IBBJ

Summer 2018, Vol 4, No 3

Review Article

Quorum Sensing in Microbial Virulence

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Submitted 8 Aug 2018; Accepted 26 Aug 2018; Published 24 Sep 2018

Cell-to cell communication occurs via a signaling pathway referred to as quorum sensing. There are four main types of these systems according to the chemical nature of signal molecules used by microorganisms to elicit expression of target genes in response to environmental stimuli or need of microbial communities. Type I system acts by using acyl homoserine lactones as signals to trigger the expression of virulence genes in *Pseudomonas aeruginosa* and members of the Enterobacteriacae family. Other groups of bacteria possess a second system which uses certain furanones as a universal language among different species. Pathogenic *Shigella spp.*, *Salmonella*, and *Escherichia coli* rely on catecholamines of the human host for inducing a third quorum sensing system in infection. Short cyclic peptides act mainly in *Staphylococcus* spp. and *Enteroccocus faecalis* to activate a forth system involved in their pathogenicity. Therefore, it is essential to analyze these systems for the design of antimicrobials that could eliminate pathogens or abolish their harmful activities.

Keywords: Autoinducer, LuxI-LuxR homologues, LuxS, pathogenicity

Bacteria synthesize and release signal molecules called autoinducers when their cell population reaches a threshold value. This cell-to-cell communication pathway is referred to as quorum sensing, through which the bacteria respond to changes in the environment. Bacteria use this pathway to control a variety of their physiological activities such as symbiosis, virulence factor production, antibiotic synthesis, movement, and biofilm formation (1, 2).

Quorum sensing system was initially described in the marine bacterium, *Vibrio fischeri* which lives in symbiotic relationship with the squid *Eupryma scolopes*, and produces light. The bacteria accumulate inside the light organ of the squid to a certain level, and bioluminescence occurs as a mechanism to avoid predation by higher animals (3).

Quorum sensing system basically is composed of two regulatory proteins, LuxI and LuxR. LuxI is the autoinducer synthase responsible for synthesis of an acylated homoserine lactone (HSL) which is N-(3-oxohexanoyl)-homoserine lactone. LuxR binds the autoinducer molecule, and activates the transcription of the luciferase *luxICDABE* operon (4, 5).

In this review, the main types of quorum sensing systems, and their relation to pathogenicity of microorganisms are discussed in addition to trials of using these systems in agriculture and pharmacology.

Main categories of quorum sensing systems

According to the chemical nature of the signal molecule operating the system, four types of quorum sensing pathways have been categorized in microorganisms (6).

LuxI-LuxR system/ autoinducer-1

In LuxI/LuxR homologs, the inducer synthase catalyzes the amide bond formation to join the acyl side chain of acyl-acyl carrier protein with S-adenosyl methionine. This step is followed by lactonization of the intermediate molecule, releasing

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methylthioadenosine, and finally forming an acylated homoserine lactone derivative compound as the autoinducer (7, 8).

Erwinia carotovora sup. Carotovora releases several degrading enzymes acting on pectin, cellulose, and proteins. These enzymes are considered as virulence factors in soft-rot disease attacking plant tissues (9). Synthesis of these enzymes is under the control of the quorum sensing system, ExpI/ExpR which is a LuxI/LuxR homolog, and acts through the autoinducer N-(3-oxohexanoyl)-L-homoserine lactone (10). Another homolog, CarI/CarR is responsible for the production of an antibiotic called carbapenem (1-carbapen-2-em-3-carboxylic acid). In *E. carotovra*, CarI catalyzes the synthesis of N-(3-oxohexanoyl)-L-homoserine lactone as an autoinducer which activates CarR to produce this antibiotic (11).

LuxI/LuxR homologs have been identified in *Serratia* species. *Serratia* belongs to entrobacteriaceae, and produces a red pigment, prodigiosin which is a tripyrrole acting as antibiotic (12). In *Serratia* spp. ATCC39006, SmaI/SmaR is responsible for the synthesis of prodigiosin, carbapenem, cellulose, and pectate lyase (13). The same system in *S. marcescens* is responsible for producing caseinase and chitinase, in addition to its role in biofilm formation (14). Another quorum sensing system,also LuxI/R homolog, called SplI/SplR in *S. proteamaculuans* B5a is involved in synthesis of lipase, protease, and chitinase (15).

In *Pseudomonas aeruginosa*, quorum sensing appears to be a circuit of more than one system with positive and negative regulators. Two pairs of LuxI/LuxR homologues, LasI/LasR and RhlI/RhlR are the main components. The first pair uses N-(3-oxododecanoyl)-homoserine lactone, and the second one uses N-(butyryl)-homoserine lactone (16). This circuit is involved in synthesis of virulence factors essential in infections caused by this pathogen (Figure 1).

LasR binds its inducer, and regulates the expression of *lasA* (protease), *lasB* (elastase), *toxA* (exotoxin A), and *apr* (alkaline phosphatase) in addition to activation of *lasI* itself as well (17-19). The system also activates the second pair, RhlI/RhlR, which is involved in the production of a hemolysin called rhamnolipid, hydrogen cyanide, pyocyanin (a phenazine compound), lectin, and stationary phase sigma factor, a product of *rpoS* in addition to autoregulation of the RhlI/RhlR system itself (20-23). Quorum sensing in *P. aeruginosa* is also essential in biofilm formation since *lasI* mutants do not develop (24).

A third system is also present in *P. aeruginosa* acting to connect RhlI/R and LasI/R, referred to as Pseudomonas quinolone signal (PQI). The lasI system activates this third system which generates 2-heptyl-3-hydroxy-4-quinolone as signal, acting to activate the transcription of RhlR. The *pqsABCD* operon is responsible for the synthesis of 2-heptyl-4-quinolone molecule, and PqsH acts to convert it to 2-heptyl-3-hydroxyl-4-quinolone. In addition to LasI/R and RhlI/R, PQS may also have a role in the expression of the elastase gene, *lasB* (16, 25). The PQS system is also important in the transcription of genes required to produce pyocyanin, and rhamnolipid (26).

Other factors contribute also in regulation of quorum sensing in this organism. *lasR* is controlled by the global regulators, GacA and Vfr while the *rhl* system is regulated by GacA (27, 28). QscR, a LuxR homolog, is induced by *N*-(3-oxododecanoyl)-homoserine lactone and controls both LasI/R and RhlI/R systems. It appears that QscR is a negative regulator and acts in suppression of subthershold activation of quorum sensing signals (29, 30).

The LuxS/autoinducer-2 system

This system has been identified in more than 55 bacterial species which suggests that autoinducer 2 (AI-2) may be a universal language molecule for communication among species (31). AI-2 is produced from *S*-adenosylmethionine (SAM) in three steps. First, SAM is a methyl donor to the toxic intermediate *S*-adenosylhomocysteine (SAH), which is hydrolyzed to *S*-ribosylhomocysteine

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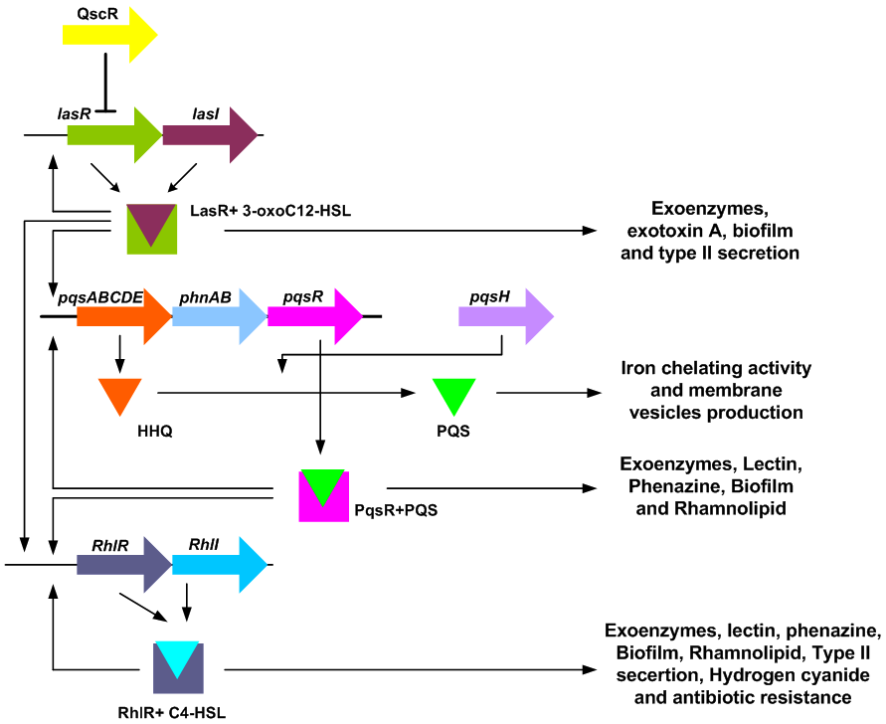


Figure 1. Quorum Sensing in *P. aeruginosa*. Reproduced by permission from Tashiro et al., (23).

(SRH) and adenine by the nucleosidase enzyme Pfs (5'methylthioadenosine/*S*-adenosylhomocysteine nucleosidase) in the second step. In the third step, LuxS catalyzes the cleavage of SRH to 4,5-dihydroxy 2,3-pentanedione (DPD) and homocysteine. DPD is a very unstable compound, and recycles therefore to form several different furanones as AI-2 (32).

In *Vibrio* spp. three quorum sensing type operate to regulate the virulence genes or luceriferase enzyme. System 1 is composed of autoinducer-1,(AI-1) and sensor 1 denoted as LuxN. System 2 consists of AI-2 and sensor 2 designated LuxPQ. AI-1 is N-(3-hydroxybutanoyl)-homoserine lactone which is synthesized by LuxM protein. A third quorum sensing system has been identified in the *V. cholerae*, composed of an autoinducer synthase, cholerae quorum-sensing autoinducer designated as Cqs, and a sensor molecule referred to as cholerae quorum-sensing sensor, CqsS. The CqsA synthesizes an autoinducer, chemically S-3-hydroxytridecan-4-one, also called CAI-1 (cholerae autoinducer-1) (33, 34).

In *V. harveyi* and other species, at a low AI-2 concentration, LuxQ is phosphorylated and transfer a phosphate group to LuxO through LuxU (35, 36). Phosphorylation of LuxO leads to its activation to synthesize small regulatory RNAs by five quorum regulatory RNA encoding genes, qrr1-5. These small RNAs act with the Hfq, a chaperone protein to destabilize mRNA of the response regulator LuxR. Therefore, at low levels of AI-2, LuxR is not synthesized and genes are not transcribed. At higher cell density, LuxP and LuxQ sense the autoinducer. The binding of LuxPQ with AI-2 initiates a switch in function from kinase to phosphatase activity, and dephosphorylation of LuxU and LuxO will occur. When dephosphorylation occurs, LuxO is rendered inactive, and does not stimulate the synthesis of small regulatory RNAs. The response regulator, LuxR is produced and activates transcription of target genes that are either luciferase gene in *V. harveyi* or virulence genes in other species (37).

One of the functions achieved by LuxS is biofilm formation. Bacterial biofilms are defined as a community of cells attached to a biotic or abiotic surface within extracellular matrix that become resistant to antibiotics and host defenses (38). In

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Klebsiella pneumoniae and *E. coli*, LuxS is responsible for biofilm formation (39, 40). AI-2 uses an adenosine triphosphate-binding-cassette transporter, referred to as the Lsr transporter, to enter the cell. This transporter consists of four proteins; LsrA, LsrB, LsrC, and LsrD that are encoded by *lsr* operon. After entering the bacterial cell, AI-2 is phosphorylated by LsrK and becomes modified by LsrF and LsrG. Phosphorylated AI-2 binds to the repressor protein LsrR, and activates the transcription of the *lsr* operon (Figure 2) (41, 42).

LuxS is also an essential enzyme in the "activated methyl cycle" in bacteria (43). In this cycle, after methyl transfer from SAM to its substrates, SAH is produced which is toxic to the cell and is eliminated by Pfs nucleotidase and LuxS to produce adenine, homocysteine and DPD (31). Thus, three different functions were proposed for this second pathway; (a) interspecies cross-talking, (b) participating in biofilm and may be other virulence factors formation, and (c) acting as a component of a metabolic function.

The autoinducer-3 system

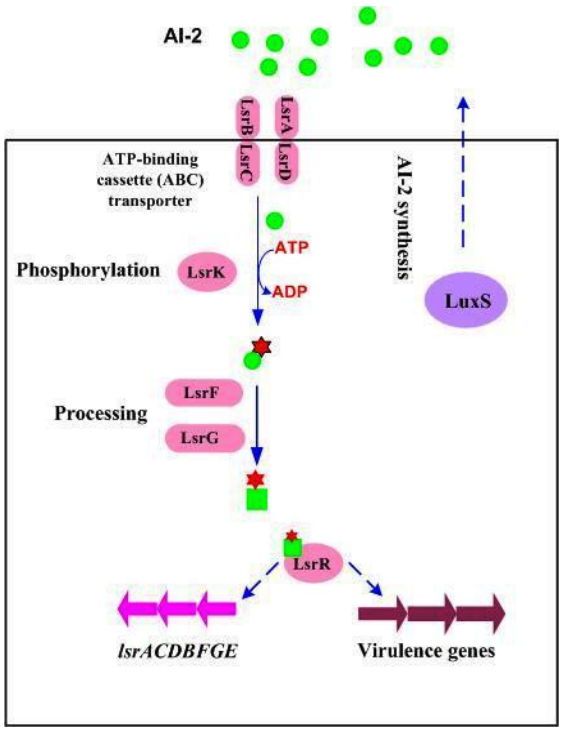


Figure 2. Autoinducer-2 system in *Salmonella* spp., reproduced with permission from Asad and Opal (6).

The epinephrine/norepinephrine system is similar to LuxS system except that it uses the epinephrine and norepinephrine secreted by human body as an inducer, suggesting interkingdom cross signaling function. It is found in *Shigella*, *Salmonella*, *Pasteurella multocida*, *Haemophilus influenza*, and *Yersinia* (44). In enterohemorrhagic *E. coli* (EHCE), QseC is the sensor kinase, and works as a receptor for epinephrine and norepinephrine while QseB is the response regulator of flagella motility gene expression. A second quorum sensing system has been identified which is composed of QseE as the sensor kinase, and QseF as the response regulator. QseF activates the transcription of the pathogenicity island, also known as locus enterocyte effacement (LEE), in this bacterium (Figure 3). A third gene in the same operon designated as QseG, is an outer-membrane protein and appears to be essential to the translocation of type III secretion system effectors into host cells. Two other proteins, QseA and QseD are also essential for the expression of LEE (45, 46). In *S. enterica* infections, QseC regulates the transcription of *Salmonella* pathogenicity island 1 (SPI-1) genes, SPI-2 effector *sifA*, and flagella genes (47).

Accessory gene regulator

Staphylococcus aureus causes many infections in human e.g. abscesses, furuncles, and toxic shock syndrome. This pathogen possesses virulence factors which include exofoliative toxins, haemolysins, and Panton-Valentine leucocidin (48, 49).

In *S. aureus*, the accessory gene regulator (*agr*) locus contains RNAII operon which harbors *agrA*, *agrB*, *agrC*, and *agrD*. AgrD is responsible for the synthesis of an autoinducer which is a short cyclic peptide, called autoinducer peptide (AIP). This autoinducer is composed of 7-9 amino acids in which cysteine is bound to a carboxyl terminal to form a thiolactone ring through post-translational modification (50, 51). AIPs are secreted outside the cell by the action of ABC-transporter system AgrB (Figure 4). When the cell density is optimum, AIPs

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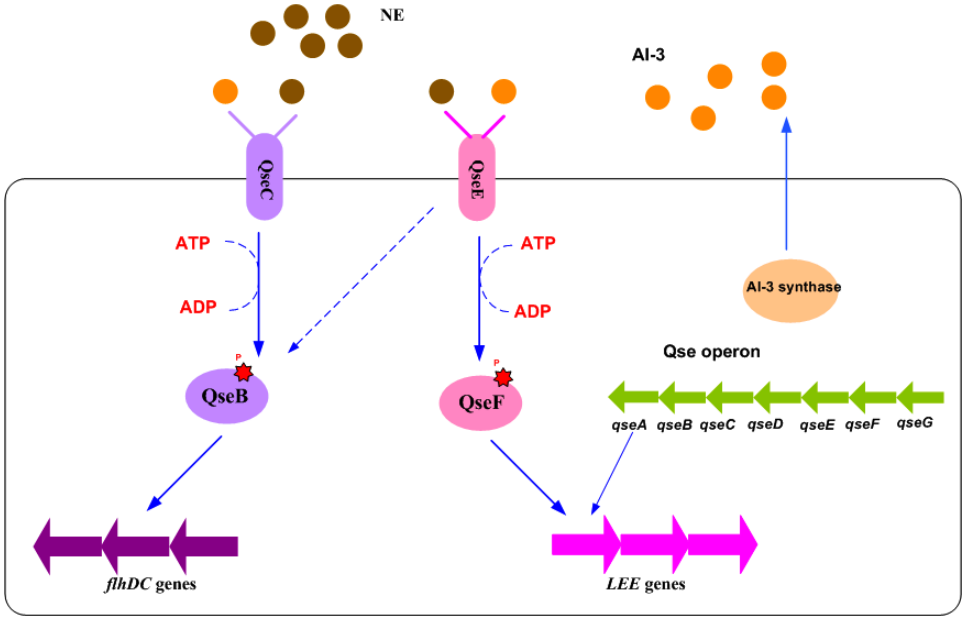


Figure 3. The autoinducer-3 system in enterohaemorragic *E. coli*. Reproduced with permission from Asad and Opal (6).

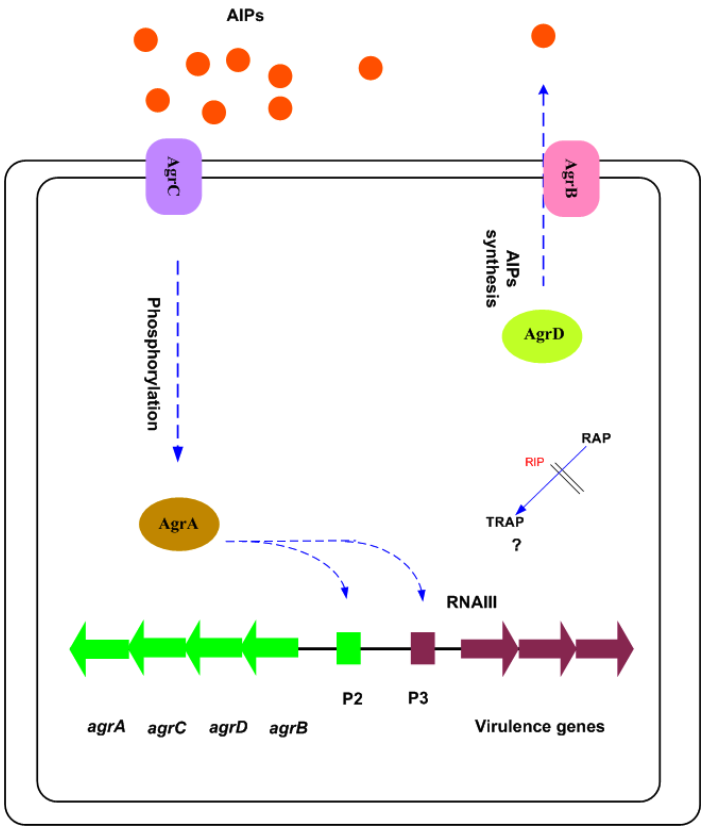


Figure 4. The accessory gene regulator system *in S. aureus*. Reproduced with permission from Asad and Opal (6).

are sensed by a transmembrane protein, AgrC which phosphorylates the transcription activator, AgrA, of both of RNAII and the effector molecule, RNAIII. It has been found that RNAIII upregulates the expression of virulence genes e.g. delta haemolysin (through *hld*) and toxic-shock syndrome-1 (TSST-1), and partially upregulates enterotoxins B, C, and D by RNAIII while enterotoxins A and K are not affected (51, 52).

However, colonization factors, microbial surface

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components recognizing adhesive matrix molecules (MSCRAMMs), and biofilm formation are downregulated by *agr* system. The low activity of *agr* operon at the beginning of infection allows the expression of colonization factors. As the process of infection progresses, virulence factors such as degradative enzymes that are needed to obtain nutrients from host tissues and to spread infection, will be expressed. Two stages of biofilm formation have been identified; the first stage is probably due to MSCRAMMs activities and involves the attachment of cells to a surface. The second stage involves multiplication of cells to form multilayered community, and is associated with the production of a polysaccharide intercellular matrix. Detachment of cells will follow in order to spread infection to other sites of human body (48, 53).

A second quorum sensing system described in *S. aureus* is called RAP-TRAP, which is triggered by cell lysis rather than population density which usually triggers quorum sensing system, and it is not fully characterized (48). The target of the RNAIII-activating protein (TRAP) is a 167-amino acids protein that promotes RNAIII synthesis (54). TRAP is conserved in *Staphylococcus*, and possesses three fully conserved histidine amino acids; His^{66}, His^{79}, and His^{154} that are phosphorylated and required for its activity. By constructing a TRAP⁻ strain via alanine site-directed mutagenesis of the conserved histidine, mutants had lost their pathogenicity both *in vitro* (as tested by RNAIII expression and hemolytic activity studies) and *in vivo* (by inducing cellulitis in animals) (38).

Similar in structure to the 50 S ribosomal protein L2, RNAIII activating protein (RAP) is composed of 277-amino acids. It activates the *agr* system by inducing the histidine-phosphorylation of TRAP (38, 55). A short linear peptide, RIP, inhibits RNAIII production and when other linear synthetic peptides for instance "YSPWTNF" were used it resulted in *agr* inhibition. The structure of RIP (YSPWTNF-NH2) is similar to the RAP, pointing to a possibility that RIP acts as activator agonist, and RIP as inhibitor TRAP (48, 56).

Inhibition of quorum sensing as new drug target

Quorum sensing can be exploited in biocontrols. For example, *Burkholderia* sp. strain KJ006 lacks pathogenicity and has a wide spectrum of antifungal action, and can be used for the biological control of the phytopathogenic *B. glumae*. This strain abolished the synthesis of quorum-sensing signals by *B. glumae* and decreased the incidence of rice seedling rot disease which is caused by the virulence factor, taxoflavin. Taken from *Bacillus thuringiensis*, a N-acylhomoserine lactonase (*aiiA*) gene was introduced into this engineered *Burkholderia* strain (pKPE-*aiiA*). Studies revealed that *aiiA* gene can be used to prevent the pathogenic *B. glumae* (57, 58). *P. aureofaciens* strain 30-84 was used to protect wheat from take-all disease. When this strain is added, it reduces the severity of the disease by producing phenazine antibiotics. These antibiotics are regulated by the PhzR-PhzI quorum sensing system (59).

Researchers are trying to find alternative targets due to resistance of microbes to most commonly used drugs. Natural products can be used to inhibit autoinducer synthesis or their detection by the transcription regulator of quorum sensing. One method is to block the receptor with a synthetic analogue of the AHL molecule made by substitutions either in the acyl side chain or in the lactone ring (60). These anti-virulence agents are not subjected to developing resistance, and would have no adverse effects since similar quorum sensing pathways are not found in human being. In addition, anti- quorum sensing agents might not affect bacterial flora that are beneficial inside human (61).

In animal models of *P. aeruginosa* infection, synergistic inhibitory effects on bacterial cell counts were found by treatment with tobramycin combined either with the furanone C-30 or ajoene from garlic. Synergistic effects of baicalin hydrate, hamamelitannin, and cinnamaldehyde with antibiotics in infections of *Burkholderia* spp., *S. aureus*, and *P. aeruginosa* resulted in enhanced

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bactericidal activities. The highest synergistic effects in *B. cepacia* biofilms occur with baicalin hydrate combined with tobramycin (62, 63). PQS production has been found to be inhibited by farnesol. Farnesol is a sesquiterpene synthesized by *Candida albicans*. Farnesol inhibition of PQS production is due to decreased expression of the pqs operon via interactions with transcriptional regulator, PqsR (64).

Several polyphenolic compounds e.g. epigallocatechin, ellagic acid, and tannic acid caused quorum-sensing inhibition (65). *Camellia sinensis* extracts have been shown to inhibit *P. aeruginosa* PAO1 growth. The mechanism of inhibition appears to be a combination of interfering with AHL synthesis and AHL activity. *C. sinensis* extracts also inhibited the expression of virulence factors that are regulated by quorum sensing in this pathogen (66). Halogenated furanones have been used to disrupt virulence gene expression in *P. aeruginosa* (61). Exoprotease, chitinase, and pyovirdin activities were reduced. Furanones improved the survival of experimentally infected laboratory animals treated by furanones compared with untreated animals (67, 68).

To identify inhibitors for quorum sensing in *Y. enterocolitica* and *E. carotovora*, ten food phytochemicals found in plants were tested. These included ellagic, gallic, chlorogenic, vanillic acids and rutin (found in berries); resveratrol (in grapes); kinurenic acid (from honey); daidzein (from soy); dimethyl-esculetin (artemisia), and pomegranate extract that were found to be inhibitory. MS spectrometry showed that ellagic acid, pomegranate extract, resveratrol and rutin were able to reduce the concentration of AHLs of both *Y. enterocolitica* and *E. carotovora* (69). These natural products may be useful as food additives to prevent food spoilage due to activities of microorganisms.

Alfaro et al. (70) synthesized *S*-anhydroribosyl-L-homocysteine and *S*-homoribosyl-L-cysteine that appear to block the biosynthesis of LuxS. The analogues, halogenated at C3 position of ribose, *S*-3-bromo-3, 5-dideoxy-D-ribofuranos-5-yl)-L-homocysteine, and *S*-(3-fluoro-3, 5-dideoxy-D-ribofuranos-5-yl)-L-homocysteine were synthesized to be inhibitors of LuxS (71). In their study, Wnuk et al. (72) also synthesized several SRH analogues modified at C3 of ribose. When tested, the best substrate inhibitors were *S*-(5-Deoxy-D-xylofuranos-5-yl)-L-homocysteine, *S*-(3, 5-Dideoxy -3-fluoro-D-xylofuranos-5-yl)-L-homocysteine, and *S*-(3, 5-Dideoxy-3-fluoro-1-O-methyl-D-xylofuranos-5-yl)-L-homocysteine.

Using molecular docking tool, Hex 8.0.0, several compounds obtained by searching PubChem database had higher binding affinity than S-ribosyl-L-homocysteine the precursor molecule. In addition, four substituted analogs of S-ribosyl-L-homocysteine had higher binding as computed by Hex 8.0.0 docking experiments. One of these is the compound (PubChem CID75179107); 2-amino-4-[[2S, 3R, 4R)- 4, 5-dihydroxy-3-methoxyoxolan-2-yl] methylsulfanyl] butanoic acid and its analogs such as (2R)-2-azaniumyl-4-{[(3, 5-dihydroxy-4-methoxyoxolan-2-yl) methyl] sulfanyl} butanoate, and (2R)-2-azaniumyl-4-{[(2S,3S,4S,5R)-4-amino-3-hydroxy-5-sulfanyloxolan-2-yl]methyl}sulfanyl)-2-azaniumylbutanoate to develop lead compounds (73).

Conclusion

Quorum sensing system is involved in various activities in microorganisms. In pathogenic microorganisms, quorum sensing inhibitors might be used as anti-virulence agents eradicating infections. This system offers new targets for antimicrobials to act. In agriculture, the bio-control of pathogens via quorum sensing may be used in prevention of disease in crops. The enzymes and antibiotics produced by these microorganisms could be used in biotechnology in which quorum sensing genes can modulate the expression of desired genes through adding synthetic inducer in the culture medium to increase the yield.

Acknowledgements

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The author would like to thank Microbes and Environment, the original publisher, for permission to reproduce Fig.1. The author also would like to acknowledge BioMed Central Ltd., the original publisher of the open access figures 2-4, for their permission. The author is grateful to Steven Opal S M, Warren Alpert Medical School of Brown University for permission to use figures.

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