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REVIEW ARTICLE

Potential Emergence of Multi-quorum Sensing Inhibitor Resistant (MQSIR) Bacteria

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Abstract Expression of certain bacterial genes only at a high bacterial cell density is termed as quorum-sensing (QS). Here bacteria use signaling molecules to communicate among themselves. QS mediated genes are generally involved in the expression of phenotypes such as bioluminescence, biofilm formation, competence, nodulation, and virulence. QS systems (QSS) vary from a single in *Vibrio* spp. to multiple in *Pseudomonas* and *Sinorhizobium* species. The complexity of QSS is further enhanced by the multiplicity of signals: (1) peptides, (2) acyl-homoserine lactones, (3) diketopiperazines. To counteract this pathogenic behaviour, a wide range of bioactive molecules acting as QS inhibitors (QSIs) have been elucidated. Unlike antibiotics, QSIs don't kill bacteria and act at much lower concentration than those of antibiotics. Bacterial ability to evolve resistance against multiple drugs has cautioned researchers to develop QSIs which may not generate undue pressure on bacteria to develop resistance against them. In this paper, we have discussed the implications of the diversity and multiplicity of QSS, in acting as an arsenal to withstand attack from QSIs and may use these as reservoirs to develop multi-QSI resistance.

Keywords Antibiotics · Bioactive molecules · Drug resistance · Quorum-sensing · Quorum-sensing inhibitors

Abbreviations

AI	Autoinducer
AHL	Acylhomoserine lactone
HSL	Homoserine lactone
C4HSL	*N*-butanoyl-*L*-HSL
C6HSL	*N*-hexanoyl HSL
C7HSL	*N*-heptanoyl-HL
C8HSL	*N*-octanoyl HSL
C10HSL	*N*-decanoyl HSL
C12HSL	*N*-dodecanoyl HSL
C14HSL	*N*-tetradecanoyl-HSL
C16HSL	*N*-hexadecanoyl-HSL
3OC6HSL	3-Oxo-*N*-hexanoyl-HSL
3OC8HSL	3-Oxo-*N*-octanoyl-HSL
3OC10HSL	3-Oxo-*N*-decanoyl-HSL
3OC12HSL	3-Oxo-*N*-dodecanoyl-HSL
3OC14 HSL	3-Oxo-*N*-tetradecanoyl-HSL
OHC4HSL	3-Hydroxy-*N*-butanoyl-HSL
OHC6HSL	3-Hydroxy-*N*-hexanoyl-*L*-HSL
OHC8HSL	3-Hydroxy-*N*-octanoyl-*L*-HSL
OHC10HSL	3-Hydroxy-*N*-decanoyl-HSL
OHC14HSL	3-Hydroxy-*N*-tetradecanoyl-HSL

Introduction

Evolution in bacteria is eminent and indispensable for their survival against unfavourable conditions. Rapid and frequent genetic transformations allow them to select out the most suitable changes and become resilient to detrimental factors [1–4]. Gene expression in bacteria occurs even at low cell densities, however, certain gene expressions, especially those involved in virulence occur only at high cell densities.

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This coordinated bacterial response, termed as quorum sensing (QS) is governed by communication through signaling molecules [5, 6]. This QS mediated multicellular behaviour is evidently a selection pressure and evolution in disguise [7]. The existence of QS systems (QSS) enlightened a galore of processes: bioluminescence, biofilm formation, antibiotic production, nodulation, swarming, conjugation, toxin secretion, exoenzyme secretion, biocorrosion, and virulence factors like siderophores [8–10]. This elaborate communication mechanism provides the bacterial population with an advantage of an evolved social behavior [6]. Multi-drug resistance has emerged as the biggest obstacle to life saving antibiotics. With ready flit contrivance, they will be able to eschew any therapeutic exertion to cease their proliferation and pathogenicity. In efforts to tackle this MDR status, certain studies have elucidated enzymes and chemical compounds, to act as QS inhibitors (QSIs) [11, 12]. Although these QSIs are effective at much lower concentrations than the antibiotics, which are generally used to kill these organisms, there is always a possibility of bacteria either acquiring or developing resistance to QSIs. The major worry associated with this scenario is: Will pathogenic bacteria exploit their repertoire of diversity and multiplicity of QSS to its full extent with positive selection and possible natural evolution at toil. With this increase in the array of new QSS, Will this communication be tailored as alternative survival mechanisms [8, 13]?

Quorum Sensing Systems

QS is a regulatory mechanism for expressing specific genes in a coordinated manner to help bacteria to adapt and survive [6]. Cues from the environment have decided effect on the bacterial population for communication: (1) intra species (Personal and Family language), and (2) inter-species (Official or Commercial languages). The number of genes regulated by QSS varies among organisms from: 25 genes (0.6 % of total genome) in *Vibrio fischeri* [14], to 350 genes (6 % of total genome) in *Pseudomonas aeruginosa* [15, 16]. QSS within the organism may vary from a single such as in *Vibrio* spp., to multiple in *Sinorhizobium* species. The diversity of signal molecules enhances the complexity of QSS [6, 17, 18].

Gram-Positive Organisms

The diversity of QSS in Gram-positive organisms is found in terms of single and multiple numbers. There is a wide variation in the type of signals, although most of them are peptide based.

Bacillus

In *Bacillus cereus* group members, QSS: (1) LuxS, (2) PapR/PlcR and (3) ComQXPA produce signals such as (a) AIP, (b) ComX peptide, (c) Competence and sporulation factor, and (d) AI-2 (Table 1) [9, 19, 20]. These QSS are responsible for the production of toxins, antibiotics phospholipases, proteases, sporulation and competence.

Clostridium

Clostridium has a broad range of biotechnological applications, but can cause illness and deadly diseases like pneumonia, bacteremia, botulism, myonecrosis, and tetanus [21–23]. *Clostridium* are noted to contain either single or multiple QSS, such as: (1) LuxS, (2) Agr, (3) Agr2 that are regulated by peptide signals e.g., AIP (Table 1) [24–29].

Streptococcus

QSS in *Streptococcus* species include: (1) ComCDE QS Pathway, (2) ComRS Pathway and (3) LuxS. These operate through the signal molecules: (a) Competence Stimulating Peptide (CSP), (b) XIP (Sig X Inducing Peptide), and (c) Autoinducer-2 (AI-2) (Table 1) [30–34].

Staphylococcus

Staphylococcus aureus a major culprit of hospital associated infections like pneumonia and sepsis, produces AI peptides as QS signals. QSS in *S. aureus* comprises of the *agr* locus consisting of pro-AIP encoding *agrD* locus, processing and transport protein AgrB, membrane bound AgrC histidine kinase and response regulator AgrA [9, 35–37]. AgrD synthesizes the 45–47 residue precursor AIP, which is then processed by the transport machinery to give a 7–9 residue processed peptide At high concentration, AIP binds to the AgrC and initiates AgrA phosphorylation cascade. Phosphorylated AgrA sticks to the *agr* operon, upstream the promoter P2 mobilizing the *agr* operon also known as RNAII and simultaneously stimulating the P3 promoter to extort RNAIII regulatory RNA responsible for mounting virulence factor expression like α-toxin [38].

In addition to the major cases described above, *Listeria monocytogenes*, *Enterococcus faecalis* are also known to possess single QSS (Table 1) [28, 39].

Table 1 Diversity of quorum sensing systems and signals in Gram-positive organisms

Organism	Type of QSS[a]	Signal	Function	References
Single QSS				
Bacillus cereus group (*B. cereus*, *B. thuringiensis*, *B. anthracis*)	PapR/PlcR	AIP	Secretion of enterotoxins, hemolysins, phospholipases, proteases	[9]
Clostridium botulinum	Agr	AIP	Production of botulinum toxin, sporulation	[26]
Enterococcus faecalis	Fsr	Cyclic peptide lactone—Gelatinase biosynthesis activation	Secretion of virulence related proteases: gelatinase and serine protease; regulation of biofilm formation by reducing surface proteins required for adhesion to collagen	[28]
Listeria monocytogenes	Agr	AIP	Biofilm formation, virulence	[39]
Staphylococcus aureus	Agr	AIP	Secretion of virulence factors (proteases, lipases, enterotoxins, superantigens, urease, hemolysins), down regulation of surface virulence factors (protein A), pathogenesis, termination of biofilm development	[9, 36, 91]
Streptococcus gordonii	Lux S	AI-2	Biofilm formation	[141]
Streptococcus pyogenes	Lux S	AI-2	Haemolysin and cysteine protease production	[38]
Multiple QSS				
Bacillus subtilis	ComQXPA	ComX peptide	Induces competence, extracellular DNA release, biofilm formation, synthesis of a lipopeptide antibiotic surfactin (biosurfactant and antiviral)	[19, 127]
		Competence and Sporulation Factor	High intracellular concentration represses competence and induces sporulation	
	LuxS	AI-2	Biofilm formation	[20]
Streptococcus pneumoniae	ComCDE	Competence stimulating peptide	Competence development, Bacteriocin production	[30, 34]
Streptococcus mutans	ComCDE	AI-2	Competence development	[34, 141]
	ComRS	AI-2		
Clostridium perfringens	Lux S	AI-2	α, κ, θ toxin production, pathogenesis	[24]
	Agr	AIP	Sporulation, expression of α toxin (CPA) and perfringolysin O	[9, 27]
Clostridium difficile	LuxS	AI-2	Production of virulence factors (Toxin A and toxin B)	[25]
	Agr2	AIP	Virulence regulation	[31]

[a] Quorum sensing system

Gram-Negative Organisms with Multiple QSS

Vibrio

The discovery of QS is accredited to the process of bioluminescence, observed initially in the marine organism *V. fischeri*. It is under the control of *luxICDABEG* gene locus. The AHL synthase LuxI coordinates the expression of the signaling molecule 3OC6HSL), which binds to a transcriptional activator protein—LuxR [40]. This complex adheres to its promoter and consequently triggers the transcription of *luxICDABEG* resulting in luminescence. Apart from the LuxI–LuxR system, there is an additional system called the AinS system (Table 2) [41]. Here, LitR plays the role of a positive regulator to the transcriptional activator LuxR but is subdued by LuxO [42]. Actuation of the *ainS* pathway relaxes LitR repression as well, to regulate the expression of luminescence in *V. fischeri*, linking the *ain* and the *lux* systems [43].

In kindred species like *Vibrio cholerae*, three QSSs, discerned, function concomitantly [44]: through regulatory small RNAs also termed as regulatory RNAs (Qrr): (1) Cholera Autoinducer-1 (CAI-1)/CqsS is responsible for communication at inter- and intra-species level [45], (2) Autoinducer-2 (AI-2)/LuxP/Q regulates inter species communication [45, 46] and (3) QSS III regulated by VarS/VarA [47]. VarS/VarA-CsrABCD system in association with the QSS of *V. cholerae* leads to the expression of the

Table 2 Diversity of multiple quorum sensing systems and signals in Gram-negative organisms

Organism	Type of QSS[a]	Signal	Function	References
Acidithiobacillus ferrooxidans	AfeI/AfeR	C12HSL, C14HSL, 3OC12HSL, 3OC14HSL, OHC8HSL, OHC10HSL, OHC12HSL, OHC14HSL, OHC16HSL	Putative role in Cu^{2+} resistance mechanism, production of capsular polysaccarides of the EPS involved in biofilm formation	[85, 86]
	act system (ortholog of *hdtS* QSS) (acyl transfer function)	C14HSL (major)	Growth and use of Fe and S containing minerals	
Burkholderia cepacia complex	CepI/CepR (BviI/BviR and CepI/R in *B. vietnamiensis*)	C6HSL, C7HSL, C8HSL (major in *B. ambifaria*, *B. cepacia*, *B. cenocepacia*, *B. multivorans*, *B. stabilis*,	Swarming motility through biosurfactant production; biofilm formation; protease, chitinase; lipase production and siderophore production	[94, 95]
		C10HSL (major in *B. vietnamiensis*),		
		C12 HSL, 3OC10HSL		
	BCAM0581 DSF synthase homologs	*cis*-2-dodecanoic acid [a Diffusible signal factor (DSF) family protein]	Regulation of virulence and biofilm development in *B.cenocepacia*	[96]
		cis,*cis*-11-methyldodeca-2,5-dienoic acid (11-Me-C_{12}:$\Delta^{2,5}$) [DSF family protein]	Bacterial–fungal interkingdom communication	
Dinoroseobacter shibae DFL-12	LuxI1/LuxR1, LuxI2/ LuxR2, LuxI3/LuxR3	3-C18en-HSL, C18-dien-HSL	Cell morphology and flagellar biosynthesis	[97]
Escherichia coli	Lux S	AI-2	Regulation of genes encoding type III secretion system, production of Shiga toxin; virulence, activation of flagella regulon; chemotaxis; motility; biofilm formation	[88]
	SdiA	No AI	Detects signals produced by other bacteria to regulate virulence; control of cell division	[89]
	Indole signalling	Indole	Inhibition of biofilm formation; Increases drug resistance; virulence	[92]
	EDF signalling	EDF (extracellular death factor) peptide, NNWNN	Activation of toxin–antitoxin module	[91]
	luxS	AI-3/epinephrine/norepinephrine system	Senses AI-3 produced by gut flora and epinephrine/ norepinephrine produced by host and induces virulence	[93]
Proteus mirabilis	Cyclopeptide synthases	Diketopiperazines:	Modulate LuxR based QSS; communication with plants and animal cells	[69, 98]
		(a) cyclo (ΔAla-L-val)		
		(b) cyclo (L-Pro-L-Tyr)		
	Two component system: RcsC-RcsB	Peptides and amino acids	Capsular polysaccharide synthesis and swarming	[99]
	LuxS/LuxQ	AI-2	Influence gene expression in other species that uses this signalling molecule	[91, 99, 100]
Pseudomonas aeruginosa	LasI/LasR	3OC12HSL (major)	Extracellular production of virulence factors (toxins, elastases, proteases); production of rhamnolipids (biosurfactant required for swarming); anaerobic respiration in *Pseudomonas aeroginosa* biofilms by both lasI/R and RhlI/ RhlR; immunomodulatory activity, increase in tissue damage and inflammation by increasing γ-interferon	[64]

Table 2 continued

Organism	Type of QSS[a]	Signal	Function	References
	RhlI/RhlR	C4HSL (major), C6HSL (minor)		
	PQS	2-heptyl-3-hydroxy-4 quinolone	In combination with RhlI/RhlR QS, PQS regulates production of Rhl dependent virulence factors; influences pyocyanin and elastase production; upregulates rhlI, siderophore mediated iron scavanging activity	[61–63]
	Cyclopeptide synthases	Diketopiperazines: (a) cyclo (ΔAla-L-Val); (b) cyclo (L-Pro-L-Tyr)	Influence cell–cell signalling by modulating LuxR mediated quorum sensing system in bacteria	[67, 68]
Pseudomonas chlororaphis (*auerofaciens*) strain 30-84	PhzI/PhzR	OHC6HSL (major), C6HSL (minor)	Biosynthesis of phenazine antibiotic (phenazine-1-carboxylic acid, 2-hydroxy-phenazine-1-carboxylic acid, and 2-hydroxy-phenazine) and antifungal compounds such as pyrrolnitrin, 2,4-diacetylphloroglucinol, hydrogen cyanide and pyoluteorin	[70, 71]
	CsaI/CsaR	C4HSL	Rhizosphere colonization and regulation of biosynthesis of cell wall components	
Pseudomonas fluorescens	MpuI/MpuR	C4HSL, C6HSL, C8HSL, C10HSL, OHC6HSL, OHC8HSL, OHC14HSL	Mupirocin and metalloprotease biosynthesis	[72, 73]
	HdtS	OHC14HSL; Diketopiperazines		
Rhizobium etli strain CNPAF512	CinI/cinR	3-OH-(slc)-HSL; slc-saturated long chain	Nitrogen fixation; symbiosome development; swarming, growth inhibition	[74, 77]
	RaiI/RaiR	C8HSL, OHC8HSL	Growth inhibition; restriction of nodule formation	
Rhizobium leguminosarum bv. Viciae	CinI/cinR/cinS	OHC14HSL, *N*-(3-hydroxy-7-*cis*-C14HSL	AHL induced inhibition of bacterial growth; regulation of *plyB* encoding an extracellular glycanase	[75, 77, 127]
	RhiI/RhiR	C6HSL, C7HSL, C8HSL	Regulation of stationary phase and rhizosphere expressed genes; nodulation efficiency	
	RaiI/RaiR	OHC8HSL	Unknown	[80]
	TraI/TraR	C8HSL, 3OC8HSL	Transfer of symbiotic plasmid pRL1JI required for nodulation and nitrogen fixation	[79]
Ruegeria sp. KLH11	SsaI/SsaR	3OC14HSL, 3OC16HSL	Flageller biosynthesis and swimming motility	[102, 103]
	SsbI/SsbR	OHC12HSL, OHC14HSL, *N*-(3-hydroxy-7-*cis*-C14HSL		
	SscI	OHC12HSL, OHC14HSL, *N*-(3-hydroxy-7-*cis*-C14HSL		
Salmonella enterica Serovar Typhimurium	LuxS/LuxPQ	AI-2: (2*R*, 4*S*)-2-methyl-2,3,3,4-tetrahydroxytetrahydrofuran	Biofilm formation	[104, 105]
	SdiA	Sense AIs produced by other bacteria	Interspecies communication; resistance to competence killing	[127]

Table 2 continued

Organism	Type of QSS[a]	Signal	Function	References
Sinorhizobium meliloti Rm1021	SinI/SinR	*N*-dodecanamide HSL; *N*-(3-oxotetradecanamide)-L-HSL; 3-oxo-*N*-(tetrahydro-2-oxo-3-furanyl)-9-*cis*-hexadecenamide (oxo-C16:1-HSL); *N*-(tetrahydro-2-oxo-3-furanyl)-9-*cis*-hexadecenamide-HSL (C16:1-HSL); *N*-octadecanamide HSL	EPSII production, succinoglycan production; nodulation efficiency; swarming	[29, 74, 82, 83]
	Mel	C6HSL, C8HSL, 3OC6HSL		
	ExpR	*N*-(tetrahydro-2-oxo-3-furanyl)-9-*cis*-hexadecenamide-HSL (C16:1-HSL)		
Vibrio cholerae	CqsA/CqsS	CAI-1, (S)-3-hyroxytridecan-4-one	Production of virulence factors (enterotoxin) and repression of biofilm formation at high cell concentration	[9]
	LuxS/LuxPQ	AI-2		
Vibrio fischeri	LuxI/LuxR	3OC6HSL	Regulation of bioluminiscence	[69]
	AinS/AinR	C8HSL	Luminiscence regulation at intermediate cell density and successful host colonization	[41]
Vibrio harveyi	Two component QSS: LuxLM/LuxN	4OHC4HSL	All three systems converge to regulate bioluminiscence, type3 secretion (TTS system), siderophore production, polysaccharide production; metalloprotease production in time and growth phase dependent manner	[50, 52]
	Two component QSS: LuxS/LuxPQ	CAI-1 [(Z)-3-aminoundec-2-en-4-one(Ea-C8-CAI-1)]		
	CqsA/CqsS	C6HSL, 3OC6HSL		
Yersinia pseudotuberculosis	YpsI/YpsR	C6HSL, C8HSL	Regulation of bacterial aggregation and motility in a hierarchical cascade	[106, 127]
	YtbI/YtbR	C6HSL, C8HSL, 3OC6HSL, 3OC7HSL, 3OC8HSL (major), 3OC9HSL, 3OC10HSL, 3OC12HSL OHC8HSL; *N*-(*3-oxononanoyl*)-*L*-homoserine lactone		
Yersinia ruckeri	YruI/YruR (may have other QS systems as well)		Putative role in pathogenesis	[107, 108]

[a] Quorum sensing system

Qrr sRNAs, which consequently regulates the QSS (Table 2) [47, 48].

In the marine bacterium *Vibrio harveyi*, *QSS*—LuxM–LuxN system, responds to AHL signal harveyi autoinducer-1(HAI-1), synthesized by LuxLM, which is recognized by the harveyi autoinducer-1sensor (HAI-1 sensor), Lux N [49–51]. Another QSS is the LuxS–LuxPQ system that operates using the signaling molecule, which is a furanosyl borate diester called autoinducer-2 (AI-2) in *V. harveyi* is also present in *V. cholerae* [52]. Both these systems control bioluminescence in *V. harveyi* but the second system modulates virulence in *V. cholerae*. The third QSS existing in the pathogenic microbe *V. cholerae* possesses the cholera QS AI synthase (CqsA) and its sensor (CqsS), identifies the signal molecule (CqsA-1 i.e., (S)-3-hydroxytridecan-4-one) instead of the LuxM–LuxN homologue (Table 2) [53–55]. The *V. cholerae* QSSs eventually lead to the expression of a transcription factor ToxT, initiating the cholera toxin and cholera toxin co-related pilus expression, otherwise repressed by HapR, with the help of quorum regulatory sRNA 1–4 (Qrr1–4) that induce AphA expression and suppress HapR expression [56, 57]. Subsequently, AphA excites the TcpP/H DNA binding protein to elicit the expression of ToxT [58, 59].

Pseudomonas

Pseudomonas species incorporate 3 QSSs of which two are homologous to the *luxI–luxR* system and the third is a discrete system named as the *Pseudomonas* quinolone signal (PQS) system (Table 2) [60]. The *luxI–luxR* homologues exhibited by *Pseudomonas* are *lasI–lasR* and *rhlI–rhlR*. 3OC12HSL and C4HSL activate the LasI–LasR and RhlI–RhlR systems respectively to turn on the virulence genes encoding exotoxin A, proteases and elastase [61–64]. In turn lasR–3OC12HSL complex activates pqsH and pqsR that targets the PqsABCDH locus for the production of the AI PQS and also triggers off *rhlI–rhlR* expression [9]. Furthermore, RhlR–C4HSL complex exerts repression on *pqsABCD* and *pqsR* creating an intricate feedback loop targeting QS controlled genes by either LasR or RhlR system [60]. Interestingly, there is one more LuxR homologue, called the QscR, which is an orphan and does not have a counter LuxI homologue [65]. This orphan LuxI homologue however, coheres to the *lasI* AI and forges inactive dimmers with LasR and RhlR, predicted to intercept anomalous QS riposte [66].

In *P. aeruginosa*, non-AHL signals such as diketopiperazines (DKPs): cyclo(DAla-L-Val) and cyclo(L-Pro-L-Tyr) were found to activate AHL biosensor (Table 2) [67, 68]. These signaling molecules were also found in *Citrobacter freundii* and *Proteus mirabilis*, whereas *Enterobacter agglomerans* was reported to possess only cyclo(DAla-L-Val). DKPs were not reported to be present in *Pseudomonas fluorescens* and *P. alcaligenes*. These *Pseudomonas* however, possessed, a third type of DKP—cyclo(L-Phe-L-Pro). Unlike the natural activator AHL (3OC6HSL) which induces bioluminescence, these DKPs could activate the biosensor at much higher concentrations. At certain concentrations, DKPs might antagonize LuxR-based QSSs, such as the swarming motility of *Serratia liquefaciens*, dependent on C4HSL [69].

In Pseudomonas chlororaphis and *P. fluorescens*, multiple QSS (PhzI/R; CsaI/R, MpuI/R, and HdytS) regulate the biosynthesis of phenazine and pyrrolnitrin, and play an active role in rhizosphere colonization through signal molecules ranging from C4HSL to C10HSL, and others like hydroxy- and oxo-substitutions, and DKPs (Table 2) [70–73].

Rhizobium

Rhizobia are known to fix molecular nitrogen in association with leguminous plants. This symbiotic relationship is mediated by multiple QSSs especially those present in *Rhizobium* sp. and *Sinorhizobium* sp. (Table 2) [74]. In *Rhizobium leguminosarum* four different AHL-based QSS (*tra*, *rai*, *rhi* and *cin*), synthesize seven different AHLs [75, 76]. The cascade of QSS is initiated by QSS—cinI–cinR through *N*-(3-hydroxy-7-*cis*-tetradecenoyl)-*L*-homoserine [74, 77, 78]. The raiI and raiR genes are involved in nodulation with the help of OHC8HSL, where as TraR leads to transfer of the symbiotic plasmid. In continuation of the QS process BisR and TraR regulate conjugation (Table 2) [79]. For nodulation efficiency, RhiI synthesized C6HSL, C7HSL and C8-HSL activate the *rhiABC* genes. These QSS also govern motility and exopolysaccharide production which is required for infection process, and biofilm formation [80, 81]. In *Sinorhizobium meliloti*, sinI/sinR and expR, regulate the Sin QSS through long chain AHLs: C12HSL to C18HSL [29, 82–84]. The phenotypes thus controlled by QSS are nodule formation swarming, motility, and chemotaxis (Table 2).

Acidothiobacillus

Acidothiobacillus ferrooxidans has two QSS, (1) Act, and (2) Lux-like (Table 2) [85, 86]. The expression of Lux-like latter system is upregulated in *A. ferrooxidans* especially in sulfur rich medium. The two QSS respond to different signals that enable the organism to colonize and utilize minerals rich in sulfur and iron [85, 87].

Escherichia

Many other organisms possessing multiple QSS include *Escherichia coli*: (1) LuxS, based on AI-2 as signal molecule [88], (2) SdiA, which detects signals produced by other bacteria [89], (3) Indole signalling system involved in drug resistance, and virulence [90–92], and (4) extracellular death factor based on peptide signals involved in activation of toxin–antitoxin module (Table 2) [93].

Others

Burkholderia cepacia complex, *Salmonella* spp., *Yersinia* spp., *Ruegeria* spp., *Proteus* spp., and *Dinoroseobacter* spp. are also known to possess multiple systems and signals (Table 2). The QS signals modulating these QSS range from unsubstituted- to substituted-HSLs, as well as peptides (DKPs), quinolones, hormones [69, 94–105]. In *Yersinia*, luxI/R homologues are majorly regulated by substituted AHLs [106–108].

Gram-Negative Organisms with Single QSS

Pseudomonas and Rhizobium

A few highly versatile organisms, which possess single and multiple types of QSS belong to *Pseudomonas* and *Rhizobium* species [77]. QSS in *Pseudomonas corrugata*, *P. mediterranea*, *P. putida*, and *P. syringae* are mediated by AHLs like C6HSL, C8HSL and 3OC6HSL and 3OC12HSL (Table 3) [70, 109–111]. QS regulated plasmid transfer in *Rhizobium etli* is under the control of 3OC8HSL and OHC8HSL signals (Table 3).

Erwinia

Virulence and secondary metabolite production in *Erwinia* is controlled by multiple QSS. *Erwinia amylovora*—EamI/EamR, *E. caratovora*—ExpI/ExpR and *E. caratovora* subsp. *caratovora* 71—AhlI/ExpR along with ExpR2 are controlled through only a single AHL–3OC6HSL. In these *Erwinia* strains certain AHL molecules are produced in majority, putting the organism to an advantage, in case of any disruption or signal blockade (Table 3) [112, 113].

Serratia

QS in *Serratia marcescens* regulated by AHL signals, allow expression of *pig* genes for the production of a red-pigmented antibiotic–prodigiosin [55, 114]. SmaI/SmaR, SwrI/SwrR, SpnI/SpnR and SplI/SplR are the four homologues of the luxIR system present across *Serratia* species that regulates phenotypes such as swarming and sliding motility, exo-enzymes, antibiotic production, biofilm formation, butanediol fermentation (Table 3) [114–118].

Aeromonas

In *Aeromonas* QSS, the following homologs of LuxI/R gene are present: *acuI/R*, *ahyI/R*, *asaI/R* and *aveI/R* [119–122]. Short chain length, C4HSL is the major signal molecule, while C6HSL is a minor QS signal—in *Aeromonas hydrophilla*, *A. salmonicida*, and *A. sobria* (Table 3) [119, 123]. 6-Carboxy-HHL (homoadipyl homoserine lactone) and long chain length, C14HSL regulate the *acuI/R* system present in *Aeromonas veronii* [120].

Agrobacterium

Agrobacterium tumefaciens is a well known plant pathogen, which efficiently utilizes the QS apparatus to accomplish the process of conjugation and virulence—crown gall tumors [124, 125]. *A. tumefaciens* embodies the tumor-inducing plasmid designated as Ti plasmid which harbours the virulent genes. Ti plasmid encodes for growth hormones auxin, cytokinin and opines. Opines are special amino-acid derivatives catabolised by the *accF* and *accG* region of the *acc* regulon, that lead to the induction of the AI 3OC8HSL encoded by *traI* region of the *tra* regulon (genes—*traI*, *traR*, *traA*, *traC* and *traM*; Table 3). The traR-AI complex is the key for the invocation of *tra* genes required for Ti plasmid transfer [124, 126].

Others

Acinetobacter, *Brucella*, *Hafnia*, *Pantoea*, *Ralstonia*, and *Rhodobacter*, are reported to possess single QSS which are regulated by AHLs signals of varying acyl chain lengths (Table 3) [127–134]. The presence of QS has been scarcely reported in extremophiles: (1) AHL based QS in haloalkaliphiles—*Natronococcus occultus* [135] and *Halomonas* [136, 137], (2) peptide-based QS in hyperthermophile—*Thermotoga maritima* [138], and (3) a QSS regulated by furanosyl-borate diester signals in archaea [139]. Gram-negative luxS based AI2 producer QSS have been reported to regulate virulence in *Helicobacter*, *Klebsiella*, *Porphyromonas*, and *Shigella*. *Rhodopseudomonas*, and *Xanthomonas* produce p-coumaroyl-HSL and DSF, as signal molecules, respectively [140–145].

Quorum Sensing Inhibition

Epidemic causing pathogens have been wiping out human settlements before the discovery of antibiotics. Haphazard use of antibiotics since a century of their discovery in early

Table 3 Diversity of single quorum sensing systems and signals in Gram-negative organisms

Organism	Type of QSS[a]	Signal	Function	References
Pseudomonas corrrugata	PcoI/PcoR	C6HSL, C8HSL, 3OC6HSL	Virulence factor and lipodepsipeptides production	[73]
Pseudomonas mediterranea	PmeI/PmeR	C6HSL	Virulence factor and lipodepsipeptides production	[73]
Pseudomonas putida IsoF	ppuI/ppuR	3OC12HSL	Regulation of biofilm structural development	[109, 110]
Pseudomonas putida PCL1445	ppuI/rsaL/ppuR	3OC12HSL	Production of cyclic lipopeptides: PutisolvinI and II	[111]
Pseudomonas syringae B728a	AhlI/AhlR	3OC6HSL	Cell aggregation and epiphytic colonization for in planta growth and disease	[70]
Erwinia amylovora OMP-BO 1077/7	EamI/EamR	3OC6HSL	Virulence and secondary metabolites	[113]
Erwinia carotovora subsp. *atroseptica* SCRI1043	ExpI/ExpR, VirR	3OC6HSL	Production of exoenzymes and virulence, secretion of Nip and Svx proteins	[113]
Erwinia carotovora subsp. *carotovora* 71	AhlI/ExpR, ExpR2	3OC6HSL	Production of exoenzymes and virulence	[113]
Erwinia carotovora subsp. *carotovora* ATCC 39048	CarI/CarR, ExpR, VirR	3OC6HSL	Production of carbapenem antibiotic, production of exoenzymes and virulence	[113]
Erwinia carotovora subsp. *carotovora* EC153	AhlI/ExpR	3OC8HSL (major), 3OC6HSL (minor)	Synthesis of plant cell wall degrading exoenzymes (proteases, pectinases, pectase lyases, cellulases)	[112]
Erwinia carotovora subsp. *carotovora* SCC3193	ExpI/ExpR, ExpR2	3OC8HSL (major), 3OC6HSL (minor)	Synthesis of plant cell wall degrading exoenzymes (proteases, pectinases, pectase lyases, cellulases) and virulence	[113]
Erwinia carotovora subsp. *carotovora* SCRI193	ExpI/ExpR, VirR	3OC6HSL	Production of exoenzymes and virulence	[113]
Erwinia chrysanthemi 3937	ExpI/ExpR	C6HSL, C10HSL, 3OC6HSL	Pectinase production	[113]
Serratia marcescens Strain 12	SmaI/SmaR	C4HSL, C6HSL	Swarming motility, haemolytic activity, production of caseinase and chitinase, biofilm formation	[114]
Serratia marcescens MG1	SwrI/SwrR	C4HSL (major), C6HSL (minor)	Attachment, serrawettin (a biosurfactant for swarming) production, protease protein production; butanediol fermentation and biofilm formation	[69]
Serratia marcescens SS-1	SpnI/SpnR	C6 HSL, C7HSL, C8HSL, 3OC6HSL	Sliding motility, biosurfactant production; prodigiosin and nuclease production	[170]
Serratia plymuthica IC1270	SplI/SplR	OHC6HSL, OHC8HSL	Negative regulation of biofilm formation	[116, 118]
Serratia plymuthica RVH1	SplI/SplR	C4HSL, C6HSL, 3OC6HSL	Production of nuclease, chitinase, protease and antibacterial compound; butanediol fermentation	[117]
Serratia proteamaculans B5a	Sprl/SprR	C6HSL, 3OC6HSL	Production of lipase, protease and chitinase	[115]
Aeromonas hydrophila	AhyI/AhyR	C4HSL (major), C6HSL, C7HSL	Serine protease and metalloprotease production; biofilm maturation; Butanediol fermentation	[117, 119, 122]

Table 3 continued

Organism	Type of QSS[a]	Signal	Function	References
Aeromonas salmonicida	AsaI/AsaR	C4HSL (major), C6HSL (minor)	Exoprotease production	[119, 122, 123]
Aeromonas salmonicida subsp. *achromogenes*	AsaI/AsaR	C4HSL	Virulence factors production (toxic protease AsaPI and cytotoxic factor)	[122]
Aeromonas sobria	AveI/AveR	C4HSL, C6HSL	Virulence	[121, 123]
Aeromonas veronii MTCC 3249	AcuI/AcuR	C14HSL, 6-carboxy-HHL (homoadipyl -HSL),	Virulence	[122]
Agrobacterium tumifaciens	TraI/TraZ	3OC8HSL	Conjugal transfer of Ti plasmid	[6, 125]
Rhizobium etli strain CFN42	TraI/TraR	3OC8HSL, OHC8HSL	Plasmid transfer	[77]
Acinetobacter baumannii	AbaI/AbaR	C12HSL, C10HSL, C14HSL, C16HSL, 3OC13HSL, OHC12HSL	Biofilm formation and surface motility; virulence; production of antioxidant enzymes—catalase and superoxide dismutase	[134]
Brucella melitensis	VjbR, BlxR (orphan LuxR homologs)	C12HSL, 3OC12HSL	Surface modifications by regulating flagellar genes and type IV secretion system genes (virulence)	[133]
Hafnia alvei FB1	Unreported	3OC6HSL, 3OC8HSL	Food spoilage and biofilm formation	[130]
Halomonas anticariensis	HanI/HanR	C4HSL, C6HSL, C8HSL, C12HSL	Growth in extreme (Halophilic) environments	[137]
Pantoea agglomerans pv. *gypsophilae*	PagI/PagR	C4HSL (major), C6HSL (minor)	Virulence and gall development	[131]
Pantoea stewartii	EsaI/EsaR	3OC6HSL	Exo/capsular polysaccharide synthesis; effective colonization of the host and virulence	[129]
Ralstonia solanacearum	SolI/SolR	C6HSL, C8HSL	Regulation of virulence by PhcA regulated pathway	[128]
Rhodobacter sphaeroides	CerI/CerR	7,8-*cis*-*N*-C14HSL	Prevents aggregation of bacterial cells	[127]
Rhodopseudomonas palustris	RpaI/RpaR	p-coumaroyl-HSL (pC-HSL)	Activates novel *rpaR* antisense transcript	[143]
Helicobacter pylori	LuxS	AI-2	Motility regulation, flagellar morphogenesis; AI-2 acts as a chemorepellant	[144]
Klebsiella pneumoniae	LuxS	AI-2	Regulation of biofilm formation and LPS synthesis	[141]
Porphyromonas gingivalis	LuxS	AI-2	Modulate protease and haemagglutinating activity	[145]
Shigella flexneri	LuxS	AI-2	Modulate expression of virulence genes	[140]
Xanthomonas campestris	DSF signalling system	DSF (diffusible signal factor): *cis*-11-methyl-2-dodecanoic acid	Regulation of virulence	[142]

[a] Quorum sensing system

1920's, has led to a complication of mammoth enormity known as multi-drug resistance [4, 146, 147]. Owing to selection pressure, bacteria have generated resistance to these antibiotics by exploiting their inherent abilities—mechanisms of efflux pumps, drug modulating enzymes and drug degrading enzymes. Bacteria can gain up to 1000 times more resistance against antibiotics by developing QS regulated biofilms [147]. Such biofilms are prevalent in water treatment plants, fisheries and also blameworthy for variegated diseases. In order to disrupt this biofilm formation, efforts have been made to effectively dismantle QS signaling and halt the formation of biofilms. These QS inhibitors (QSIs), either chemical, natural or synthetic have provided an alternate therapeutic approach to combat infections and industrial biofouling nuisance [6, 146–152]. Scientists are now focusing to disrupt QS regulated infection process by: (a) inhibiting synthesis of signal molecules, (b) quenching the signal molecules, (c) disrupting the receptor molecule binding [2, 147]. This problem is of great magnitude due to the variety of the systems and the signals that they produce. QSIs can be used to narrow down this threat and effectively aim at inhibiting various bacteria preferably using a single molecule. Enzymes such as AHL-lactonases and AHL-acylases are used as QSIs [146, 153]. These enzymes act by hydrolysing the lactone ring and the amide bond, which is a characteristic of an AHL signal. There is a vast majority of organisms, both plants and microorganisms that produce QSI enzymes naturally in the environment. Chemical analogues of AHL molecules have also been engineered by: (1) altering the lactone ring structure, (2) substitutions in the acyl side chain, and (3) modifications of both the components [6]. The expression of LuxR and LasR is totally blocked by analogues with an S substitution at C3 in acyl side chain. Likewise, in another case, the growth of *S. aureus* was hindered when substitutions were made at C3 in C10 or C14 length acyl chain. QSI enzymes reported in mammals are called as paraoxonases (PONs) that degrade bacterial AHLs [17]. Furocoumarins extracted from grapes inhibit the activities of AI-1 and AI-2 of *Salmonella typhimurium*, *V. harveyi*, *P. aeruginosa*, *E. coli* O157:H7 [6]. RS2-IG9 is an anti-AHL antibody developed against RS2, which is a 3-oxo-AHL analogue and successfully quenches 3OC12HSL signal of *P. aeruginosa*. XYD-11G2 is another antibody that quenches the 3OC12HSL signal most effectively from a number of potential candidates [154]. Fimbrolide is a halogenated furanone that does not compete with the 3OC12HSL, instead it increases the LuxR turnover for the receptor binding site. Desferrioxamine-gallium is a metallo-complex that inhibits biofilm formation via disruption of iron metabolism in *P. aeruginosa* and has also been used with gentamicin in a rabbit model to treat *Pseudomonas* keratitis [6]. Apart from these, various other QSIs have been found and synthesized. These QSIs have been shown to have a great scope for biotechnological applications [155, 156]. These have been described extensively in recent reviews on QSIs [6, 146].

Bacterial Strategies for Developing "Resistance" to QSIs

Bacteria vary in their ability to withstand environmental stresses and show great resilience when their survival is under great threat e.g., resistance to antibiotics. These properties of the pathogenic bacteria have been attributed to genetic changes, which arise due to mutations and transfer of genes across species. The high frequency of evolution of multidrug resistant bacteria has deterred scientific community involved in developing novel antibiotics. So much so that pharmaceutical companies are hesitant to make any financial investments [157–159]. It's rightly said, as mentioned before that to counter environmental constraints and natural selection bacterial pathogenicity has to and will evolve over time and inhibition of QS has been gauged as the ticket out of this scramble. Having seen the fate of antibiotics developed over the last century, we are obliged to pose a question: Will bacteria also develop resistance to QSI? In fact, certain observations to support this potential threat have been reported in the last few years [2, 3, 160–162]. Here, we are presenting the strategies, which bacteria may exploit to evade the attack of QSIs and may even undergo permanent genetic changes to develop resistance to QSIs i.e. multiQSI-resistant (MQSIR) strains may evolve by perpetual and indiscriminate usage.

Diversification and Multiplicity of QSS

Most bacteria possess single QSS but there are others with multiple systems. This multiplicity in QSS is also accompanied by numerosity and diversity of the signals and overlapping regulations [147]. It is a new paradigm of bacterial evolution of advanced robustness to withstand environmental hindrances and a grave issue of intricately evolving pathogenicity. The frequency and variation in number of systems such as LuxI/R homologs in different strains might have the potential to circumvent communication blockades that may arise through the usage of QSIs [2]. This multitudinosity and variety endows the bacteria with an escape route so that inhibiting one communication molecule would not let the machinery stop (Table 2). In human pathogens like *V. cholerae*, the plurality of QSSs, and their ability to function in parallel allows it to evade any efforts targeted towards their elimination. Regulatory

RNAs (Qrr) named as CsrB, CsrC and CsrD, direct the functioning of the global regulatory protein, CrA. The activities of VarS/VarA–CsrA/BCD system along with QSS regulate the expression of the Qrr sRNAs, in brief the whole QS regulon [47].

Duplications in QSS

Another case of parallel evolution is prominent in the CsaI/R and PhzI/R systems of *P. chlororaphis*, and the RhlI/R and PhzI/R systems in *P. fluorescens*, which seems to be the outcome of a duplication event, prior to the speciation in their ancestral genome and are involved in the regulation of phenazine production [163]. *Rhodospirillum rubrum* has been reported to have 6 LuxR homologs with a single LuxI homolog. In this particular case, a combination of different LuxR homologs code for 6 different AHLs: C8HSL, C10HSL, OHC6HSL, OHC8HSL, OHC10HSL and OHC12HSL [164]. In *Burkholderia mallei*, 2–5 homologs of LuxR exist and it may overcome the effect of QSI by over expressing the signal molecule for one such homolog [165]. This repertoire of different signal synthases and signals provides a safeguard. However, the loss of the singular LuxI homolog may hamper the communication system.

Mutations

Mutations are genetic changes that allow organisms to develop strategies to circumvent environmental stresses. For example, virulence is not displayed by a LasR defective mutant *P. aeruginosa* PAO-R1 but it is speculated that a reverse mutation would undo this effect [166]. Similarly QscR, forms a dormant heterodimer with LasR, as well as RhlR and impedes QS mediated genes. So any mutation rendering QscR ineffective may lead to a constitutive expression of virulence due to an interminable signal production [147]. Such mutations can lead to a rekindling of dead pathways of QS and even attainment of new ones, coupled with HGT. AHLs defective *P. aeruginosa* strains, negative for *lasR* gene, produced less virulence factors and formed less biofilm than PAO1. One of the isolate PA41 was reported to produce slightly more pyocyanin than PAO1 strain. These observations indicate that, although QS is implicated in the pathogenic behaviour of *P. aeruginosa*, AHLs-deficient strains could cause infections in human [167].

It has been revealed that mutations in *luxS* gene of *S. mutans* resulted in alterations in: (1) biofilms structures, (2) bacteriocin and mutacin I production [54, 168]. Mutacin production in *Serratia marcescens* and *E. coli* depends upon the expression of *lexA* and *recA*, whereas *S. mutans*, can manage the same only with a Lex-A like factor, IrvR [169]. In AI-2 dependent multispecies biofilm communities, suppression of *luxS* gene expression is expected to lead to variation in interspecies behavior [170–172].

A natural genetic variation in the *hapR* gene of the QSS in *V. cholerae* results in EPS and biofilm formation even in non-EPS, non-biofilm producing strains. This frame shift mutation in *hapR* was also recorded in many toxigenic strains of *V. cholerae*. The loss of QS functions in this aquatic pathogen due to genetic mutation hereby confers a selective advantage. It elucidates the inherent ability of bacteria to counter the attack of QSI by undergoing such insignificant looking changes [46].

Pseudo-Expression of QS

Vibrio cholerae has evolved a QSS which allows expression of virulence factors at low cell density for evading attack by antibacterial or QSIs [46]. An interesting scenario was revealed by conducting experiments in small volumes, where the bacterial density per unit volume turned out to be more important for initiating QSS than the absolute number of cells. As low as 1–3 cells confined within a small volume by using the strategy of microfluidics were sufficient to allow expression of QS mediated growth and pathways of *P. aeruginosa* [173].

Horizontal Gene Transfer

Occurrence of horizontal gene transfer (HGT) and despotic mutations favour the prospects of bacterial evolution [174, 175]. It is also the reason for multiplicity and the complexity of QS based communication network. HGT has been found to be largely indicative of the present QSS distribution traversing bacterial species. The RhlI-R system in *P. areuginosa*, the carR genes in *S. marcescens* and *E. caratovora* are all examples of HGT for the LuxS system from Firmicutes. The gain of such genes and systems in various bacteria in antecedent regulatory pathways exemplifies the prospects of coadunation of an acquired gene and expanding the regulatory network. In the case of *Burkholderia vietnamensis*, the receptor of the BviI/R system resembles the *P. aeruginosa*, PhzR receptor, which is most likely a result of acquisition of a new receptor from the other lineage [163]. Another possibility is that HGT might let the organism gain a new pathway additionally regulated by a new LuxI homolog [55].

Opinion

Bacterial virulent response elicitation manifests largely at high population density [6, 176]. The bacteria modify their behavior and act like a "multi-cellular" organism. Bacterial communication efficiency and complexity is enhanced by the multiplicity of QSS and their signals, which is proving to be advantageous in their battle for survival. Recent studies have thrown light on the evolutionary facet of this diversity and its ecological as well as pathological implications. Transposability and genomic flexibility along with random mutations widen the horizon of bacterial sustainability. Will it make bacteria armed for any and every attack on its communication and social circuitry? How will QSI perform in a specified way in this particular test? Is it a lost battle, remains to be seen, as it is premature to pitch the multiplex QSSs with eclectic QS signals disregarding their unexplored counterparts as of now. Looking at the bigger picture, it is of concern that targeting QS as an alternative, to antibiotic therapy, should not lose it's merit, due to the process of natural evolution that constantly checks for perquisites to engender a new version of protection and prolongation of a particular species.

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