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REVIEW

Disruption of Bacterial Cell-to-Cell Communication by Marine Organisms and its Relevance to Aquaculture

F. M. I. Natrah · Tom Defoirdt · Patrick Sorgeloos · Peter Bossier

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Abstract Bacterial disease is one of the most critical problems in commercial aquaculture. Although various methods and treatments have been developed to curb the problem, yet they still have significant drawbacks. A novel and environmental-friendly approach in solving this problem is through the disruption of bacterial communication or quorum sensing (QS). In this communication scheme, bacteria regulate their own gene expression by producing, releasing, and sensing chemical signals from the environment. There seems to be a link between QS and diseases through the regulation of certain phenotypes and the induction of virulence factors responsible for pathogen–host association. Several findings have reported that numerous aquatic organisms such as micro-algae, macro-algae, invertebrates, or even other bacteria have the potential to disrupt QS. The mechanism of action varies from degradation of signals through enzymatic or chemical inactivation to antagonistic as well as agonistic activities. This review focuses on the existing marine organisms that are able to interfere with QS with potential application for aquaculture as bacterial control.

Keywords Quorum sensing inhibitors · Quorum sensing interference · Inhibition · Quenching · Marine organisms · Aquaculture

Abbreviations
QS Quorum sensing
QSI Quorum sensing inhibitor(y)

Introduction

The global decline of world fish supplies and the increase in domestication of aquatic animals have spurred the rapid growth of aquaculture (FAO 2009; Duarte et al. 2007). Despite its crucial role in the seafood industry, aquaculture is not without problems. Various diseases from parasites (e.g., sea lice; refer to Johnson et al. 2004), viruses (e.g., herpesvirus, birnavirus; refer to Muroga 2001), and bacteria (e.g., vibriosis, pasteurellosis; refer to Muroga 2001) affect numerous host species in aquaculture systems through different routes (Murray and Peeler 2005). Immense economic losses to aquaculture sectors are suffered (as the diseases cause a huge mortality toll to cultured organisms).

Normally, high organic matter content and high density of the cultured organisms in aquaculture systems increase the proliferation of opportunistic bacteria, such as vibrios (Bachère 2003). This scenario further induces stress to the cultured organisms, making them more susceptible to diseases. Vibriosis is reported to cause high mortalities in

F. M. I. Natrah · T. Defoirdt · P. Sorgeloos · P. Bossier (✉)
Laboratory of Aquaculture and Artemia Reference Center,
Ghent University,
Rozier 44,
9000 Ghent, Belgium
e-mail: Peter.Bossier@Ugent.be

F. M. I. Natrah
e-mail: natrah@putra.upm.edu.my

T. Defoirdt
e-mail: Tom.Defoirdt@ugent.be

P. Sorgeloos
e-mail: Patrick.Sorgeloos@ugent.be

F. M. I. Natrah
Department of Aquaculture, Faculty of Agriculture,
University Putra Malaysia,
43400 Serdang, Selangor, Malaysia

almost any type of cultured organisms (from molluscs over crustaceans to fish) (Defoirdt et al. 2007a).

In aquaculture, different methods to control bacterial disease exist, and more solutions are still being investigated. Immunostimulants, vaccines, water disinfection, and probiotics are among the treatments being proposed (Verschuere et al. 2000; Defoirdt et al. 2007a). A fast and common solution to cure bacterial diseases is through the use of antibiotics. Nevertheless, this solution has its downfalls—as the overuse of antibiotics can cause bacteria to become resistant. The problem worsens as these bacteria can transfer their resistance genes not only among themselves but to other bacteria as well (Verschuere et al. 2000). It has also been demonstrated that bacteria can transfer their resistance genes to human pathogens, thus endangering human health (Guglielmetti et al. 2009). Although the use of antibiotics is basically forbidden in Northern Europe and North America (Sommerset et al. 2005), it is still used in other parts of the world (Tendencia and dela Peña 2001; Roque et al. 2001). In addition to the resistance problem, residual antibiotics can also have adverse effects on the organism's welfare and on the environment (Cabello 2006).

Chemotherapeutic treatments with biocides and disinfectants are another common method for bacterial disease control. Mainly used to prevent disease outbreaks, chemotherapeutics are either incorporated in the feed, added to the culture water, or used for surface disinfection (Planas and Cunha 1999; Subasinghe et al. 2000). Akin to antibiotics, chemotherapeutic agents are also questionable in terms of environmental safety. Their effects to the environment and humans are still not fully understood and are very unpredictable. They may affect non-target organisms such as probiotics and can be toxic to higher organisms. Furthermore, resistance to these compounds can also occur (Subasinghe et al. 2000).

As the traditional solutions have significant drawbacks, novel approaches of bacterial disease treatment in aquaculture are needed. One of them is the disruption of bacterial cell-to-cell signaling or quorum sensing (QS) (Defoirdt et al. 2004). Quorum sensing is a type of bacterial communication whereby bacteria regulate gene expression through the presence or absence of small signal molecules (or autoinducers) (Schauder and Bassler 2001; Waters and Bassler 2005). This mechanism is ubiquitous in bacteria and is known to control the pathogenesis of many medically important organisms (De Kievit and Iglewski 2000; Donabedian 2003). Also, aquaculture pathogens use QS to regulate the expression of important virulence phenotypes. Thus, given the importance of QS in virulence development, it is attractive to understand how other organisms interfere with bacterial QS. This review will discuss on the existing organisms, which could interfere with such systems and evaluate their applicability in aquaculture sectors, taking into account the ecological and physiological implications.

Quorum Sensing

The bacterial QS mechanism was first discovered in *Vibrio fischeri* in its symbiotic association with squid (Nealson et al. 1970; Nealson and Hastings 1979). The Hawaiian bobtail squid *Euprymna scolopes* acts as a host to *V. fischeri*, which provides light to avoid predators and to assist in feeding (Visick and McFall-Ngai 2000). Meanwhile, *V. fischeri* benefit from this association through high nutrient supplies, enabling them to grow to a very high density up to 10^{11} cells/mL (Nyholm and McFall-Ngai 1998). The bioluminescence was found to be regulated by signal molecules (or autoinducers) known as acylated homoserine lactones (AHLs). In *V. fischeri*, AHL is synthesized by the LuxI protein and is detected by the LuxR protein. When a certain threshold concentration of signals is achieved, LuxR binds to the autoinducer and activates the transcription of the *luxICDABE* operon that encodes the genes responsible for luminescence production (Miller and Bassler 2001).

Subsequently, increasing evidence showed that similar mechanisms exist in several Gram-negative bacteria and has been described in at least 70 genera of Proteobacteria (Boyer and Wisniewski-Dyé 2009). This led to LuxIR as one of the most extensively studied QS mechanisms to date. Typical AHL molecules contain invariable lactone rings which connect to variable acyl chains (four to 18 carbons in length) through an amide bond. The acyl chain can contain a substitution of oxo or hydroxyl at the third carbon position. Examples of AHL structures are depicted in Fig. 1. It is important to note that Gram-negative bacteria also employ other autoinducers such as 4-quinolones, fatty acids, and fatty acid methyl esters (for a review, refer Williams et al. 2007). As these signal molecules are not the focus of this review, they will not be further discussed.

To date, different hypotheses on the role of quorum sensing in bacteria have been proposed. Originally, QS was considered as "population density sensing" by which, through signal molecules, bacteria determine the population cell density in the environment and express certain phenotypes accordingly (Miller and Bassler 2001). Others coined it as "diffusion sensing", where signal molecules act as a sensor to individual cells in order to monitor the diffusion rate in the surrounding medium. The expression of more expensive extracellular products is then based on the assessment of diffusion rate. This will result in minimal losses of energy due to extracellular diffusion and mixing (Redfield 2002). At low diffusion rates, a QS response could be attained in small communities. These two concepts were recently combined and redefined into a more ecologically relevant description as "efficiency sensing" (Hense et al. 2007), i.e., bacteria use quorum sensing to release extracellular products when it is efficient to do so:

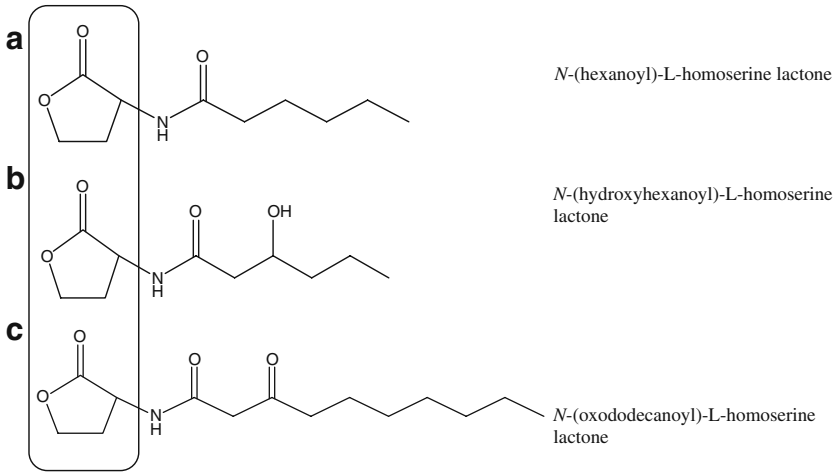


Fig. 1 Representative structures of different AHL molecules. Every AHL contains an invariable lactone ring (*rectangular box*). This lactone ring is connected to a variable acyl chain through an amide bond (*a*). Substitutions can also occur such as *b*, a hydroxyl group, and **c,** a keto group, at the C3 position. The three signals depicted here are produced by the aquaculture pathogen *V. anguillarum*

either when a sufficient cell density is reached or when there is low diffusion in the environment.

In Gram-negative bacteria, QS can be generalized into a one or multi-channel system circuits (Manefield et al. 2002; Wang et al. 2008). In the one-channel system, bacteria use AHLs as the sole signal molecules. AHL signals are produced by LuxI homologues and either diffuse freely in and out of the cells or are actively transported. When a certain threshold is reached, the signals are detected by a LuxR homologue. The LuxR signal receptor is highly specific and only binds to the signal molecules produced by cognate LuxI family proteins. Binding of the signal results in conformational changes of the regulatory protein which allows binding to the promoter region of the target genes. Due to its specificity, it is mainly used for intra-species communication. Certain bacteria have multiple LuxI/LuxR with different AHLs which are hierarchically organized (Waters and Bassler 2005). AHL-mediated QS in Gram-negative bacteria is shown in Fig. 2.

In addition to the classic system, vibrios use a multi receptor-regulatory pathway with different signal molecules that operate in parallel with different receptors, feeding a phosphorylation/dephosphorylation cascade with a single master regulator at the end (Henke and Bassler 2004a). Among the common signals are Harveyi autoinducer 1 (HAI-1), autoinducer 2 (AI-2), and cholerae autoinducer 1 (CAI-1) (Fig. 3). Harveyi autoinducer 1 is an AHL, 3-hydroxy butanoyl-L-homoserine lactone (Cao and Meighen 1989). This signal is produced by *luxM* which shows no homology with *V. fischeri luxI*-type AHL synthases and is detected by LuxN. Harveyi autoinducer 1 appears to be specific only to *Vibrio harveyi* and closely related bacteria such as *Vibrio parahaemolyticus* (Bassler et al. 1997). The second signal, AI-2, is a furanosyl borate diester, 3A-methyl-5,6-dihydro-furo(2,3-$_D$)(1,3,2)diox-aborole-2,2,6,6A-tetraol (Chen et al. 2002). This autoinducer is synthesized by the LuxS enzyme and detected by the LuxPQ proteins (Xavier and Bassler 2003). Autoinducer-2 and LuxS are widespread and have been found in several bacterial species, both Gram-negative and Gram-positive, which reflect their possible role in interspecies communication (Sun et al. 2004). Meanwhile, CAI-1 is (*S*)-3-hydroxytridecan-4-one (Higgins et al. 2007). This signal is found only in *Vibrio* species including *Vibrio cholerae*, *Vibrio alginolyticus*, *V. parahaemolyticus*, *Vibrio furnissii*, and *Vibrio anguillarum* (Henke and Bassler 2004a) but has not been found in other types of bacteria, suggesting that it is probably used for genus-specific communication.

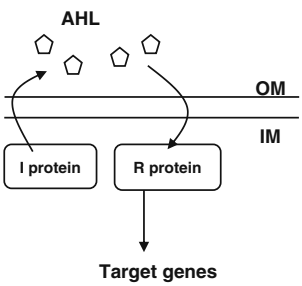


Fig. 2 AHL-mediated quorum sensing in Gram-negative bacteria. The I protein synthesizes the AHL. If a certain concentration threshold is reached, the signal binds to the R protein molecules and the complex activates or deactivates the expression of target genes

Figure 4 illustrates the multi-circuit systems in vibrios. When the concentration of the signals is low, all of the receptor proteins (LuxN, LuxQ, and CqsS) autophosphorylate and transfer phosphate through a phosphotransferase protein, LuxU, to the LuxO protein. The phosphorylation activates LuxO and, in concert with sigma-54, it stimulates the expression of five small regulatory RNAs. These small regulatory RNAs, with the RNA chaperone Hfq, destabilize the mRNA that encodes the LuxR$_{Vh}$ master regulator which either represses or activates the transcription of target genes (depending on the gene) (Lenz et al. 2004; Waters and Bassler 2005). On the other hand, when sufficient signal amounts bind to the receptors, these lead them to change from kinases to phosphatases that dephosphorylate LuxO. The

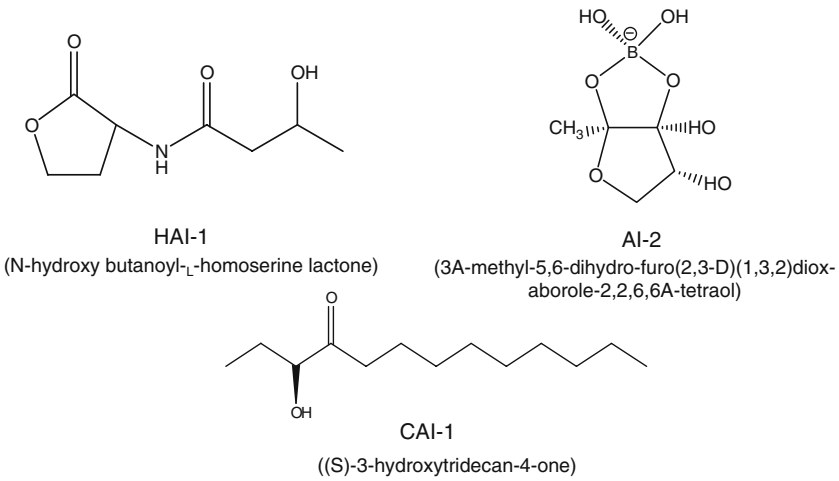


Fig. 3 Autoinducers produced by *V. harveyi*

dephosphorylated LuxO is inactive, which gives way to the translation of $LuxR_{Vh}$ mRNA. The regulator then regulates the transcription of target genes (Henke and Bassler 2004a).

Impact of QS on Aquaculture Disease

High mortalities in different aquaculture organisms are observed when exposed to AHLs. Mixtures of different AHL molecules at 1 mg/L significantly reduced the development and survival of giant freshwater prawn (Baruah et al. 2009) and turbot larvae (Tinh et al. 2008a). Moreover, high AHL levels are detected in different organs of rainbow trout during infection of *V. anguillarum* (Buch et al. 2003). However, the relationship between the molecules and the pathogenicity is still unknown. The negative impact of AHLs is probably due to the stimulation of bacterial virulence factors that are controlled by QS because, when bacterial growth is counteracted by the addition of antibiotics together with the AHLs, the effect is not observed (Tinh et al. 2008a). Several phenotypes and gene products associated with virulence in aquaculture pathogens have been shown to be QS-regulated (Table 1). The link between QS and virulence can be illustrated by the report of Denkin and Nelson (2004), who found that the expression of the *empA* metalloprotease in *V. anguillarum*, which is responsible for bacterial virulence in Atlantic salmon, is regulated by the three-channel QS system (Croxatto et al. 2002). Another virulence factor, toxin T1, responsible for the virulence of *V. harveyi* in *Penaeus monodon* has also been shown to be under quorum sensing control (Manefield et al. 2000). Virulence of *Aeromonas hydrophila* is diminished when the *luxR* homologue *ahyR* is inactivated as the response regulator attenuates some of the virulence determinants that are responsible for pathogenesis (Bi et al. 2007).

Other signals such as autoinducer-2 can also play a significant part in virulence. This autoinducer is needed for the virulence of *V. harveyi* towards brine shrimp (Defoirdt et al. 2005) and rotifers (Tinh et al. 2007a). Indeed AI-2 is important in mediating virulence in a number of medically related pathogens (Ohtani et al. 2002; Xavier and Bassler 2003). Recently, Brackman et al. (2009) showed that interference with the AI-2 signal transduction pathway through competition for the LuxPQ receptor is sufficient to reduce the virulence of *V. harveyi* towards brine shrimp.

On the contrary, Defoirdt et al. (2005) reported that inactivation of QS by mutation did not affect the virulence of *A. hydrophila* and *V. anguillarum* towards brine shrimp. Similarly, it has been reported that the QS mutants of *V. anguillarum* had the same virulence as the wild type in rainbow trout (Milton et al. 1996; Milton et al. 2001; Croxatto et al. 2002). Meanwhile, Rasch et al. (2007) noticed that for *Aeromonas salmonicida* there is no correlation between AHL and virulence factor expression.

Based on the findings mentioned above, it can be concluded that QS is not the sole mechanism to control virulence and that the mechanism by which QS regulates virulence differs between species and the type of virulence factors (refer to Table 1). Indeed a specific virulence factor can be under QS control in one species whereas it is not in another species or a virulence phenotype can be positively regulated by QS in one species whereas it is negatively regulated in another species. Biofilm formation, for instance, is induced by QS in *V. anguillarum*, whereas it is repressed by QS in *V. cholerae* (Milton 2006). In *V. harveyi*, metalloprotease is positively regulated (Mok et al. 2003) whereas chitinase A is negatively regulated (Defoirdt et al. 2010). Timing is critical for virulence production, and the production and detection of signal molecules might enable the optimal timing of virulence factor expression (Ohtani et al. 2002). It is apparent that the exact relation and the mechanism of virulence of pathogen towards host remain unclear and warrant further investigation.

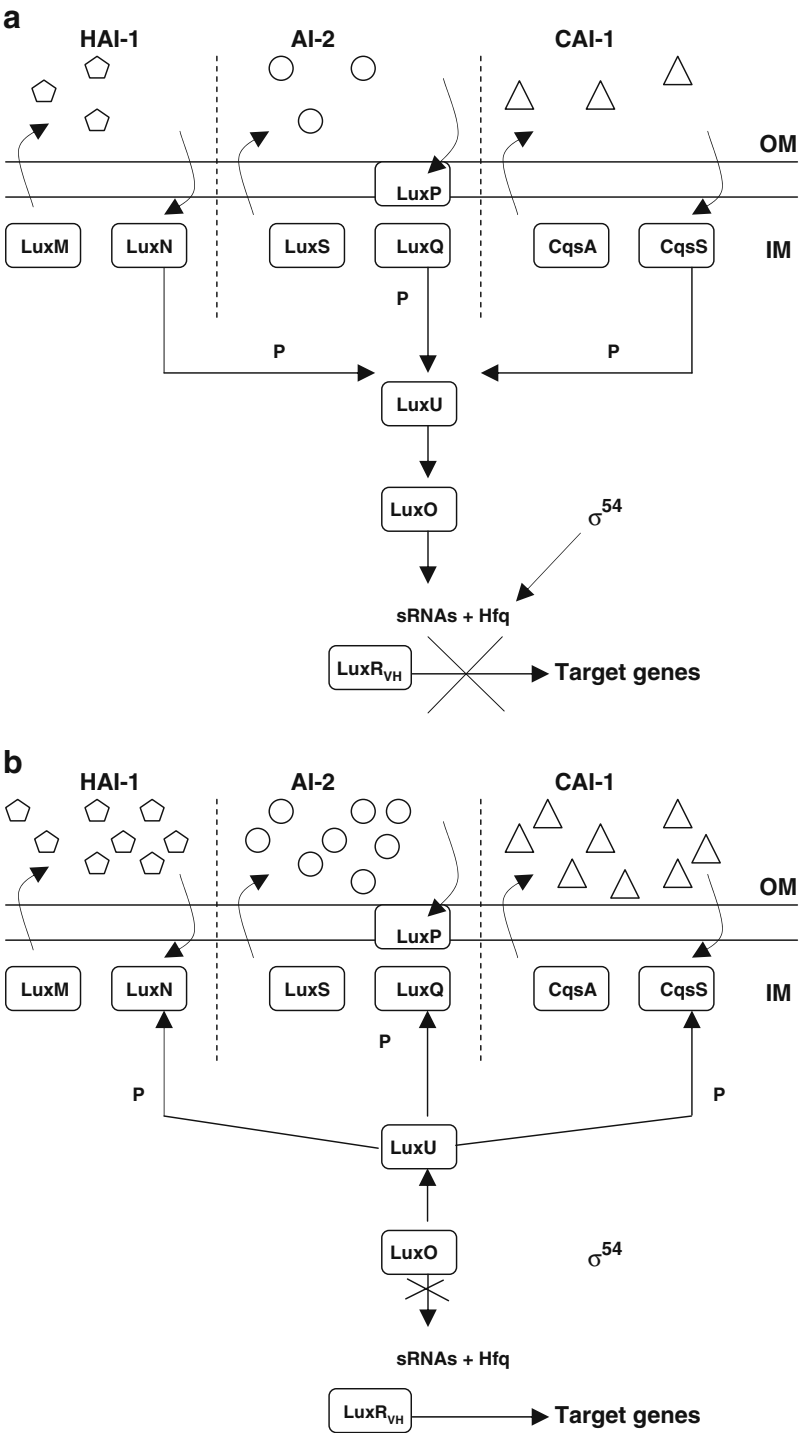


Fig. 4 Multi-channel signaling in *V. harveyi*. **a** Quorum sensing at low and **b** at high signal molecule concentration. Refer to the text for more details. *Arrows* show the flow of signal transduction and phosphorylation/dephosphorylation. *IM*, inner membrane; *OM*, outer membrane (redrawn from Henke and Bassler 2004a with some modifications)

Quorum Sensing Inhibition—Mode of Action

Quorum sensing inhibitors (QSI) are non-bacteriostatic organisms/molecules that can restrain the virulence of pathogens through interference with quorum sensing, enabling the host to use its own defense mechanisms to control the pathogen (Wang et al. 2008). The two common approaches to intervene with QS are briefly discussed (for a detailed review, refer to Rasmussen and Givskov 2006 and Ni et al. 2009).

Signal Degradation

The lactone ring of AHL is unstable at alkaline conditions (pH>7) and high temperature (>37°C) causing lactonolysis (Yates et al. 2002). This provided an evolutionary insight in

Table 1 Bacterial pathogens in aquaculture and the link with quorum sensing

Pathogens	Signals	Regulatory proteins	Phenotypes and virulence factors	References
Aeromonas hydrophila	BHL[a], HHL, one AHL[b]	AhyI/AhyR	Biofilm[c, d], serine[c, d], glycine[c, d], metalloprotease gene *empA*[c, d], pigment[c, d], hemolysin[c, d], type VI[c, d], siderophores, enterotoxin	Bi et al. 2007; Bruhn et al. 2005; Lynch et al. 2002; Swift et al. 1997; Swift et al. 1999
Aeromonas salmonicida	BHL[a], HHL, DHL, OHHL, one AHL[b]	AsaI/AsaR	Serine[c, d], metalloprotease[c, d], lipase, pigment, α-hemolysin, glycero-phospholipid-chloresterol acyltransferase, siderophores, enterotoxin	Bruhn et al. 2005; Swift et al. 1997
Edwardsiella tarda	BHL, HHL, OHHL, HeHL AI-2[a]	EdwI/EdwR LuxS homologue	Virulent-strain-specific protein[c, d], hemolysins, chondroitinase	Han et al. 2009; Morohoshi et al. 2004
Hafnia alvei	OHHL	[b]	siderophore production type I and type III, fimbriae, resistance to the bactericidal effect of serum,	Padilla et al. 2005
Vibrio anguillarum	ODHL[a] HHL, OHdHHL[a], one AHL[b] AI-2 CAI-1[b]	VanI/VanR VanM/VanN VanS/VanPQ VanT master regulator	Biofilm[c, d], metallo-exoprotease through *empA* expression[c, d], serine and glycine synthesis[c, d] melanin pigment[c, d], Siderophore, exopolysaccharide, probably haemolysin, lipase, neurotoxic acetylcholinesterase	Buchholtz et al. 2006; Milton et al. 1997; Milton et al. 2001
Vibrio alginolyticus	AI-2	Luxo homologue to regulatory protein column, LuxS homologue	Flagellar biosynthesis[c, d], protease[c, d], polysaccharide[c, e], biofilm[c, e]	Ye et al. 2008; Wang et al. 2007
Vibrio harveyi	OHdBHL AI-2 CAI-1	LuxLM/LuxN LuxS/LuxPQ CqsA/CqsS $LuxR_{Vh}$ master regulator	Siderophore[c], type III secretion[c, e], chitinase[c, e], exotoxinT1[c, d], polysaccharide[c], metalloprotease[c], bioluminescence[c], cysteine protease, caseinase, gelatinase, lipase, phospholipase, haemolysins,	Darshanee Ruwandeepika et al. 2010; Defoirdt et al. 2010; Henke and Bassler 2004a; Henke and Bassler 2004b; Lilley and Bassler 2000; Manefield et al. 2000; Zhang and Austin, 2000
Vibrio ichthyoenteri	Three AHLs[b], AI-2	LuxS[b] homologue	Biofilm	Xuan et al. 2010
Vibrio mimicus	AI-2 homologue	LuxS, LuxO and LuxR homologues	Protease[c, d], hemolysin	Sultan et al. 2006
Vibrio parahaemolyticus	[b]	LuxI/LuxR homologues	Type III secretion[c, e], Opacity, protease	Henke and Bassler 2004b
Vibrio salmonicida	OHHL, HHL	LuxI/LuxR homologues	Cryptic bioluminescence	Nelson et al. 2007
Vibrio scophthalmi	OHdDDHL, Two AHLs[b] AI-2	LuxS[b] homologues	[b]	García-Aljaro et al. 2008
Vibrio vulnificus	BHL, ODHL, ODDHL, minor HHL, OHL, OTHL, AI-2	LuxU, LuxO, SmcR transcriptional regulator LuxS/LuxPQ	Metalloprotease[c, d], cytolysin[c, e], hemolysin[c], extracellular capsular polysaccharide, siderophore,, toxin RTX	Bruhn et al. 2005; Kim et al. 2003
Yersinia ruckeri	OOHL[a], HHL, OHHL, OHeHL, OHL, ONHL, ODHL, ODDHL	YenI/YenR	Metalloprotease, protein secretion, siderophores, heat sensitive factors	Bruhn et al. 2005; Kastbjerg et al. 2007

[a]Dominant signal

[b] Unknown/predicted

[c] Both are controlled by QS to hemolysin and siderophore

[d] Positively regulated to metalloprotease

[e] Negatively regulated to siderophore

BHL N-butanoyl-L-homoserine lactone, *OHdBHL N*-(3-hydroxybutanoyl)-L-homoserine lactone, *HHL N*-hexanoyl-L-homoserine lactone, *OHHL N*-(3-oxohexanoyl)-L-homoserine lactone, *OHdHHL N*-(3-hydroxyhexanoyl)-L-homoserine lactone, *HeHL N*-heptanoyl-L-homoserine lactone, *OHeHL N*-(3-oxoheptanoyl)-L-homoserine lactone, *OHL N*-3-octanoyl homoserine lactone, *OOHL N*-(3-oxo-octanyl)-L-homoserine lactone, *ONHL N*-3-oxononanoyl-L-homoserine lactone (*Y. ruckeri*), *DHL N*-decanoyl-homoserine lactone, *ODHL N*-(3-oxodecanolyl)-L-homoserine lactone, *ODDHL N*-(3-oxo-dodecanoyl)-L-homoserine lactone, *OHdDDHL N*-(3-hydroxydodecanoyl)-L-homoserine lactone, *OTHL N*-(3-oxo-tetradecanoyl)-L-homoserine lactone, *AI-2* furanosyl borate diester 3A-methyl-5,6-dihydro-furo(2,3-*D*)(1,3,2)dioxaborole-2,2,6,6A-tetranol, *CAI-1* (*S*)-3-hydroxytridecan-4-one

the reasons of pH increase in some plants infected with *Erwinia carotovora* (Byers et al. 2002) as well as the pH increase in the gut of animals such as Lepidopteran larvae (Funke et al. 2008), which is probably to control the associated microbiota. Some organisms such as bacteria and micro-algae are also able to raise the pH (particularly during the late growth phase), which can affect the stability of QS molecules in their surroundings. This has been observed by Yates et al. (2002) who found that the AHLs produced by *Pseudomonas aeruginosa* and *Yersinia pseudotuberculosis* in unbuffered media were inactivated by the hydrolysis of the lactone ring at high pH. They also found that, in order to stabilize AHLs, a minimum acyl chain length of four carbons is needed and long-chain AHLs are more stable than the shorter-chain AHLs. Another example of chemical inactivation is through oxidized halogen antimicrobials (Borchardt et al. 2001), reacting to keto-substituted AHLs. However, they are inactive towards unsubstituted AHLs.

Signal molecules can also be inactivated through enzymatic destruction (Dong et al. 2007). Enzymes capable to degrade AHL, e.g., lactonases and acylases, are ubiquitous in prokaryotes and eukaryotes (Dong and Zhang 2005). The mechanism of enzymatic inactivation is shown in Fig. 5. Acylase (also known as amidase) acts by cleaving the amide bond between the acyl chain and the homoserine lactone moiety, giving a fatty acid and homoserine lactone. Meanwhile, lactonase hydrolyzes the lactone bond, resulting in acylated homoserine (Dong and Zhang 2005; Czajkowski and Jafra 2009).

Furthermore, these AHL-degrading enzymes are highly specific towards AHLs but without any influence to other molecules (Wang et al. 2004). The microorganisms probably produce such enzymes as a defense strategy against their competitors. The fact that some organisms are able to utilize AHL and the enzymatic degradation products as sole carbon and nitrogen sources (Leadbetter and Greenberg 2000; Tinh et al. 2007b) opens the possibility to use them as probiotics in aquaculture. The AHL degrading activity directly breaks down the signals and influences QS-regulated activity.

Receptor Blocking/Antagonists

Currently, the most extensively studied QSI activity is the use of signal molecule analogs to block the signal molecule receptors. Molecules that are structurally similar to AHLs or AHL mimics are capable to interfere with the LuxR-type signal receptors. Such molecules could not only bind to LuxR and dislocate AHL but at times also activate the protein (Schaefer et al. 1996). Signal mimics can also block the receptor either through competition for a receptor site or displacement of the original AHL, downregulating the receptor concentration and QS-regulated activity (Manefield et al. 2002). Attenuators range from synthetic compounds which are similar in structure to AHL molecules or with some minor modifications on the acyl chain to diverse natural compounds from living organisms (Rasmussen et al. 2005).

Quorum Sensing Inhibition by Marine Bacteria Degrading Signals and/or Producing Signal Antagonists

Tinh et al. (2007b) pioneered the work of isolating bacteria capable to grow on AHLs as carbon and nitrogen sources from the gastrointestinal tract of aquaculture organisms, i.e., microbial communities from the *Penaeus vannamei* shrimp gut were collected and grown in the presence of a mixture of different short-chain AHLs as sole carbon (and nitrogen) source, eventually resulting in three enrichment cultures. The enrichment cultures were shown to degrade *V. harveyi* HAI-1 in vitro and to improve the growth rate of rotifers challenged to pathogenic *V. harveyi.* In addition, the cultures enhanced the survival of turbot larvae through direct feeding or bioencapsulation in live food (Tinh et al. 2008a). Similar studies were conducted by Cam et al. (2009) using AHL degraders from the gut of European seabass, *Dicentrarchus labrax* L., and Asian seabass, *Lates calcarifer.* The degraders, which were grown using glycerol released by *Artemia* during hatching, improved the survival of *Macrobrachium rosenbergii* prawn larvae. The larvae also had a better physiological condition, displaying higher ammonia tolerance.

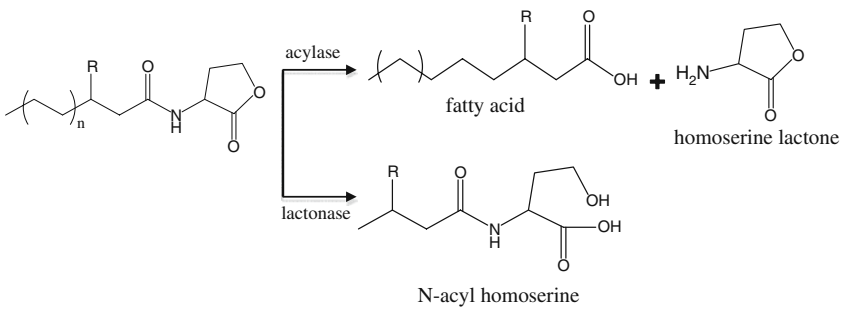


Fig. 5 Enzymatic degradation of AHLs. The degradation mechanism of acylase and lactonase (refer to the text for further details). The R is substitutions (hydroxyl or keto group) that can occur at C3 position. The *n* corresponded to alkyl group consisting between four and 18 carbons (redrawn after Dong and Zhang 2005)

Two Gram-negative strains with different roles in QS were isolated from the intestinal microbial flora of Ayu fish, *Plecoglossus altivelis,* with *Aeromonas* sp. strain MIB015 as AHL producer and *Shewanella* sp. strain MIB010 as AHL degrader, respectively (Morohoshi et al. 2005). The AHL degraders disintegrated 1 μM of synthetic HHL in 3 days and interfered with the exoprotease activity of *Aeromonas*. Further investigation showed that the activity was due to AHL-acylases encoded by the *aac* gene (Morohoshi et al. 2008). The expression of this gene was also found to quench AHL production in the fish pathogen *V. anguillarum*, thus disrupting QS-regulated biofilm formation (Morohoshi et al. 2008). Other bacterial degraders include Gram-positive *Bacillus thuringiensis*, *Bacillus cereus*, and *Bacillus mycoides* which produce the AiiA protein that catalyzes the lactonolysis of AHLs (Lee et al. 2002; Dong et al. 2002). The ability of this genus to produce endospores which are resistant to high heat and chemical agents makes it ideal to be adapted for use in aquaculture environments since spores are stable and retain their beneficial properties for a long time. This makes them worthwhile to explore in the future.

Bacteria can also act as antagonists by releasing molecules that can block QS. Marine actinomycetes screened by You et al. (2007) inhibited the biofilm formation of different *Vibrio* species. Thirty-five out of 88 actinomycetes inhibited the biofilm formation of *V. harveyi, Vibrio vulnificus*, and *V. anguillarum* without affecting their growth. The best strain, strain A66 (identified as *Streptomyces albus*), dispersed the biofilm structure and this may have been linked to the inactivation of the AHL QS system. As indigenous species of the marine environment, Actinomycetes predominantly from the genera of *Streptomyces*, *Micromonospora*, and *Salinispora* could offer interesting options for probiotics in aquaculture (Das et al. 2008).

A Gram-positive strain isolated from seagrass communities, *Halobacillus salinus* C42, inhibited the bioluminescence of *V. harveyi* in a co-cultivation assay through the diffusion of small molecules identified as phenetyhlamide compounds, with 2,3-methyl-*N*-(2′-phenylethyl)-butyramide being the most effective one (Table 2). The compounds blocked the expression of several QS-controlled phenotypes in Gram-negative bacteria such as violacein pigment in CV026, fluorescence in AHL reporter strain JB525, and planktonic luminescence in *V. harveyi*. The structural similarities of the compounds with the AHL suggest that they might compete with AHLs for receptor binding (Teasdale et al. 2009).

Other AHL-like molecules are the tumonoic acids from the marine cyanobacterium *Blennothrix cantharidosmum*. Although no significant QSI activity was detected in a green fluorescent protein AHL detection assay, some of the compounds (Table 2) were shown to moderately inhibit the bioluminescence of wild-type *V. harveyi* with the highest inhibition by tumonoic acid F (Clark et al. 2008). However, it is not known whether the luminescence inhibition is of actual QSI activity or other factors associated with bioluminescence chemistry.

Quorum Sensing Inhibition by Macro-algae

Eukaryotes such as algae, protozoa, and fungi live in close proximity with both pathogenic and beneficial bacteria in the aquatic environment. Thus, it is not surprising that eukaryotes have developed different defense mechanisms to interact with bacteria, e.g., by producing secondary metabolites (Rasmussen et al. 2005) impacting QS (Dudler and Elberl 2006).

Marine plants are important potential candidates to interfere with QS (Kjelleberg and Steinberg 2001). The first QS inhibitor was isolated from the red macro-alga (also known as seaweed), *Delisea pulchra,* which showed a high antifouling activity (Givskov et al. 1996). The antifouling activity apparently is caused by a broad range of secondary metabolites, halogenated furanones found at the surface of the alga (Dworjanyn and Steinberg 1999). These halogenated furanones (Table 2) are similar in structure to AHL, except that furanones have a furan-ring instead of a homoserine lactone ring. Among the earliest investigations on the effect of this alga on bacteria is the addition of *D. pulchra*'s crude extract to cultures of the human pathogen *Proteus mirabilis* (Gram et al. 1996), where the extract was found to inhibit swarming motility. Although not as strong as the crude extract, the halogenated furanones isolated from the sample also decreased the swarming velocity.

The most well-studied natural compound to date is probably (5*Z*)-4-bromo-5-(bromomethylene)-3-butyl-2(5*H*)-furanone (Table 2). This compound is shown to have high inhibitory activities in several biological assays of AHL-controlled expression in different Gram-negative bacteria (Rasmussen et al. 2000; Hentzer et al. 2003) and also blocks AI-2 signaling (Ren et al. 2001). The results triggered the chemical synthesis of several furanone analogs as QS inhibitors such as (5Z)-4-bromo-5-(bromomethylene)-2(5H)-furanone.

Using a gnotobiotic model system, Defoirdt et al. (2006) demonstrated that natural and synthetic brominated furanones (Table 2) are able to protect brine shrimp (*Artemia franciscana)* from pathogenic isolates belonging to the species *V. harveyi, V. campbellii* and *V. parahaemolyticus*, respectively, through the disruption of AI-2 QS. The natural furanone was also found to counteract the negative effect of different pathogenic *V. harveyi* strains in the rotifer *Brachionus plicatilis* (Tinh et al. 2007a). Moreover, Manefield et al. (2000) showed that the natural furanone

Table 2 Different molecules from bacteria with QS inhibition activity

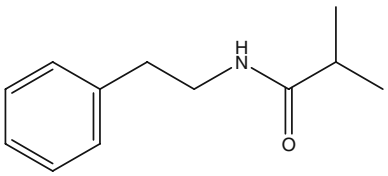
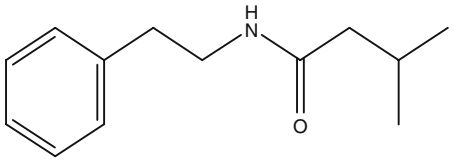
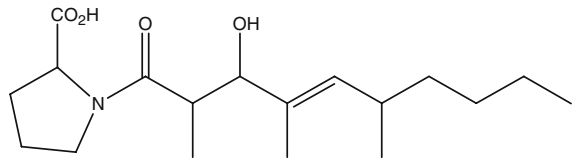
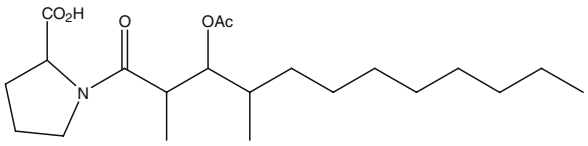
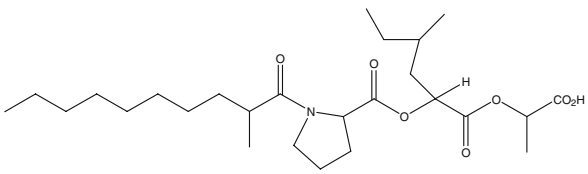
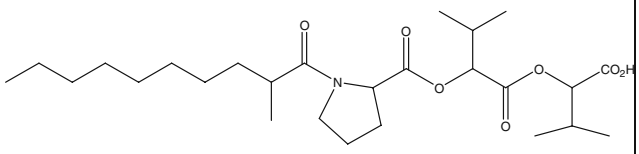
Type of molecules	Type of organisms	Effect on AHL/QS phenotype	Reference
 *N*-(2'-phenylethyl)-isobutyramide  *2,3-methyl-N-(2'-phenylethyl)-butyramide*	Gram positive *Halobacillus salinus*	Inhibition of bioluminescence, violacein and fluorescence production in the presence of *N*-(3-oxohexanoyl)-L-homoserine lactone (OHHL)	Teasdale et al., 2009
 Tumonoic acid E  Tumonoic acid F  Tumonoic acid G  Tumonoic acid H	Cyanobacteria *Blennothrix cantharidosmum*	Detection of modest bioluminescence inhibition	Clark et al., 2008

Table 2 (continued)

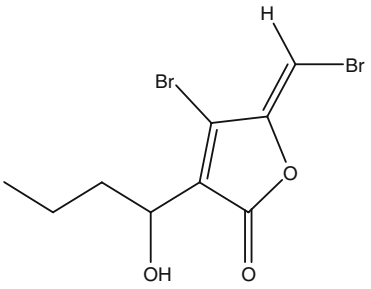
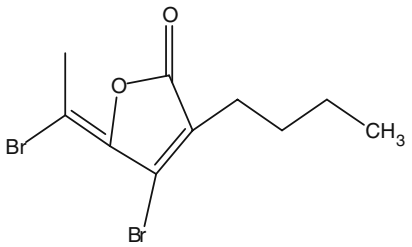
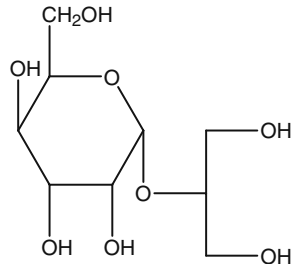
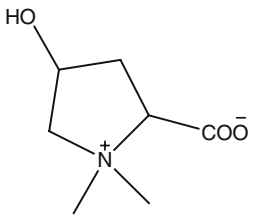
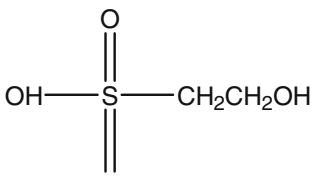
Type of molecules	Type of organisms	Effect on AHL/QS phenotype	Reference
 Halogenated furanone	*Delisea pulchra*	Inhibition of swarming motility in *Proteus mirabilis*	Gram et al., 1996
 (5Z)-4-bromo-5-(bromomethylene)-3-butyl-2(5H)-furanone (Natural furanone)	*Delisea pulchra*	Inhibition of luminescence detection and toxin production	Manefield et al., 2000; Defoirdt et al., 2007
 Floridoside  Betonicine  Isethionic acid	*Ahnfeltiopsis flabelliformis*	Reduction of N-3-octanoyl homoserine lactone (OHL) detection	Kim et al., 2007

Table 2 (continued)

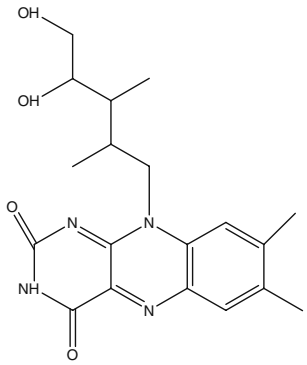
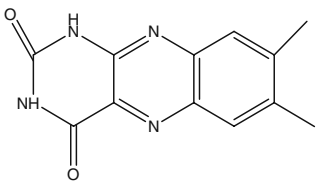
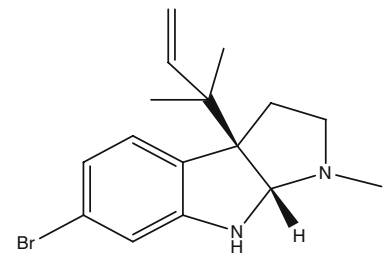
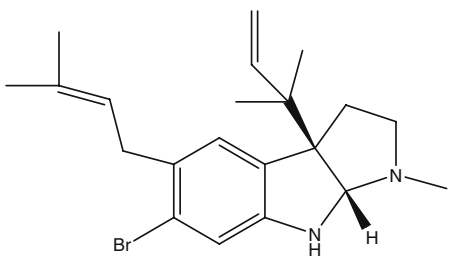
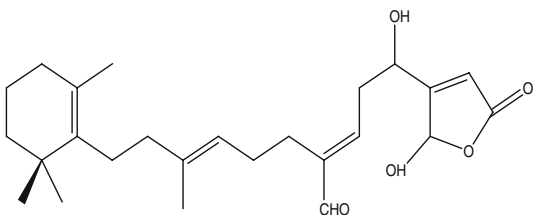
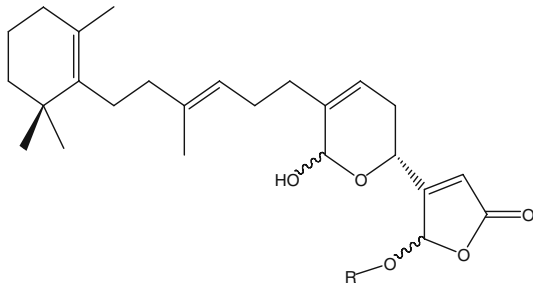
Type of molecules	Type of organisms	Effect on AHL/QS phenotype	Reference
 Riboflavin Vitamin B2  Lumichrome	*Chlamydomonas reinhardtii* CC2137	Stimulation of N-3-oxo-dodecanoyl homoserine lactone (3-oxo-C12-HSL) detection	Teplitski et al., 2004; Sayre et al., 2006; Rajamani et al., 2008
  Bromo-tryptamine based alkaloids	*Flustra foliacea* (bryozoans)	Reduction of *N*-3-oxododecanoyl-homoserine lactone (ODDHL), *N*-octanoyl homoserine lactonoe (OHL), *N*-oxohexanoyl-homoserine lactone (OHHL) detection	Peters et al., 2003

Table 2 (continued)

Type of molecules	Type of organisms	Effect on AHL/QS phenotype	Reference
 Secomanoalide  Manoalide	*Luffariella variabilis* (Sponge)	Reduction of *N*-3-oxo-hexanoyl-homoserine lactone (OHHL), *N*-3-oxododecanoyl-homoserine lactone (ODDHL), *N*-butanoyl-homoserine lactone (BHL) detection	Skindersoe et al.,2008

blocked the luminescence and toxin T1 production (both of which are QS-regulated) of *V. harveyi* that were pathogenic to farmed shrimp. This compound also decreased death in rainbow trout infected with *V. anguillarum* (Rasch et al. 2004). These data showed that furanones could act as anti-infective compounds in different aquatic host–microbe systems

In general, at a concentration of 50–200 μM, the natural furanones exhibit QSI without any non-bacteriostatic effects (Manefield et al. 1999; 2000). However, furanones appear to be toxic to higher organisms where concentrations above 1 μM are lethal to rainbow trout (Rasch et al. 2004). The doses that were used to test the QSI activity on aquatic organisms were 0.01–0.1 μM for trout (Rasch et al. 2004), ±10 μM for rotifer (Tinh et al. 2007a), and ±50 μM for *Artemia* (Defoirdt et al. 2006).

The antagonistic effects of furanones are attributed to their ability to destabilize *V. fischeri* LuxR-type proteins, thus reducing the amount of the protein to act as a AHL-mediated regulator (Manefield et al. 2002). In *V. harveyi*, the natural furanone was found to directly target the QS master regulator LuxR (which is not homologuous to *V. fischeri* LuxR), obstructing the ability of LuxR to bind to target gene promoter sequences, probably by inducing certain molecular structure modifications (Defoirdt et al. 2007b). In addition, recent findings by Zang et al. (2009) demonstrated that the molecules also disrupt AI-2 synthesis by covalently modifying and inactivating the LuxS enzyme. The furanones were shown to bind to thiol groups in cysteine residues in the LuxS protein and can therefore be hypothesized to be non-specific. The apparent specificity in activity towards QS-regulated phenotypes might be due to the fact that relatively small changes in the activity of QS regulatory genes have large effects on the phenotypes regulated by QS.

Interestingly, another seaweed belonging to the same family, *Bonnemaisonia hamifera*, also showed antifouling activities (Nylund et al. 2005). The seaweed inhibited the growth of nine different bacterial strains from five different groups. As for other antibacterial compounds, it might exhibit QSI activity if used in subinhibitory concentrations, which would explain the antifouling activity. The chemical structure of the algal metabolites responsible for the inhibition activity is still unknown, although it was speculated to be polyhalogenated 2-heptanones. In addition to this, Kim et al. (2007) discovered three new AHL antagonists in the red alga *Ahnfeltiopsis flabelliformis* through bioactivity-guided fractionation. The metabolites from the polar active fractions were identified as α-D-galactopyranosyl-(1-2)-glycerol(floridoside), betonicine, and isethionic acid (Table 2). Due to the inavailability of other pure compounds, only commercial isethionic acid was further tested. However, the compound did not show any QSI activity and it was speculated that it worked synergistically with other compounds to block QS. Minor antagonist activity was also observed in algae of the families Caulerpaceae, Rhodomelaceae, and Galaxauraceae

(Skindersoe et al. 2008). Finally, brown algae from the family Laminariaceae were reported to produce hypobromous acid, which deactivates 3-oxo-acyl-HSL molecules (Borchardt et al. 2001).

Since the furanones are released on the surface (thallus) of the algae (Maximillen et al. 1998), they might be easily integrated as a biocontrol measure in aquaculture. The range of individual furanones on the surface is observed to be between 10 and 250 ng cm^{-2}. The integration of macro-algae in aquaculture is not a new practice. Macro-algae have been integrated in the culture of fish and shellfish in coastal open water- and land-based systems since the 1970s. The focal motivation behind the integration is to come to a more sustainable aquaculture in a sense that macro-algae are able to maintain good water quality and function as additional feed for the animals (Neori et al. 2004). The additional putative role of macro-algae as bacterial control agents might further justify their use in multi-trophic aquaculture. The macro-algae to be used in a system could be selected based on their capacity to produce QSI compounds.

Quorum Sensing Inhibition by Micro-algae

Another bacterial control approach in aquaculture is the use of the so-called green water technique. The term "green water" denotes the addition or integration of different algal mixtures into the tanks and ponds (Palmer et al. 2007). Although green water seems to give good results in practice, the positive effects of micro-algae are not yet fully understood. Similar to bacteria, micro-algae are always present in the aquatic environments. Larvae reared in green water tend to show better survival and growth rate compared to larvae reared in clear water (Palmer et al. 2007). Although the exact mechanisms are still unknown, the nutritional value of the algae, stimulatory effects on the digestive system and beneficial effect on the gut microbiota (Reitan et al. 1997; Tinh et al. 2008b), and improvement of several abiotic factors (Muller-Feuga 2000) are probably involved. In addition to this, they might have inhibitory activity towards pathogenic and opportunistic bacteria (Kellam and Walker 1989). To date, the effect of micro-algae in QS interference have only been reported for freshwater species. Examples are the unicellular green algae *Chlamydomonas reinhardtii* and different *Chlorella* sp. which stimulated the luminescence of *V. harveyi* (Teplitski et al. 2004). Further separation of *C. reinhardtii* culture filtrates through chromatographic techniques revealed the presence of compounds capable to stimulate QS of LasR of *P. aeruginosa* and CepR of *Pseudomonas putida*, respectively, with higher activity in older cultures. However, no significant QS activities, neither inhibitory nor stimulatory, were detected in biosensors with LuxR, AhyR, and CviR reporter constructs. In addition, a significant part of the proteome in the soil bacterium *Sinorhizobium meliloti* was altered when treated with partially purified LasR stimulatory algal substances (Teplitski et al. 2004; Sayre et al. 2006). One of the agonistic compounds was later shown to be lumichrome, a derivative of vitamin B_2 riboflavin (Table 2) (Rajamani et al. 2008) which specifically stimulated the LasR receptor. Even though there are very little structural similarities with AHL, both AHL and the compound were found to interact with the same amino acid residues in the AHL binding pocket.

Quorum Sensing Inhibition by Other Organisms

Other organisms with the potential to be utilized in aquaculture systems include sponges and aquatic invertebrate and the compounds produced by these organisms. The North Sea bryozoan *Flustra foliacea* releases brominated alkaloids (Table 2) that reduce the signal intensities of different QS biosensors with 20–50% at a concentration of 20 mg/L. Furthermore, the metabolites also inhibit QS-regulated phenotypes, such as protease in *P. aeruginosa* (Peters et al. 2003). A strong QS inhibition has also been observed for the sponge *Luffariella variabilis* in LuxR-regulated systems. The secondary metabolites manoalide, manoalide monoacetate, and secomanoalide (Table 2) were found to be responsible for the inhibitory activity present in this sponge (Skindersoe et al. 2008).

Ecological Implications

It is becoming more and more evident that bacteria not only regulate their own behavior but also modulate the behavior of certain microorganisms around them through QS. It is anticipated that these types of interactions are of importance in ecological niches where a high concentration of microorganisms is available such as biofilms or flocs. However, the ecological significance of QS molecules would greatly benefit from a more accurate knowledge of in vivo concentration of QS molecules in these niches. Although distantly related, there are numerous evidences on prokaryotic and eukaryotic interactions within a wide range of niches. Since bacteria diffuse their signals into the environment, it is possible that other organisms can utilize them as chemical cues for their own benefit.

An important example of cross-signaling across two kingdoms is that between bacteria and macro-algae (for a review, refer to Joint et al. 2007). A high correlation has been identified between the number of green algae *Ulva*

zoospores and bacterial density in a biofilm (Joint et al. 2002). Further studies revealed that zoospores, for example, those of *Ulva* sp. and the red algae, *Acrochaetium* sp. (Weinberger et al. 2007), are in fact attracted to bacterial signals. This is shown through preference to release their unicellular zoospores in the presence of bacterial biofilms where AHL act as chemoattractants and cues for the settlement. Interestingly, the spores only settle to biofilms with high AHL concentrations (Tait et al. 2005). These attractions are found to be eliminated in the absence of QS in the biofilms. For example, a reduced amount of zoospores from *Ulva* is observed in biofilms of *V. anguillarum* mutants that could not produce any signal molecules when compared to biofilms of the wild type (Joint et al. 2002). Apparently, the absence of bacterial signal molecules lowers the chances for the zoospores to settle (Tait et al. 2005). The effect of AHLs on zoospore settlement was found to be due to alterations in chemokinesis activity (Wheeler et al. 2006). AHLs decrease the swimming behavior of zoospores, causing them to settle. Additionally, the mechanisms are dependent on the zoospores' ability to detect concentration gradients. Too high levels of AHLs can cause the zoospores to become insensitive and will lead to low zoospores settlements (Joint et al. 2002).

The preference to settle on biofilms is also exhibited by larvae of several invertebrates such as abalone (Daume et al. 1999), oyster (Zhao et al. 2003), polychaete, barnacles (Lau et al. 2005), sea urchin (Huggett et al. 2006), and mussel (Bao et al. 2007). In all of these species, larvae responded directly to biofilms, which induced their settlement and metamorphosis. The microbial community composition of biofilms appears to influence the choice of settlement area (Lau et al. 2005), although it is not yet known whether QS is involved in this process. The connection of QS and larval attachment was verified by Huang and colleagues (2007) through the reduced swimming rates of polychaete larvae *Hydroides elegans*, causing them to settle in the presence of AHL in biofilms. When using C12-HSL as attractants at 100 μmol l^{-1}, 80% of the larvae started to crawl at the surface of biofilm while the other 20% exhibited reduced swimming speed. The capability of larvae and algal spores to perceive cues from bacteria can be exploited in aquaculture where a more controlled settlement of larvae could be advantageous. Finally, Dobretsov et al. (2007) found that different QS inhibitors at a concentration of 0.01–0.001 M are able to interrupt biofilm formation through modification of the bacterial community composition. Furthermore, larvae of the polychaete *H. elegans* and the bryozoan *Bugula neritina* avoided settlement on biofilms that had developed in the presence of the QS blockers. These findings suggest that QS can influence larval attachment to bacterial biofilms by altering biofilm properties.

Conclusion and Further Perspectives

The discovery that several marine organisms can interfere with QS inhibitors, together with the findings that QS controls the virulence of many pathogenic bacteria, suggests that these organisms could be used to control bacterial diseases in aquaculture. In order to utilize this kind of organisms in practice, a better understanding of the processes involved is needed. First, it is important to explore in depth the virulence mechanisms of the pathogens and particularly the connection with QS. Secondly, there is also a need to investigate the precise relationship between the diverse organisms present in the aquatic environment (micro-organisms and cultured organisms) and the effect of QS on this interaction. A thorough understanding of the beneficial organisms' mode of action will eventually allow the consideration of protocols for application in aquaculture systems.

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