosphere substantially different to life in the terrestrial soil rhizosphere. Robust and efficient mechanisms are thus required to mediate the complex ecological relationship between algae and bacteria. As our understanding of QS signals improves, researchers are increasingly recognizing their role as intelligent cues. In the next section, we will discuss how QS affects certain algae and/or bacteria physiological features, such as nutrient acquisition, biofilm formation, ecological niche construction, and self-motility.

A. Nutrient acquisition

1. Carbon resources—Phytoplankton can provide a variety of carbon resources to heterotrophic bacteria, especially the dissolved organic carbon (DOC). There is a close link between DOC features (biomass and types) and bacterial diversity in the phycosphere. Amin *et al.* (2012) reported that different DOC compounds produced by diatom could regulate the microbial communities of associated symbionts. Among the DOCs, a typical example is glycolate (a type of water-soluble, low molecular weight compound). To some extent, glycolate can shape the structure of bacterial communities through the glycolate-producers in response to diatomic signaling molecules (Haynes *et al.*, 2007). Bacteria may sense these signals, enhancing their ability to assimilate glycolate. In symbiotic environments, only bacteria that have the glycolate utilization gene *glcD* benefit from associations with glycolate-releasing phytoplankton (Lau and Armbrust, 2006). These bacteria use QS molecules to regulate their density and improve their ability to assimilate glycolate before it diffuses away or is consumed by competing *glcD*-containing bacteria (Leboulanger *et al.*, 1997). For instance, during spring phytoplankton blooms, *glcD* transcripts increase when glycolate production peaks over the diel cycle (Lau *et al.*, 2007). As a result, bacteria may respond to QS signals by modulating organic carbon metabolism based on glycolate availability.

2. Nitrogen resources—Nitrogen-fixing bacteria are critical in the nitrogen cycle because they convert dinitrogen gas into more available forms, such as ammoniacal-nitrogen. In leguminous plant, QS intercedes in the signal exchange process and may play a role in coordinating the nitrogen-fixing rhizobia during the establishment of the symbiosis (González and Marketon, 2003). In aquatic plants, some green algae such as *Caulerpa taxifolia* and *Codium fragile* capitalize on the nitrogen fixation capabilities of associated bacteria to support their invasion in oligotrophic environments (Chisholm *et al.*, 1996). Wyss (2013) recently reported that bacteria use a quorum-sensing-like mechanism to sense algal culture density in *Chlorella vulgaris,* and repress nitrogen fixation gene expression at high algal culture density to deprive the algae of bioavailable nitrogen. Although the available examples are still limited, the knowledge obtained so far provides a foundation for understanding the role of QS in regulation of genes involved in nitrogen metabolism during host-bacterium interactions.

3. Sulfate resources—In addition to macronutrients, important microelements are also present in the phycosphere, such as dimethylsulfonio-propionate (DMSP), which is a major source of organic sulfur produced by dinoflagellates (Moran *et al.*, 2003). DMSP is the favored source of reduced sulfur for bacteria from the *Roseobacter* clade, even though it is present at 10^7-fold lower concentrations than sulfate in seawater (Raina *et al.*, 2009). Flagella have been shown to enable chemotaxis towards DMSP in some *Roseobacter* members, which prompted Belas *et al.* (2009) to suggest a link between this observed phenotype with QS substances. Geng and Belas (2010) further pointed out that DMSP exchange between *Roseobacter* and dinoflagellates involves a *vir*-gene-mediated Type 4 secretion system (T4SS) and/or QS by certain chemicals.

Another important micronutrient is tropoditheietic acid (TDA). TDA is a dual-sulfultropolone produced by oxidative ring expansion of phenylacetic acid via the shikimate-chorismate pathway (Geng *et al.*, 2008; Geng and Belas, 2011). TDA prevents algicidal bacteria from damaging phytoplankton, and boosts symbiosis with *Roseobacter* by reducing competition with other species. In dinoflagellates, the associated bacterium *Silicibacter* sp. TM1040 produces TDA in a population density-dependent manner. Although TM1040 does not produce canonical AHL signals, molecular analysis revealed that other chemicals may replace AHLs in TM1040 (Geng and Belas, 2010, 2011), thus providing the link between QS and the observed phenotype (i.e. signal molecules participate in the regulation of TDA synthesis).

4. Iron resources—Marine microbial communities and structures are often regulated by the availability of iron, which is necessary for photosynthesis and respiration (Coale *et al.*, 1996). Dissolved iron is present at an extremely low concentrations in seawater (10^{-10}–10^{-9} moles kg^{-1}) (Geider, 1999), and in some open ocean regions these low concentrations can limit primary productivity and bacterial growth (Tortell *et al.*, 1999). In the last decade, iron acquisition has been a major focus of studies on algal-bacterial interactions because its scarcity in the marine environment has driven the evolution of numerous nutrient acquisition strategies in bacteria (Boyd and Ellwood, 2010). One strategy used by marine bacteria is the production and secretion of siderophores, which bind to iron, and thus increases its solubility (Vraspir and Butler, 2009). Bacteria then reacquire soluble Fe(III)-siderophore complexes by using specific outer-membrane transporters.

Unlike bacteria, eukaryotic phytoplankton that produce siderophores, or that directly take up bacterially derived Fe(III)–siderophore complexes, have not yet to be identified up to now. However, phytoplankton may obtain iron by using QS signaling to regulate the siderophore biosynthesis in siderophore-producing bacteria, and quickly mobilize iron assimilation mechanisms (Amin, 2010). There is also genomic evidence that some phytoplankton obtain iron from siderophores or other chelates using ferrireductase and cell-surface Fe (II)-transporters (Kustka *et al.*, 2007). This dynamic process modulated by QS indicates that the regulation of QS signaling is ecologically driven. In addition, AHLs from QS may also be involved in iron uptake in algal populations. Different algal species use different forms of iron, often complexed with siderophores. In contrast, diatoms use iron complexed with porphyrins (Hutchins *et al.*, 1999).

B. Biofilm formation and ecological niche construction

Algae are coated with specific communities of bacteria, fungi, protozoa, and other eukaryotes. In these epiphytic communities, “biological films” (or biofilms) are among the most common. The primary bacterial phyla participating in algal biofilm formation include proteobacteria (alpha-, beta-, and gamma-type), nitrospira, actinobacteria, acidobacteria, and firmicutes (Souza-Eqipsy *et al.*, 2008). These “microepibionts” are multi-functional, and are involved in obtaining nutrients, acquiring new genetic traits, and providing some measure of chemical defense against pathogens (Wahl *et al.*, 2012).

Biofilms are chemically mediated. The communication, construction, and breakdown of many algal biofilms are regulated by the symbiotic microbial QS system, which helps to control film formation, development, maturation, and dispersal (Parsek and Greenberg, 2005). Algae are phylogenetically and morphologically diverse organisms that often host multiple species in the stereoscopic biofilms on their surfaces. Diverse bacteria live within the biofilm; however, these bacteria are not randomly distributed among different algal species. Each algal species hosts and supports bacterial communities with different species compositions, and the same algal species tends to host the same bacterial community, even in different environments (Lachnit *et al.*, 2009; Trias *et al.*, 2012). This phenomenon may occur because the host species may have markedly different spatial environments, physiological states, and chemical factors (including QS metabolites), which determine the composition of the associated bacterial community. AHLs and their inhibitors influence the behavior of various biofilm-associated bacteria, confirming that marine epibiotic communities produce and use QS in signaling (Maximilien *et al.*, 1998). Thus, it is important to determine the functional consequences and gene expression patterns associated with QS in biofilm communities, which will improve our understanding about the structure and function of “ecological biofilms”.

Biofilm also promote the construction of algal ecological niches. Newly generated bacteria or algae must locate suitable sites for colonization, which is a critical stage in the life cycle. Settlement takes place in three steps: contact, temporary adhesion, and irreversible adhesion (Fletcher and Callow, 1992). It is well-known that biofilms provide niches for new colonizers, and enables bacteria to coordinate and respond quickly to environmental changes. Over time, biofilm structure matures to reflect the cooperative division of labor in which multiple cells undergo specialization leading to complementary and synergistic behaviors (Chen, 2013). Meanwhile, mature biofilms modulate bacterial settlement by regulating the flow of energy and matter across the host surface, thus altering its chemical properties (Davey and O’toole, 2000). Ecologically, the concept of modulating bacterial settlement to occupy an appropriate niche represents a fascinating evolutionary strategy, as it provides a competitive advantage in addition to regulating the associated microbial community (Hentschel *et al.*, 2001). Biofilms also regulate algal larval colonization by modifying the surfaces of potential settlement sites, as well as through the molecular signaling. In recent years, some studies have demonstrated that biofilms provide ideal sites for the metamorphosis of coralline algae (Tebben *et al.*, 2011), release of diatoms (Zargiel and Swain, 2014), and swarming of dinoflagellates (Alagely *et al.*, 2011).

The selection of colonization sites and associated behaviors are QS mediated (Joint *et al.*, 2007). In some marine species, signal substances affect multiple life cycle functions, such as contributing towards the initiation of *Hydroides elegans* larval colonization with C6-, C12-, and 3-oxo-C8-HLS (Huang *et al.*, 2007), promoting spores release with C4-HLS (Weinberger *et al.*, 2007), and providing protection to algal surfaces with polybrominated 2-heptanone (Nylund *et al.*, 2008). Certain examples of QS-mediated behaviors in microalgae are also implied. In the planktonic life-phase of two bacteria, *Pseudomonas* spp. and *Rhizobium* spp. (isolated from *Botryococcus braunii*), short chain AHLs (C4 or C6) were detected during biofilm formation (Rivas *et al.*, 2010). Seven long-chain AHL producers (*Psychrobacter cryohalolentis*, *Providencia sneebia*, *Pseudomonas stutzeri*, *Exiguobacterium*

sp. AT1b, *Klebsiella oxytoca*, *Lysinibacillus sphaericus and Acinetobacter baumannii*) isolated in our lab could promoter or inhibit *Scrippsiella trochoidea* growth (Lv *et al.*, 2016).

In some cases, QS molecules could prevent certain bacteria from occupying certain niches. Algae reduce the harmful effects of bacterial overpopulation by interfering with bacterial QS systems controlling bacterial colonization through regulating biofilm formation (Steinberg *et al.*, 1997; Dworjanyn *et al.*, 1999). Some algae are able to stimulate, inhibit, and/or inactivate QS signals in bacteria by producing QS inhibitors or their analogues. The best-investigated example is that of an Australian red alga, *Delisea pulchra*, which produces metabolites known as halogenated furanones. These molecules interfere with AHLs through competitive inhibition at the *LuxR*-type receptor site, and selectively inhibits bacterial colonization and biofilm formation on algal surfaces (Mclean *et al.*, 2004). Other bacteria and eukaryotes produce dipeptides that act as AHL mimics. For example, AHL mimics affect QS-regulated behaviors (like biofilm formation) in the genus *Vibrio* (Dickschat, 2010). These examples suggest that QS and QS-related molecules may help balance the niche of symbionts and the stability of their habitats.

C. Self-motility

Because bacteria live in diverse areas, they often need to migrate to favorable environments to acquire nutrients and information, and use a variety of strategies to find and exploit advantageous niches. Various molecular processes drive migration, including phototaxis (response to light), thermotaxis (response to temperature), aerotaxis (response to oxygen), and chemotaxis (response to chemical cues) (Gluch *et al.*, 1995; Paerl, 1996). The most common and best studied of these migratory processes is chemotaxis. Chemotaxis allows bacteria to swim toward ideal conditions, thus providing bacteria with a competitive advantage in obtaining nutrition in natural environments (Wadhams and Armitage, 2004). Early work on chemotaxis in marine bacteria also suggested that this ability is a critical component of bacterial-phytoplanktonic interactions. To date, microfluidic visualized methods have been used to demonstrate that marine bacteria use chemotaxis to respond to chemicals released by certain phytoplankton, including *Pfiesteria piscicida*, *Dunaliella tertiolecta*, and *Thallassiosira weissflogii* (Miller and Belas, 2006; Stocker *et al.*, 2008; Seymour *et al.*, 2008, 2009). Marine bacteria may even use chemotaxis to track swimming phytoplankton cells (Barbara and Mitchell, 2003). For instance, *Pseudoalteromonas haloplanktis* and *Shewanella putrefaciens* bacteria respond to nutrient or oxygen gradients released by phytoplankton, attaining high swimming speeds and exhibiting quick directional changes to reach them (Stocker and Seymour, 2012). DMSP and amino acids present in dinoflagellate homogenates are essential attractant molecules for the marine bacterium *Silicibacter* sp. (strain TM1040), and the bacterial motility is an important factor in the symbiosis between dinoflagellates and bacteria (Miller *et al.,* 2004; Miller and Belas, 2006). Genomic analyses further demonstrated that TM1040 contains genes that are necessary to sense and respond to chemical attractants (Moran *et al.*, 2007; Geng and Belas, 2010). More than half of the sequenced genomes of *Roseobacter* sp., which is another free-living bacterium found in phycospheres, contain homologs to known genes for chemotaxis and chemoreceptors (Slightom and Buchan, 2009). In addition, Thar and Fenchel (2001)

observed that free-swimming *Thiovulum majus* cells exhibit versatile chemotactic behavior, including both a phobic response and true chemotaxis in oxygen gradients.

Bacterial motility and chemotaxis are ecological behaviors that are partly regulated by social signals, such as QS, as well as other chemical signals. In terrestrial environments, the soil bacterium *Serratia liquefaciens* modulates swarming by using AHLs or their regulators (the gene *surR* or synthase *swrI*, which respond to C4- and C6 AHLs) (Lindum *et al.*, 1998). Researchers have also found that certain marine bacteria, including *Vibrio alginolyticus*, *S. putrefaciens,* and *P. haloplanktis*, exhibit "run-reverse-flick" and "run-reverse" swimming strategies to trigger biofilm formation. These movements affect chemotactic drift speed and responses to surrounding signals (Taktikos *et al.*, 2012, 2013). Daniels *et al.* (2004) suggested that QS mediates the swarming behavior of bacteria, with AHLs, diketopiperazines, and signal mimics causing the flagella-propelled movement of cells that are elongated, multinucleated, and hyper-flagellated.

In addition to modulating bacterial motility, QS also regulates the swimming ability of algal spores. Wheeler *et al.* (2006) demonstrated that QS-modulated biofilms use AHL-regulated chemokinesis to enhance algal motility, and that spore swimming speed was reduced by up to 27% and 47% within four minutes of adding 25 and 125 μmol L^{-1} of 3-oxo-C12-HSL, respectively. This effect was further enhanced by AHLs with long side chains (10–12 carbon atoms), which have low solubility in water (Yates *et al.*, 2002). The cellular mechanism involved in this chemokinetic effect involves an influx of Ca^{2+} in the spores, which alters the flagella-driven pattern of movement in a Ca^{2+}-dependent manner (Joint *et al.*, 2007). The resultant decrease in swimming speed may effectively increase the chances of locating suitable sites for settlement by spores.

D. Others (virulence and reproduction)

Signaling molecules also guide other physiological processes in algal-bacterial symbiosis, including virulence factor production and reproductive behavior. For instance, dinoflagellate-associated *Vibrio* spp. sense and respond to small signaling molecules produced by host organisms. This interspecies communication influences pathogenic virulence, bacterial development and host infectious processes (Tsim *et al.*, 1996). One example of this was provided by Natrah *et al.* (2011), who showed that microalgae *Chlorella saccharophila* and *Chlamydomonas reinhardtii* interfere with bacterial QS signals and reduce the virulence of the pathogen *V. harveyi*.

Reproductive parameters, such as diatom gametogenesis and cell division, are regulated by environmental chemical signals, with a similar effect to terrestrial pheromones. For instance, QS induces the switch from asexual to sexual reproduction in the centric diatom *Thalassiosira weissflogii* (Falciatore and Bowler, 2002). The timely formation of gametes is critical for the efficient operation of the phytoplanktonic sexual cycle. Using the Kolmogorov model, Peperzak (2006) speculated that QS regulates this process, whereby cells sense the number of conspecifics through the quantity of secreted secondary metabolites, and adjust the induction of gamete formation accordingly. Kouzuma and Watanabe (2015) suggested that bacteria secrete chemical signals (such as QS) to induce the morphogenesis and germination of algae. Hence, QS may regulate the switch to sexual

reproduction by phytoplankton at high population densities, along with the synchronization of sexual activities, such as encystment.

Therefore, QS signals are multi-functional modulators that regulate a variety of phenotypes in symbiotic relationships between phytoplankton and bacteria, primarily through three main cascading processes: i) QS molecule producion and transport in the bacterium cell; ii) microbial cross-talking (intraspecies and interspecies) by QS molecules; and iii) QS-mediated social behavior in algal-bacterial symbionts, including mutualistic, antagonistic, and commensalistic interactions (Fig. 3).

V. ANTAGONISTIC INTERACTIONS

In some of the more complex and dynamic symbiotic relationships, algal holobionts occur in close proximity to various species, including fungi, bacteria, and protozoa. These relationships may be both beneficial and deleterious. Thus, competition is widespread among bacteria, as well as between algae and bacteria. Antagonistic interactions between different species may be equally important for the initiation and establishment of symbiotic relationships (Filzgerald, 1969; Duval and Margulis, 1995).

A. QS modulates antagonism between bacteria

Dynamic equilibrium exists among various species in bacterial community structures. To maintain the structural stability of a population and ensure population success, bacteria use antagonistic strategies, including the secretion of secondary metabolites, which may be harmful or lethal to the target cells (Hibbing *et al.*, 2010). However, these metabolites may not be released at the concentrations necessary to produce toxic effects. Furthermore, the microbes secreting these molecules must deliver a toxic dose sufficiently high to be effective, while also minimizing subsequent self-exposure to potentially damaging toxin levels. QS may help realize this strategy, whereby antimicrobial release only occurs once a threshold number of antimicrobial-producing cells are present. Hence, it is not surprising that QS is used to modulate antimicrobial production and functioning in a large number of organisms (Hibbing *et al.*, 2010).

Many competitive elements are also regulated by QS. For example, QS inhibitors are produced by some bacterial species to avoid succumbing to competition, thus allowing them to compete in the symbiotic environment without needing to produce antibiotics to any toxic metabolites that may be present. Recently, several QS inhibitors of this kind have been found. Honaucins, a structurally analogue of AHLs from a marine cyanobacterium, can inhibit bioluminescence in *V. harveyi* (Choi *et al.*, 2012). Tumonoic acid produced by *V. harveyi* in non-toxic concentrations can modestly inhibit QS without affecting host growth (Clark *et al.*, 2008). In addition, two QS inhibitors in the form of phenethylamide metabolites were identified in *Halobacillus salinus*. These two molecules prevented QS-regulated violacein biosynthesis by *Chromobacterium violaceum* at non-toxic concentrations by competing with AHLs for receptor binding (Teasdale *et al.*, 2009). Among the QS inhibitors, PQ (2-*n*-pentyl-4-quinolinol) is impressive in that it can modify bacterial metabolism, shift the composition of bacterial populations, and further change their interactions in marine environment (Long *et al.*, 2003). The effects of antimicrobials on

interbacterial interactions may significantly modify the structure of the food web and biogeochemical dynamics, as bacteria use these enzymatic substances to interrupt QS signaling by other species that may compete for space and food. Furthermore, a link between enzymatic degradation and the ability to gain a competitive advantage has been demonstrated. Evidents showed that degradation enzymes such as lactonases, acylases and oxidoreductases affect the signaling processes of QS or degrade AHL molecules (Dong *et al.*, 2001; Park *et al.*, 2006), as bacterial strains that enzymatically inactivate AHLs and thus inhibit QS process were observed (Romero *et al.*, 2011).

B. QS modulates antagonism between bacteria and algae

Competition between algae and bacteria is common because of food and space limitations. Bacteria use several strategies to obtain resources, including secreting toxins and producing compounds harmful to algae or other organisms that affect the algal lifecycle. Among these ecological strategies, the role of algicides has received much scientific focus, due to potential repurposing of these elements as biocontrol agents against harmful algal blooms (HABs) (Mayali and Azam, 2004; Kodama *et al.*, 2006).

1. Bacterial effects on algae—Algicidal bacteria secrete chemical substances that inhibit or kill algae in phycospheres, and the biosynthesis and release of these algicides is regulated by AHLs. That is, QS is used by bacteria to control algicidal activity. For example, the flavobacterium *Kordia algicida*is releases a protease that acts against a subset of its symbiotic hosts, including *Skeletonema, Thalassiosira,* and *Phaeodactylum* spp. (Paul and Pohnert, 2011). This protease is only secreted when the bacterial population level reaches a certain threshold controlled by QS (Paul and Pohnert, 2011). Another clue is exemplified by the discovery of nine algicidal bacteria isolated from microalgae, which could inhibit several red-tide algae such as *Prorocentrum donghaiense*, *P. globosa*, *Thalassiosira* sp., and *Heterosigma akashiwo*, to different degress (Xu *et al.*, 2012). Interestingly, these nine strains produce C6–C14 HSL, with their physiological behavior being controlled by HSL molecules (Xu *et al.*, 2012). Furthermore, the inducer role of QS was also pointed out for bacteria producing and secreting algicide molecules (Demuez *et al.*, 2015). Recently, data mining of the genome of a *Rhodobacteraceae* strain isolated from the microalga *Prorocentrum donghaiense* also provided hint of QS-regulated algicidal activity in bactera (Zheng *et al.*, 2015).

Though many phenomenons of QS-regulated algicidal activity in bacteria are clearly observed, limited information on how the algal cell lysis process takes play hinders insights into the molecular mechanisms of QS-regulated algicidal activity. Up to now, limited studies arround AI-1 and AI-2 system have been preliminarily carried out. Two novel G^+ bacterial strains (*Zobellia* sp. and *Planomicrobium* sp.) were shown to exhibit algicidal activity against the toxic dinoflagellate *Gymnodinium catenatum*, and the algicidal functions was modulated by AI-2 system (Skerratt *et al.*, 2002). Nakashima *et al.* (2006) subsequently showed that PG-L-1 (a prodigiosin pigment produced by gamma-proteobacterium), exhibits algicidal activity against various red tide phytoplankton under AHL singals control. The authors suggested that AHL signals might also regulate the production of other algicidal molecules by marine bacteria. As a result, these bacteria may modulate blooms of harmful

algae through a QS system (Nakashima *et al.*, 2006). Recently, some authors investigated the potential role of AI-1/AI-2 systems in cultures of a Florida dinoflagellate *Karenia* sp. and associated algicidal bacteria; they concluded that algae-associated bacteria, including those that are algicidal, depend on autoinducer systems (Blair and Marshall, 2013). These mentioned above examples tell us, use of QS systems for this purpose would introduce a new paradigm for understanding algal-bacterial relationships and the biotic regulation of bloom dynamics.

2. Algal defense against bacteria—Many algae use defense strategies to protect themselves from antagonistic bacteria. These algae secrete metabolites that act as antibacterial substances and influence bacterial growth or biomass. Such metabolites include polyunsaturated fatty acid that inhibits algicidal bacteria (Lebeau and Robert, 2003), eicosapentaenoic acids that inhibit pathogens (Desbois *et al.*, 2008), and polyunsaturated aldehydes that suppress unfavorable bacterial growth (Wichard *et al.*, 2007). From a signaling regulation perspective, phytoplankton have an additional defense strategy in their arsenal. Like terrestrial plants, algae may be able to disrupt harmful bacterial behavior by interfering with QS signals. For instance, algae produce halogenated furanones, which are structural analogues of AHLs. These products protect algal surfaces by interfering with AHL-regulated processes, in addition to selectively inhibiting bacterial colonization and biofilm formation (Manefield *et al.*, 2002). Another well-characterized natural compound is 5-4-5-bromomethylene-3-butyl-2-5H-furanone, which effectively inhibited AHL-regulated gene expression in several G^- bacteria (Defoirdt *et al.*, 2007). This compound was shown to inhibit AI-2 signaling by inactivating the *LuxS* enzyme, and interrupting the production of AI-2 through covalent modification (De Keersmaecker *et al.*, 2006). Kjelleberg *et al.* (1996) further reported that eukaryotes produce cyclic dipeptides that act as AHL mimics, and affect QS-regulated behavior in symbiotic microbes. Other secondary metabolites (such as manoalide, brominated alkaloids, and kojil acid) are also antagonistic to QS through inhibiting QS production, degrading the *LuxR* activator, and blocking the *LuxR*-based reporter (Skindersoe *et al.*, 2008; Dobretsov *et al.*, 2011). Syrpas *et al.* (2014) demonstrated that the haloperoxidase mediated loss of β-keto-AHL activity in the benthic diatom (*Nitzschia* cf. *pellucida*) is caused by the final cleavage of the halogenated N-acyl chain of the signal molecules. Other algae, such as *Asparagopsis taxiformis*, produce QS inhibitors as a safeguard against biofilm formation (Jha *et al.*, 2013). In these cases, algal hosts secrete compounds that mimic bacterial QS signals, allowing the hosts to manipulate (blocking or disrupting) bacterial QS-regulated gene expression. Rajamani *et al.* (2011) also suggested that the secretion of lumichrome by *C. reinhardtii* might serve as either a QS signal or interkingdom signal mimic capable of manipulating QS in bacteria possessing a *LasR*-like receptor.

Enzymes may also be used to modify QS signals to defend against unfavorable or harmful bacteria. A typical example is haloperoxidases, which regulate AHLs by modifying their acyl side chains, and prevent binding between QS factors and their related regulators. Borchardt *et al.* (2001) confirmed that one haloperoxidase family member, *Vanadium haloperoxidases,* interferes with QS by brominating AHLs. Some haloperoxidases deactivate AHLs on contact with the surface of bacteria (Butler and Sandy, 2009). Therefore, the study

and characterization haloperoxidases is essential to understanding diatom defense systems against antagonistic bacteria (Amin *et al.*, 2012).

The aforementioned examples show that algae and bacteria clearly use QS to regulate their own behavior, in addition to the behavior of other organisms. Prokaryotes and eukaryotes diffuse their signals and metabolites into the environment, which are then recognized as chemical cues by surrounding organisms to establish ecological niches, following the principle of "ecological regulation serves ecological function."

3. Defense aganist eukaryotic grazers—Protozoans often graze on phytoplankton, which reduces phytoplankton biomass and the diversity of bacterioplankton communities. Marine bacteria have developed several mechanisms to protect themselves and their hosts against this type of predation (Jousset, 2012). Over the last 20 years, studies have shown that cyanobacteria from the genera *Lyngbya* and *Microcoleus* produce a wide range of metabolites (including the lipopeptide polyamide, malyngamides, and majusculamides) to prevent protozoa from consuming their mats (Nagle *et al.*, 1996; Pennings *et al.*, 1996; Capper *et al.*, 2006; Berry *et al.*, 2008). In addition, some species of marine heterotrophic bacteria exhibit anti-grazing-mediated behavior (Wietz *et al.*, 2013). For instance, *Pseudoalteromonas luteoviolacea* produces an anti-grazing compound called purple pigment violaceins. At very low concentrations (nanomolar level), this compound triggers the autolysis of bacterivorous dinoflagellates, and may provide defense within biofilms (Matz *et al.*, 2008). *Vibrio cholera* produces an extracellular protease that provides resistance against the flagellate *Cafeteria roenbergensis* and the ciliate *Tetrahymena pyriformis* (Vaitkevicius *et al.*, 2008). In this form of self-defense, chemical signals serve as modulators and guides. *V. cholerae* also produces a QS-regulated antiprotozoal factor that prevents the flagellate *Rhynchomonas nasuta* from growing, which reduces grazing losses (Erken *et al.*, 2011). Sun *et al.* (2013) further showed that polysaccharide production induced by the QS regulator *HapR* acts as inhibitor to suppress *R. nasuta* growth.

In addition to self-defense, symbiotic microbes protect their hosts through associated metabolites. The microalgae-associated bacterium *Theonella swinboei* and those of *Paederus* spp. protect their hosts by producing polyketides (Kellner and Dettner, 1996). *Pseudomonas* spp. use 2,4-diacetylphloroglucinol and pyoluteorin as antibiotics to prevent host infection by the pathogens *Pseudoalteromonas elyakovii* and *Algicola bacteriolytica* (Nagel *et al.*, 2012). *Marinobacter* sp. uses a different host protection strategy, which involves secreting lipopolysaccharides to trigger early algal defense reactions by inducing oxidative bursts (Kupper *et al.*, 2006). While it is well known that anti-molecules must reach a certain concentration to be effective, it remains unclear whether QS contributes to these processes. QS regulates the population density of bacteria based on the concentration of biological activators that they secrete. Thus, it is important to obtain direct proof of QS involvement in host-protection mechanisms to advance this area of research.

In summary, compounds that obstruct QS may have a positive or a negative effect on bacterial responses modulated by QS. Eukaryotic hosts or phytoplankton produce these QS-inhibiting compounds are listed in Table 2.

VI. ENVIRONMENTAL FACTORS AFFECTING QUORUM BEHAVIOR

To understand quorum behavior, it is important to fully characterize microbial phenotypic plasticity in response to environmental factors. Natural environments are often heterogeneous, and feature strong spatial variation in both abiotic and biotic factors. For holobiont systems, all of the requirements for an organism (such as temperature, pH, salinity, light, and nutrients) are rarely optimal. Therefore, species have evolved to withstand intermittent, non-optimal conditions. In phycospheres (particularly in coastal environmnts), microorganisms are subject to various environmental threats, including ocean acidification, nutrient unavailability, temperature changes, water pollution, and eutrophication. These environmental threats damage holobiont health by decreasing the biodiversity of algae and surrounding aquatic microorganisms. Furthermore, these threats interfere with the symbiotic interactions between bacteria and algae, which impede cellular communication. These issues raise questions of how symbionts adapt to complex systems and how they modify their behavior in response to environmental changes.

To understand how environmental threats influence the symbiotic relationship between microbes and their hosts, a comprehensive characterization of how QS is used in symbiotic relationships is needed (Generous, 2014). In some extremophile ecosystems, there is considerable evidence about the function of QS. Averhoff and Muller (2010) reported that *Halobacillus halophilus* (a G^+ bacterium) from a coastal salt marsh in Germany tolerates high-salt environments by forming biofilms and producing an extracellular polymeric substance (EPS), both of which are regulated by AHLs. Wenbin *et al.* (2011) confirmed that the *A. ferrooxidans* (5Z)-4-bromo-5-(bromomethylene)-2(5H)-furanone acts as a QS blocker of Cu^{2+} in other turbulent environments (such as polluted and high-pressure conditions). In addition, the deep-sea bacterium *Photobacterium profundum* SS9 contains a putative AI-2 signaling system; the comparative genomic studies have shown that this signal has approximately 35% sequence conservation with the *LuxMN* and *AinSR* systems in *V. harveyi* and *Aliivibrio fischeri* (Reen *et al.*, 2006). This observation supports the concept that QS is critical in high-pressure environments. Other studies have shown that bacteria trigger QS and downstream reactions to adapt to various extreme environments, including thermophilic (Nichols *et al.*, 2009), psychrophilic (Riley *et al.*, 2008), and acidified (Montgomery *et al.*, 2013) conditions.

Although interactions between algae and bacteria are well studied, knowledge about QS systems in extremophiles remains incomplete, the development of genomic sequencing techniques, bioinformatics analysis, and plasmid-based biosensors have been prompting the elucidation of the functional plasticity of QS in response to environmental cues.

VII. ROLE OF QS IN ALGAL AND BACTERIAL CO-EVOLUTION

Co-evolution is a form of evolutionary change that involves give-and-take between interacting species. Co-evolution dynamically shapes the intricate symbioses as well as the organization of interactions among free-living taxa, which ultimately affects populations, communities, and ecosystems (Palkovacs and Hendry, 2010; Thompson, 2012). The earliest evidence for ancient interactions between algae and microbes derives from the fossil record,

confirming that phytoplankton and phytobacteria closely coexisted (Cernichiari *et al.*, 1969). The first suggested incidence of co-evolution occurred between the red alga *Prionitis* and its gall-forming *Roseobacter* symbionts, based on comparison of the molecular phylogenies of the symbiont and its host (Ashen and Goff, 2000). Subsequently, genes from marine sponges and their associated bacteria, including a mitochondrial cytochrome oxidase subunit 1 gene, *co1*, and its bacterial homolog were identified (Dunn *et al.*, 2002). Based on this gene, a phylogenetic tree was constructed for six putatively alpha-proteobacterial symbionts, which were found to correspond to a tree generated using sequences from associated host sponges. This finding implied that these two groups of organisms co-evolved (Dunn *et al.*, 2002). Recent research has supplied further convincing evidence for co-evolution. Qiu *et al.* (2013) pointed out that red algae are one of the major players in eukaryotic genomic evolution because of their ability to act as “sinks” and “sources” for foreign genes through horizontal or vertical gene transfer and endosymbiosis, respectively. Hollants *et al.* (2013) provided evidence for non-random associations between Bryopsis and its flavobacteriaceae endosymbionts. Specifically, host species that are more closely related tend to contain genetically similar endosymbionts. Schaum and Collins (2014) further suggested that plasticity could be used to predict the magnitude of evolutionary responses by phytoplankton populations under global change.

Throughout the long evolutionary process, algal-bacterial symbionts lacked a central nervous system to aid in decision-making. Instead, these two groups rely on genetic regulatory networks to adapt and adjust their phenotypic states in response to the environment and selective pressures (Harrington and Sanchez, 2014). Among the tools available to these symbionts, QS might serve as a decision-making mechanism, because it provides an effective and complex strategy for regulating microbial social behaviors. In terrestrial soil-dwelling plants (such as opine), QS has been shown to indirectly impact the evolution between the host and their associated bacterium (Oger and Farrand, 2001). In this pairing, signaling affects certain clustered genotypes, such as the *comQXPA* locus, which has a large number of genetic polymorphisms and encodes the QS-transduction system that controls QS in *Bacillus* spp. (Tran *et al.*, 2000; Stefanic *et al.*, 2012).

In marine environment, co-evolution between algae and bacteria is regulated in part by “public goods” or “cheaters” (i.e., organisms that use but do not contribute resources), which arise from ecological and social interactions. These interactions generate selective pressure based on the frequency of certain traits within a population. These pressures help to maintain genes at a moderate frequency within a population or reduce the frequency of certain genes. For example, despite the benefits of siderophore production, only 40% of the population produces these molecules (Cordero and Polz, 2014). Over time, the siderophore operon has undergone genetic recombination from the population gene pool between the “cheaters” and the “producers” (Sandy and Butler, 2009; Amin, 2010). This phenomenon enhanced the co-evolution of these groups or the co-evolution of algae and their associated bacteria. This process is modulated by QS, because QS affects vibrioferrin production (Iqbal *et al.*, 2012). Taylor *et al.* (2007) and Coelho *et al.* (2013) suggested that antagonistic co-evolution has occurred between algae and bacteria involved in QS-regulated biofilm formation, although the evidence for this phenomenon remains inconclusive.

In addition to co-evolution, algae and bacteria evolve independently, and this process is influenced by various eco-environmental factors, such as competition (Hibbing *et al.*, 2010), cooperation (Zhang *et al.*, 2009), genomic diversity (Cordero and Polz, 2014), and ocean acidification (Collins *et al.*, 2014). Furthermore, the evolution of the QS system itselfis is influenced by social conflict (Eldar, 2011), different cues (Diggle *et al.*, 2007), and dynamic environments. Therefore, it is necessary to investigate the combined evolutionary processes of algae, bacteria, and QS signals, because QS allows bacteria to adapt and respond to their social and physical environments (Cornforth *et al.*, 2014). Eco-evolutionary feedback loops and cascades of genes, behaviors, communication, populations, and ecosystems should also be incorporated into studies on these phenomena.

VIII. POTENTIAL APPLICATION OF QS IN ALGAL ECOLOGICAL ISSUES

QS and QS-related mechanisms are of particular interest to the scientific community because of their possible biotechnological applications. At present, hundreds of patents involving QS and QS inhibitors exist globally (Jiang and Li, 2013). These applications are separated into three categories: (i) medical uses of AHLs and AHL analogs, (ii) agricultural uses of QS and QS-blockers, and (iii) QS compounds used to scale-up the production of microbial products. In marine ecology field, several diverse applications have been considered, including anti-biofouling (Dobrestov *et al.*, 2009) and algal culturing (Mendes and Vermelho, 2013). According to the scope of this review, we focus on the ecological issue of harmful algal blooms (HABs), and discuss the potential use of QS to predict and/or control HABs.

Over the last 20 years, HABs caused by cyanobacteria and planktonic protists have increased in frequency worldwide, with considerable threats to human health and aquatic-based economies (Anderson *et al.*, 2012). The severe socioeconomic impacts of HABs have prompted the development of technologies and approaches for their prediction and control. The detrimental effects of HAB species are primarily due to the highly toxic compounds produced and accumulated in the food web (Hallegraeff, 1993). Microoragnisms provide some of the necessary nutrients and resources for the toxin-producing species, during the process of cell growth and division in microbial populations. As is well-known that the density in microbial populations is modulated by QS, making it a target for anti-HABs treatment, developing QS inhibitors that block the biological function of QS may provide a way to control algae concentrations to limit the impacts of their toxins (Zhou *et al.*, 2014). A QS-based method is an attractive alternative to antibiotics because it hinders the colonization of bacteria without removing native flora or increasing the risk of antibiotic resistance. Application of QS inhibitors for anti-HABs has been reported. For example, by using ethyl 2-methyl acetoacetate (EMA) as a signal inhibitor, Hong *et al.* (2008) successfully disrupted the equilibrium of cellular redox process to inhibit blue-green algae (*Microcystis aeruginosa*) growth. Polyunsaturated aldehydes (PUAs) acts as chemical signal to initiate cell death by affecting the QS-regulated bacteria symbiotic with diatoms, therefore, is a potential anti-HABs compound in bloom resistance and novel biosensors for predicting HABs (Ribalet *et al.*, 2009; Vardi *et al.*, 2008).

In preliminary experiments carried out by the authors, we screened hundreds of QS-producing bacteria and biofilm-forming bacteria isolated from dinoflagellates, *Scrippsiella*

trochoidea and *Gambierdiscus taxicus*, using the reporter strains *Chromobacterium violaceum* CV026 and *Agrobacterium tumefaciens* A136. Bacterial behavioris known to be partly modulated by long- or short-chain AHL molecules and exhibits significant labor division (Chen, 2013). Some bacterial strains significantly inhibited algae or were algicidal; however, we have yet to determine whether these abilities are quorum-regulated (Wang, 2014; Tan *et al.*, 2015). We are currently conducting genomic analyses and investigating the functional proteins of these strains. This information is expected to help clarify the underlying mechanisms about how HAB formation and development is influenced by bacterial behavior, which is, to some extent, regulated by AHL molecules (Wang and Zhou, 2015; Zhou *et al.*, 2016). Amin *et al.* (2015) suggested that interactions based on signal substances demonstrate how the bacterial influence on phytoplankton physiology is linked to the global carbon cycle and algal bloom formation. Thus, future studies should focus on obtaining details about the efficacy and molecular mechanisms underlying QS in HABs.

IX. CONCLUSIONS AND FUTURE PERSPECTIVES

Signal-mediated behavior is omnipresent, and has a considerable impact on the structure and function of populations, communities, and ecosystems of symbionts (Zhang and Dong, 2004). Quorum and quorum-related signals are involved in regulating the physiological behavior of bacteria at multiple aspects, and facilitate indirect communication that extends throughout communities and modifies the organization of the food web, community structure, and ecosystem-wide events, such as nutrient and element cycling. In phycosphere environment, dynamic and complex interactions occur between different species of algae, bacteria, archaea, predators, and viruses, all of which co-exist through the mediation of signals. An overarching objective in the field of signaling biology is the comprehension of mechanisms that modulate marine biotic communication, involving the network of direct and indirect relationships that regulate community organization and ecosystem functioning. However, gaps remain in our knowledge about these mechanisms. For this field of research to realize its goals and fill these gaps, we should advance our knowledge in the following areas:

1. Understanding the specifics of cross-talking. One challenge faced by research on inter-kingdom relationships is differentiating between algal and bacterial metabolic responses to QS, particularly between their downstream interactions. Co-culture model systems could be developed to overcome this challenge, which would also facilitate the characterization of signaling molecules and the resulting responses.

2. Improved coupling between chemical and biomolecular techniques. In aquatic environments, chemical signals may only be present as complex mixtures at low concentrations, rather than as individual compounds, and may degrade quickly. These issues increase the challenge of separating them and characterizing their structure (Hay, 2009). Combining chemical and molecular methods would help to improve our understanding about the dynamics of these chemical languages. For instance, imaging mass spectrometry provides unprecedented opportunities to study signaling molecule-mediated phenomena visually (Shih *et al.*, 2014).

This visualization technology may help us identify more natural products. In addition, approaches based on metabolism and the use of combined metabolic models for algae and their associated bacteria are important to enhance our understanding of the complexity of holobiont systems (Dittami *et al.*, 2014). This information could guide us to a thorough understanding of the biological effects induced by QS, and eventually allow us to assess QS-related co-evolution.

3. The fate of QS molecules in natural environment. Because QS relies on chemicals, a number of factors affect its rate, including abiotic hydrolysis, enzymatic degradation, and oxidation. These factors have a particular effect on odd-number chain AHLs (such as C7 AHLs) (Pedroza *et al.*, 2014). Thus, knowledge about QS rates and range of functions under natural conditions could help us understand how the environment alters the rate of QS and associated sociobiological behaviors (Decho *et al.*, 2011).

4. Screening, isolation, and identification of additional QS signal molecules, such as AI-3. Establishing whether AI-3 affects host cells and if so, whether AI-3 signaling is adrenergically mediated would generate both expected and unexpected results. This information would improve our understanding about the potential mechanisms that use these diverse QS signaling components.

5. Investigate QS systems in archaea. QS systems in the phycospheres of archaea receives comparatively less research focus than those in bacteria (Mackin, 2011). Archaea are important members in ocean and are critical for marine biogeochemistry process. The ecofunctions of archaea rely on population-level traits for survival and physiological activities. Therefore, archaeal QS requires further study. Social network involving QS in archaea may also provide new knowledge about the lifecycle and dynamic processes of algae. The lack of current knowledge about specific interactions between archaea and algae represents an exciting new area of research.

6. Application of QSIs and QQ signals to prevent HABs. The use of QSIs and QQs against HABs requires further investigation to characterize their efficacy, stability, and degradability in water bodies. Some QSIs and QQs may be toxic or may adversely affect the QS of favorable bacteria. Possible negative impacts on marine organisms or humans require investigation.

7. Investigate climate-related effects of QS processes. Marine environments are rapidly changing because of global climate change. Important questions include (i) how temperature increases will affect QS behavior, (ii) how ocean acidification will influence microbial communities and their interactions, and (iii) how extremophiles disrupt the social language of organisms in phycospheres. Identification of QS-related genes and hypotheses about the use of these genes by organisms to respond to their environments are now possible due to the development of genomic sequencing and bioinformatics databases.

8. Investigate practical applications of QS compounds. Compounds or chemicals, such as QSI and biofilm inhibitors, that may be used to resolve ecological issues

(e.g., HABs) may be of great value and should be developed. For example, the unicellular alga, *C. reinhardtii,* inhibits bacterial QS and produces more than a dozen previously unidentified substances capable of activating *LasR* and *cepR* (but not *luxR, AhyR,* or *CviR* QS) reporter stains. Furthermore, *C. reinhardtii* extracts exhibit the highest biological activity in polar solvents (Teplitski *et al.*, 2004). Thus, identification of these compounds could have a broad influence across scientific fields, as well as for management and exploitation of algal and bacterial populations globally, among many other uses.

In conclusion, research on QS between algae and bacteria continues to provide detailed knowledge about signal regulation mechanisms in algal-bacterial interactions. This field offers an exciting and open arena for dedicated research to improve our understanding of these intriguing and biologically relevant mechanisms, which underpin ecosystems and may provide economically beneficial remediation.

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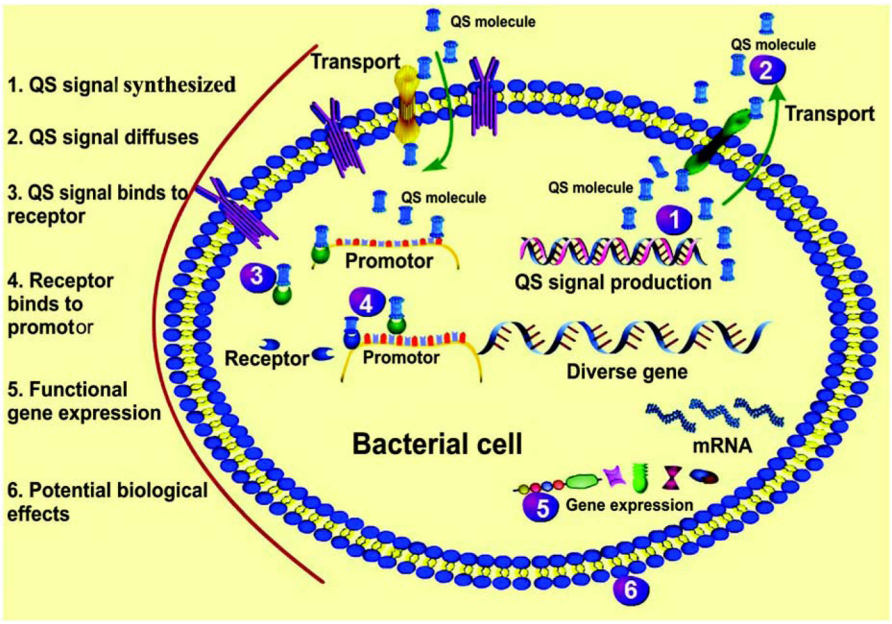


Figure 1.

The molecular formation mechanisms of quorum sensing (QS) and the subsequent cascade response, using the example of gram-negative bacteria. The numbers represent different stages of the QS process. Arrows show the main direction of signal transport due to active transport or diffusion.

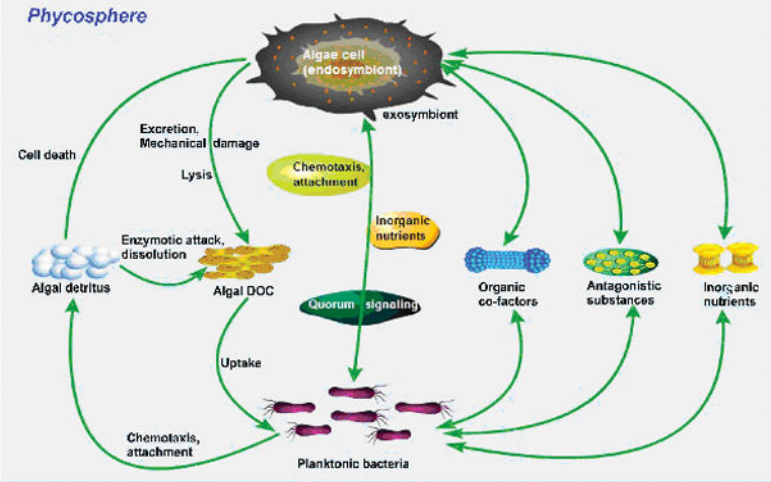


Figure 2.

Flow chart of the biological processes in the phycosphere micro-environment. This schematic excludes a number of indirect interactions, such as bacterial metabolism and signaling substances (such as quorum sensing and allelochemicals). The arrows show the predominant direction of a process.

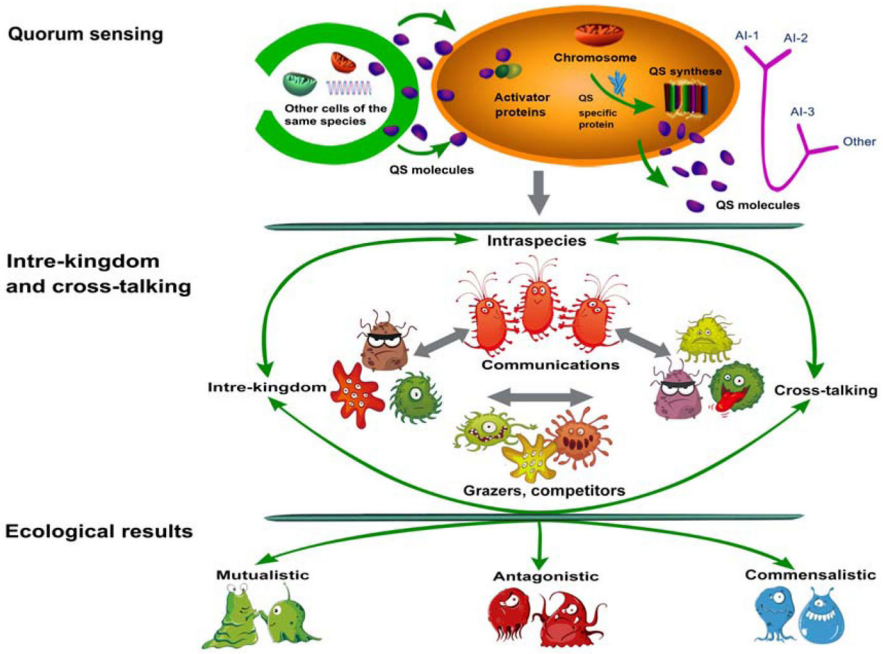
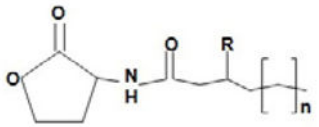


Figure 3.

Formation and multifunctional roles of QS in algal-bacterial symbiosis. Top: quorum sensing (QS) molecules are produced in the bacterium by QS synthesis and diffuse from the cell to enter neighboring bacteria. QS signaling molecules bind to the receptor polypeptide, leading to formation of active dimers. The receptor dimers bind to specific promoter sequences in the bacterial genome and activate the transcription of certain sets of genes. Middle: microbial communication by QS molecules, including intre-kingdom and intra-species communication, interspecies cross-talking, and other communication among different species. Bottom: QS-mediated social cooperation and conflict in algal-bacterial symbionts, such as mutualistic, antagonistic, and commensalistic symbionts.

TABLE 1

nicroorganisms

Producing species	Chemical structure	Physical properties	Molecular synthase	Regulated protein	Ecological function	References
Vibrio harveyi	Homoserine lactone (HSL) ring with a variable acyl side chain. 	Molecular weight: from 171.9 Da for a C4- to 367.57 Da for an unsubstituted C 18-AHL (Decho *et al.*, 2011). Solubility: low-molecular-weight AHLs tend to be relatively water soluble, and it is unlikely that communal responses based on their presence would ever be limited by their solubility. However, as molecular weights increase significantly above 520 g/mol, the saturation concentration of the AHL is expected to drop below 1μM AHL (Decho *et al.*, 2011). Diffusivity: from 10 to 78 μm AHL (Decho *et al.*, 2011). Dispersion: from 10 s micrometers to 100 s micrometers AHL (Decho *et al.*, 2011).	*LuX-M*	*LuxR* type protein	Bioluminescence	Waters and Bassler (2005)
Pseudomonas aeruginosa			*RH II*		Biofilm maturation	Waters and Bassler (2005)
Aeromonas hydrophyla			*Ahy I* *Asa I*		Biofilm formation, Enzyme production	Tebben *et al.* (2011)
Serratia marcescens			*SWrI*		Swarming	Miller and Bassler (2001)
Erwinia stewartii G⁻			*LuXI*	*LuxR* type protein	Exopolysaccharide	Watson *et al.* (2002)
Vibrio fischeri G⁻					Light production	Nealson *et al.* (1970)
P. fischeri G					Virulence	Eberhard *et al.* (1981)
A. salmonicida			*Ahy I*	*LuxR*type protein	Biofilm formation	Swift *et al.* (1999)
Chromobacterium Violaceum			*CV I*		Violacein, antibiotics, and enzyme production	Cha *et al.* (1998)
Yersinia enterocolitica, Y. pseudotuberculosis			*Yen I, Yps I*		Motility aggregation	Miller and Bassler (2001)
Vibrio sp. (algae-associated)			*LuxI*		Settlement activity	Taylor *et al.* (2007)
Vibrio alginolyticus			*LuxI*		/	Huang *et al.* (2007)
Agrobacterium tumefaciens			*Tra I*		Virulence factors	Fuqua *et al.* (2001)
Y. pseudotuberculosis			*Yps I*		Potential regulate cells wimming	Miller and Bassler (2001)
Roseobacter spp., *Marinobacter* sp.			/		/	Taylor *et al.* (2007)
Vibrio anguillarum			*Van I*	*LuxR*	Virulence	Defoirdt *et al.* (2004)

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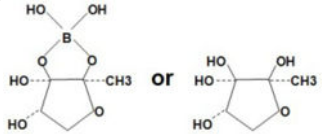
Producing species	Chemical structure	Physical properties	Molecular synthase	Regulated protein	Ecological function	References
Vibrio alginolyticus			*Las I*	*LuxR*	Virulence formation	Pearson *et al.* (1994)
			/	*LuxR*	/	Huang *et al.* (2007)
Roseobacter sp.			/	*LuxR*	/	Mohamed *et al.* (2008)
Vibrio harveyi			*Ai-2*		Bioluminescence	Bassler *et al.* (1993)
V. cholerae			*Ai-2*		Virulence	Chen *et al.* (2002)
V. harveyi			*Ai-2*		Virulence	Henke and Bassler (2004)
V. parahaemolyticus	The proposed structure contains two fused five member rings containing one boron atom bridging the diester. 		*Cqs A*		Virulence	Miller *et al.* (2002)
V. cholerae		/	*Ai -2*		Virulence	Miller *et al.* (2004)
Salmonella enterica					Virulence gene expression	Sperandio *et al.* (2001)
Escherichia coli					Type II secretion	Day and Maurelli (2001)
Shigella flexneri			*LupX*		Virulence factor virB expression	Mcnab *et al.* (2003)
Streptococcus pordonii					Biofilm formation	Li *et al.* (2002)
E. coli, Xanthomonas campestris	DSF:cis-11-methyl-2-dodecenoic acid. 	/	*LuxS*	*Lux P/Q* type protein	Biofilm formation	Barber *et al.* (1997)
				Lux O type protein, mRNA-dependent regulation, such as 5RNAs		Reading and Sperandio (2006); Wang *et al.* (2004)
Pseudomonas sp. *Streptomyces griseus Staphylococcus aureus*	Diketopiperazines (DPKS)* cyclo (L-Ala-L-Val) and cyclo (L-Pro-L-Tyr).	/	*LuxR*		Activates AHL biosensors. *: the induction threshold for DKPS is higher than AI-1, which indicates that DKPS may not have a	Degrassi *et al.* (2002) Waters and Bassler (2005)

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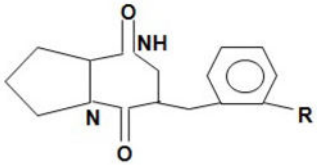
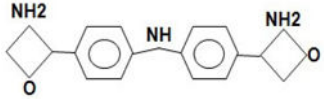
Producing species	Chemical structure	Physical properties	Molecular synthase	Regulated protein	Ecological function	References
					significant role in the marine environment	Lyon *et al.* (2000); Zhang and Dong (2004)
Bradyrhizobium japonicum G⁻, *Rhizobium* sp., *Alphaproteobacteria* sp., *Pseudomonas aeruginosa*	2-{4-[[4-(3-aminooxetan-2-yl)phenyl](amino)methyl]phenyl} oxetan-3-yl amine.	/	*Nod* gene	*Nod* gene	Nitrogen-fixing	Loh *et al.* (2002a,b)
Ralstonia solanacearum			*PhcS-phcR*	Iron concentration	Polysaccharide biosynthesis	Flavier *et al.* (1997)
Xanthomonas campestris			/		Virulence	Zhang and Dong (2004)
Algae symbiotic bacterium			/		Competence, Morphogenesis	Decho *et al.* (2011)

TABLE 2

Natural QS inhibitors observed in algae and major symbiotic bacteria

Species	Compound	Mode of action	Biological role	QS system affected	References
Red alga, *Ahnfeltiopssis flabelliformis*	α-D-galactopyranosyl-glycerol (Floridoside), betonicine, and isoethionic acid	Competes with AHL signals			Kim *et al.* (2007a, b)
Red alga, *Galaxa uraceae, Laurencia* sp.	Unidentified algal extract	AHL inhibitor			Skindersoe *et al.* (2008)
Green alga, *Chlamydomonas reinhardtii*	Unidentified AHL mimics, Lumichrome	Blocks AHL molecules			Rajamani *et al.* (2008); Teplitski *et al.* (2004)
Brown alga, *Laminaria digitata*	Oxidized halogen HOBr, Hypobromous acid	Deactivates AHL by interfering with QS genes			Borchardt *et al.* (2001)
Macroalga, *Delisea pulchra*	Furanone	MimicsAHLsignals, inhibits gene expression	Affects biofilm formation, swarming motility, toxin production, chemotaxis	*Swr* system of *S. liquefaciens* and other gram negative bacteria	Givskov *et al.* (1996); Gram *et al.* (1996); Manefield *et al.* (2000)
Macroalga, *Chlorophyta, Caulerpa* sp.	Unidentified extract	AHL inhibitor			Skindersoe *et al.* (2008)
Marine algal	Honaucin, coibacin, laurencione, tumononic acid, and malyngamide	QS inhibitor		*Vibrio harveyi*	Gerwick *et al.* (2013)
Microalga, *Chlamydomonas reinhardtii*	Lumichrome	Mimics AHL signals			Rajamani *et al.*(2008)
Bacteria					
Penicillium spp.	Penicillic acid, patulin			*Las* and *RhI* system of *P. aeruginosa*	Rasmussen *et al.* (2005)
Bacillus spp., *Agrobacterium tumefaciens, Arthrobacter* sp.	Lactonase	Degradation of AHL signals			Romero *et al.*(2011)
Bacillus spp., *Alteromanas* sp., *Tenacibaculum discolor* strain; *Nocardioides* sp. *Streptomycetes* sp.	Acylase	Degradation of C4-HSL, 3-O-C12-HSL, and long chain AHLs			Kang *et al.* (2004); Nithya and Pandian (2010); Romero *et al.* (2011)
Bacillus megaterium	AHL-oxidase	Degradation of C4 HSL and 3-O-C12 HSL			Choudhary *et al.* (2007)
Burkholderia strain *GC4*	AHL-oxidoreductase	Degradation of 3-O-C6 HSL			Chan *et al.* (2011)
Streptomycetes spp.	Lactones	Mimics AHL signals			Cho *et al.* (2001)
Xanthomonas campestris	Cys-11-methyl-2-dodecenoic acid	Mimicsfarnesoic acid signals of *C. albicans*			Zhang and Dong (2004)
Staphylococcus xylosus	RNA III inhibiting peptide	Competes with QS signals			Gov *et al.* (2004)
Halobacillus salinus	Phenethylamide	Antagonist of AHLs			Teasdale *et al.* (2009)
Cyanobacteria, Blennothrix cantharidosmum	Tumonoic acids	Competes with QS signals			Clark *et al.* (2008)