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Chapter

Quorum Sensing in Biofilm

Zahra Sedarat and Andrew W. Taylor-Robinson

Abstract

Quorum sensing (QS) is a complex system of communication used by bacteria, including several notable pathogens that pose a significant threat to public health. The central role of QS in biofilm activity has been demonstrated extensively. The small extracellular signaling molecules, known as autoinducers, that are released during this process of cell-to-cell communication play a key part in gene regulation. QS is involved in such diverse intracellular operations as modulation of cellular function, genetic material transfer, and metabolite synthesis. There are three main types of QS in bacteria, metabolites of which may form the target for novel treatment approaches. The autoinducing peptide system exists only in Gram-positive bacteria, being replaced in Gram-negative species by the acyl-homoserine lactone system, whereas the autoinducer-2 system occurs in both.

Keywords: bacterium, gram-positive, gram-negative, biofilm, quorum sensing, quorum quenching, autoinducer, accessory gene regulator, acyl-homoserine lactone, LuxS, luminescence, *Staphylococcus aureus*, *Vibrio fischeri*, *Vibrio harveyi*

1. Introduction

More than half a century ago, pioneering experiments performed on *Streptococcus pneumoniae* discovered the existence of bacterial communication through hormone-like molecules that were later defined as peptides [1, 2]. These findings were accomplished by studying *Vibrio fischeri*, which is able to produce luminescence at high levels of cell density. The luminous system in this marine bacterium is characteristically self-regulated and is provoked at a threshold level of signal molecules. This so-called "autoinduction" provides an environmental sensing mechanism [3]. Known as "quorum sensing," this type of regulation is a form of information sharing used by bacteria through intercellular communication to regulate gene expression. This process is described in many Gram-positive and Gram-negative bacteria. It is facilitated via autoinducers (AIs) or extracellular signaling molecules that produce, release, and detect as well as respond to them [4]. By increasing bacterial cell density, accumulated AIs in the outer cell will lead to changes in gene expression. This communication is detected in inner species and also between species. Among multiple cell activities that are under the control of QS, biofilm formation, virulence factor formation, sporulation, motility, conjugation, symbiosis, competence, and sporulation are each of note [5–8]. In addition, a number of studies have shown the key role of quorum sensing in metabolic processes, involving a high portion of the bacterial genome (corresponding to more than 20% of the proteome) that facilitates adaptation to metabolic needs

[9]. The bacteria belonging to the same colony may exhibit heterogenous phenotypic behavior in order to respond to environmental fluctuations and interbacterial interactions. These are coordinated with each other via quorum sensing, which adapts bacterial traits and behaviors (both group and individual) to ensure their compatibility [10]. In short, QS plays a fundamental role in production, detection, and response to AIs [11].

In the QS system used by various bacteria, there are differences in terms of target genes, types of chemical signal molecules, and mechanisms [8]. Emerging evidence points to several types of signaling molecules, including methyl dodecanoic acid, N-acyl homoserine lactones (AHLs), furanosyl borate, oligopeptides, and hydroxy palmitic acid methyl ester [12]. Although there are multiple QS systems described in bacteria, these are broadly categorized into three groups that we will describe in detail in this chapter. The first major group belongs to Gram-negative bacteria and uses AHLs as the signaling molecule [6]. The second group, only found in Gram-positive bacteria, utilizes small, processed oligopeptides [8]. The third group, in which autoinducer-2 (AI-2) is produced, applies to both Gram-positive and Gram-negative bacteria and has been reported in over 55 species [13].

1.1 Quorum sensing in Gram-negative bacteria

Some characteristics of QS are common to Gram-negative bacteria. The main feature is the ability of AHLs and s-adenosylmethionine-synthetized molecules to diffuse within the bacterial membrane. The receptors for these are located either in the cytoplasm or on the inner membrane. Additionally, numerous cell processes are affected by QS, which directly modifies the relevant genes [14, 15]. Different types of autoinducers are used by Gram-negative bacteria, whereas the most common type, Acyl-HSL, is found in many bacterial species [14, 16, 17]. The AHLs (lux operon) were first described in *Vibrio fischeri*, which will be discussed as a model in this section [18]. An important reason why *V. fischeri* QS is suitable to study is its high sensitivity to AIs, which means it is activated even when they are at low levels [19–21].

In general, AHL-mediated QS involves either LuxI or LuxR proteins [22]. These are engaged in multiple cell functions including biofilm formation, pathogenesis, antibiotic production, and genetic competence. Hence, LuxI-LuxR is considered an excellent research model [23]. Indeed, the operon LuuxICDABEG is activated by LuxR [22]. More than 20 LuxR analogous families exist in Gram-negative bacteria, of which LuxR is the most studied [24]. LasI and EsaI in *Pseudomonas aeruginosa* and *Pantoea stewartii*, respectively, are of note [25, 26].

LuxR should first be activated by the AIs, N-(3-oxohexanoyl)-L-homoserine lactone (abbreviated to 3-oxo-C6-HSL). This is a diffusible signal catalyzed by a 193-amino acid protein that is encoded by LuxI from a precursor of host metabolism (s-adenosyl methionine) as well as a cofactor acyl carrier protein. In addition to 3-oxo-C6, the other products of LuxI, are apo-ACP and 5′-methylthioadenosine [8, 22, 24, 27, 28]. Thus, in the presence of AI (3-oxo-C6), LuxR activates LuxICDABEG operon expression, and overexpression of LuxR will be followed too [29]. The C-terminal region of LuxR is responsible for DNA-binding as well as RNA polymerase interaction (resulting in activation of the Lux promotor), whereas the N-terminal binds to AIs [30–32].

Other parts of the Lux operon are associated with diverse activities. LuxAB is in charge of encoding luciferase (a heterodimer of two subunits, alpha and beta). LuxC, LuxD, and LuxE are responsible for encoding aldehyde substrate, whereas LuxG

regenerates FMNH2 from FMN [24, 33, 34]. In this regard, luciferase and flavin-dependent monooxygenase, which produce light photons from chemical energy via catalyzing a bioluminescent reaction, facilitate an enzymatic reaction to produce aliphatic acid (RCOOH) as well as FMN from substrates including FMNH2, O2, and long-chain fatty acids (RCHO). In this way, bacteria regulate luminescence production in light organs of fish at high cell density and switch on *lux* genes (**Figure 1**) [34–37].

Lastly, an intergenic region known as Lux box (a 20-bp palindromic sequence) is located inside the LuxI promoter within 42.5 bp of the LuxICDABEG operon start site. This acts as a transcriptional activator that is responsible for the overexpression of the LuxI promotor [38–40]. Although the Lux box plays an essential part in luminescence gene activation, its precise role and structure remain to be identified [39].

1.2 Quorum sensing in Gram-positive bacteria

Autoinduction by Gram-positive bacteria is achieved via autoinducer peptides (AIPs) that require postproduction processing. AIPs are not permeable and require carriage across the host cell membrane by transporter proteins [41–43]. Additionally, two types of transcription factors are recognized, Rgg and RNPP, the latter of which is found in all Gram-positive bacteria and is equipped with a binding domain that facilitates its binding to signaling peptides [44].

In the model bacterium *Staphylococcus aureus* (**Figure 2**), there are four types of two-component regulator system, namely, *agr*AC, *sae*RS, *arl*RS, and *srr*AB. Of these,

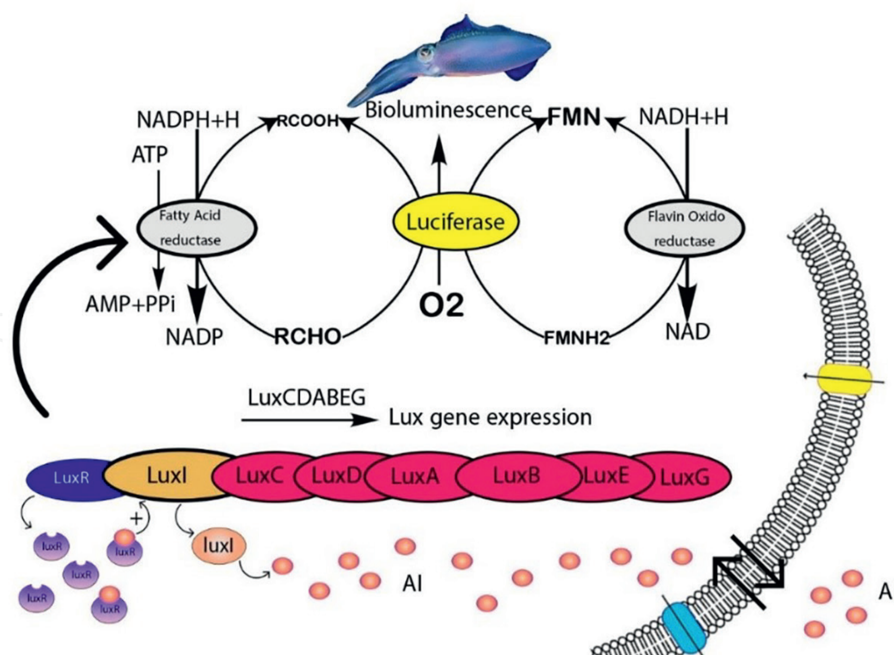

Figure 1.
Lux quorum sensing system in Vibrio fischeri. Autoinducers (AIs) are synthetized by LuxI which later attaches to the LuxR protein at threshold concentration. LuxR protein acts as receptor and its complex with AIs raises LuxI gene expression and thus AI production. AIs diffuse through the cell membrane and thereby activate LuxR protein. LuxCDABEG encodes the structural components of light production in which LuxAB encodes luciferase. Bioluminescence and light production happen after oxidation of RCHO and FMNH2. Production of fatty acids and activation of fatty acyl groups are functions performed by LuxD and LuxC, respectively. Activated fatty acyl groups are then reduced to long-chain aldehydes by LuxE. Recycling of components such as fatty acids as well as FMN, which is produced as a result of the luciferase reaction, are carried out by LuxC/E and LuxG, respectively.

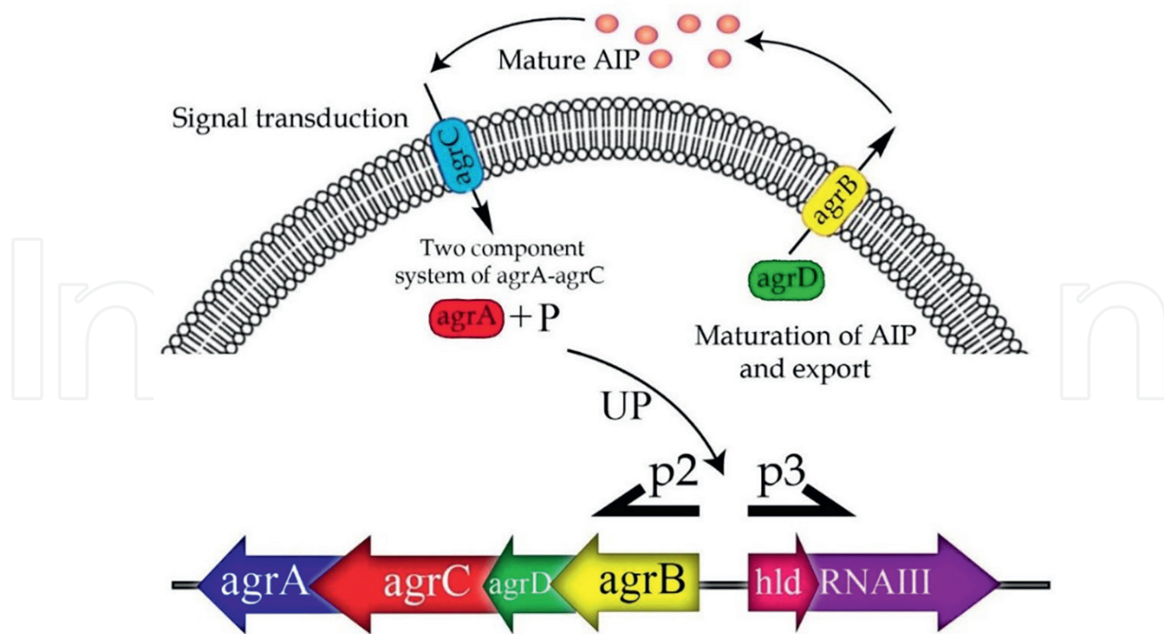

Figure 2.
agr quorum sensing system in Staphylococcus aureus. Autoinducer peptides (AIPs) are produced from the agrD precursor by agrB. Mature AIPs are then exported outside the cell till their concentration reaches a threshold when the two-component system (agrC/agrA) becomes activated. Afterwards, agrA is phosphorylated, enabling it to activate transcription of the P2 and P3 promotors (upregulation). Also, agrA is involved in encoding phenol-soluble modulin peptides (via increasing transcription of psmα and psmβ operons). RNAIII is responsible for regulation of most agr targets as well as delta-toxin (hld).

accessory gene regulator (*agr*) and *sae* are capable of sensing environmental stimuli, whereas *arl*RS is thought to play a part in antibiotic resistance as well as autolytic activity. The last two-component system, *srr*AB, has a role in energy metabolism and RNAIII inhibition [45]. In addition, *agr* is responsible for controlling virulence factor gene expression by *S. aureus*. The *agr* locus is a density-dependent system, composed of two QS components [46]. There are four main subgroups of *agr*, each of which produces a distinctive AIP. Meanwhile, a two-component system comprising *agr*A and *agr*C is responsible for AIP identification. These AIPs are similar in terms of thiolactone ring structure but differ in amino acid sequence. Moreover, QS is regulated via the *agr* locus, which comprises two transcripts, RNAII and RNAIII. Their expression is induced via P2 and P3 promotors, respectively [45, 47–51]. Activation of *agr* is not limited to AIPs, as additional proteins such as SarA, SrrAB, and other environmental factors can also activate the system [52, 53]. Initially, when *S. aureus* population density is not sufficiently high to induce *agr* expression, colonization occurs through the production of surface proteins, followed by *agr* expression upon increasing cell density. Therefore, *agr* timing adaptation is an indicative of infection progression [54, 55].

In the *agr* system, RNAIII has an important function as an intercellular effector in controlling target gene expression. It also controls other virulence factors, including protein A, Rot protein, leukocidins, enterotoxins, and alpha toxin [50]. Moreover, the four genes *agr*B, *agr*C, *agr*D, and *agr*A are located in the RNAII operon. Initially, *agr*D encodes a 46-amino acid peptide (pro-AIP), which is later processed to yield a 9-amino acid residue. This AIP precursor undergoes modification to C-terminal cleavage before exportation from the cell via *agr*B (a transmembrane endopeptidase). AIP signaling molecules are released into the extracellular environment and have

accumulated there until a threshold concentration is reached when they are detected by specific sensors. *agr*C, a transmembrane histidine kinase protein, is phosphorylated and attaches to AIPs, thereby enabling gene regulation in QS to be followed. This is also responsible for the activation of *agr*A, which is a response regulator [8, 49, 50, 56, 57]. In an autofeedback cycle, upregulation of RNAII and RNAIII transcription is driven by the binding of *agr*A to P2 and P3 promoters, respectively [50]. In short, the simultaneous activation of *agr*A and *agr*C, which act as transcription factors for RNAIII, induces the RNAII operon [49, 58]. Upon activation, RNAIII can trigger the production of alpha toxin. Meanwhile, the RNAIII is able to quench the expression of certain surface virulence factors (including coagulase, peptide A and FNPA, B; [59].

A further activation pathway has been reported in various Gram-positive bacteria. This involves interaction between signaling molecules and receptors inside the cell, after which the expressed products are transported to the external environment [60, 61]. This is exemplified by *Enterococcus faecalis*, in which the interaction between peptides and PrgX proteins alters the activity of conjugative plasmids [62, 63] and by Phr peptides acting as phosphatase inhibitors in *Bacillus* species [62, 63]. Finally, a strong relationship between *agr* and σ^B, a biofilm formation regulator, has been identified [64]. Formation and dispersal of biofilm are associated with the downregulation and upregulation of *agr*, respectively [65, 66].

1.3 Autoinducer-2 in Gram-positive and Gram-negative bacteria

AI-2 is found in both Gram-positive and Gram-negative bacteria, where it facilitates intra- and inter-species communication [67, 68]. AI-2 signals have been described as providing an "interconversion nature", meaning that this molecule is utilized by different bacteria as a universal tool for communication [68]. Support for this notion comes from the observation that, unlike for single-species oral biofilm formation, in mixed populations of *Porphyromonas gingivalis* and *Streptococcus gordonii*, LuxS expression by each species is required. Further evidence shows that if there is a deficiency of *Streptococcus mutans,* other species of oral bacteria supplement with *luxS* mutation in biofilm formation [69].

In this system, the enzyme LuxS catalyzes the synthesis of AI-2 or its precursor 4,5-dihydroxy-2,3-pentanedione [70]. Two receptors, LuxP (a periplasmic-binding protein) and LsrB, are detected. Biofilm formation, virulence factor production, and other density-dependent phenotypes are attributed to the former, with delivery of AI-2 into cells ascribed to the latter [67, 70, 71]. They differ in structure, exemplified by LuxP-AI-2 in *Vibrio harveyi* being composed of furanosyl borate diester, whereas LsrB-AI-2 in *Salmonella typhimurium* lacks boron [71, 72]. Molecular analysis indicates that the type of AI-2 varies with bacterial species [72]. Multiple bacteria have been identified that can react to AI-2, including *Staphylococcus epidermidis*, *Helicobacter pylori*, *Bacillus subtilis, Pseudomonas aeruginosa*, *Campylobacter jejuni*, *S. mutans,* and *Listeria monocytogenes* [73–79]. To date, most information on this system comes from *V. harveyi* [69], for which three-channel quorum sensing is proposed, involving AI-1, AI-2 and, cholerae AI-1 [80].

The *V. harveyi* protein LuxQ has a cytoplasmic histidine-kinase domain, a response regulatory domain, and a periplasmic sensor domain. Interestingly, upon binding to the AI-2, LuxQ functions as a kinase and as a phosphatase at low and high cell densities, respectively [70, 81]. Another protein known as LuxP is able to modify LuxQ activity (through a histidine-kinase sensor), and it is this union that regulates

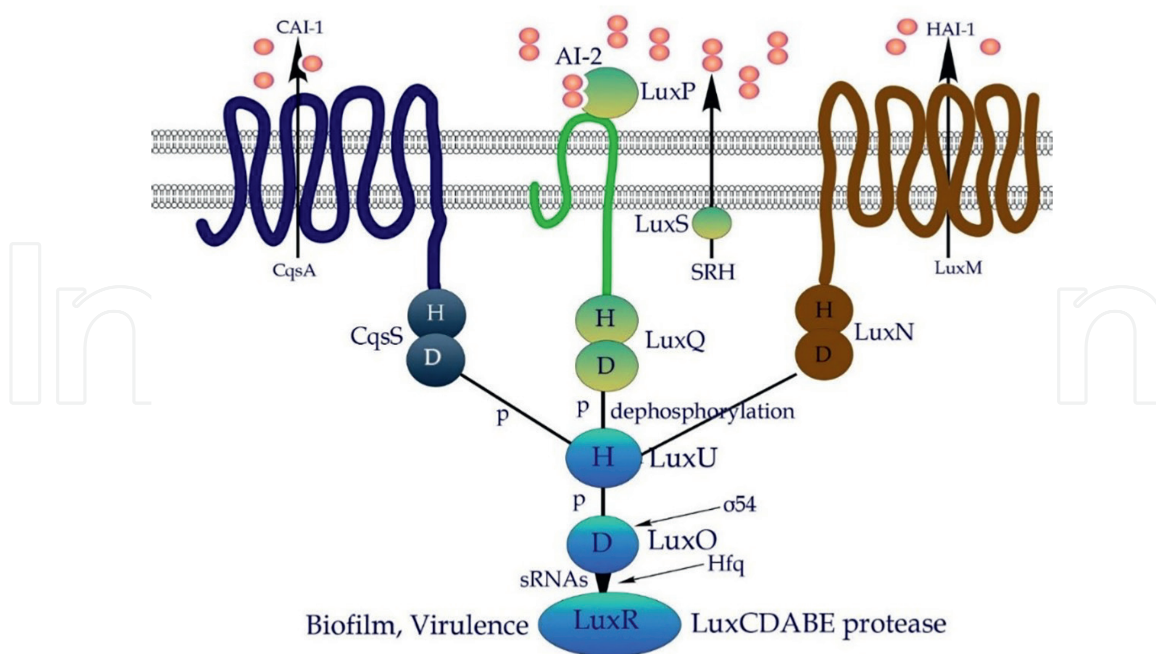

Figure 3.
AI-2 quorum sensing system in Vibrio harveyi. The three autoinducers HAI-1, AI-2 and CAI-1 are synthesized by LuxM, LuxS and CqsA, respectively. LuxS produces AI-2 by converting S-ribosylhomocysteine (SRH) to dihydroxypentane-2,3-dione (DPD) in the cell cytoplasm. This occurs when LuxS participates in the activated methyl cycle, which generates and recycles methyl donors. DPD is a by-product of the LuxS reaction that produces SRH. Later, DPD undergoes cyclization and rearranges without enzymatic support to produce AI-2 prior to export across the outer membrane. A two-component signal regulator is responsible for the responding pathway in vibrio spp., while for Salmonella enterica this is identified as an ABC transporter. In V. harveyi, furanosyl-borat-diester and periplasmic LuxP together form active AI-2, inducing phosphatase activity in LuxQ. This leads to phosphate transfer from LuxU to LuxO, which is the response regulator. Finally, several cell changes take place, including bioluminescence. In contrast, when cell density is low and there is no AI-2, phosphorylated LuxO as well as σ^{54} produce small regulatory RNAs. Their interaction with $LuxR_{Vh}$ mRNA causes destabilization of Hfq-dependent chaperone proteins. This results in suppression of transcription of the lux operon and a reduction in bioluminescence. Meanwhile, dephosphorylated LuxO, the level of which increases in the presence of AI-2, reverses the flow of phosphate.

the AI-2 QS regulon (**Figure 3**) [70, 82]. Following the conversion of LuxQ activity from kinase to phosphatase via the transmembrane sensor histidine kinase, LuxP bound to AI-2 regulates gene expression of phenotypes such as biofilm formation and bioluminescence [67, 70, 83].

2. QS and biofilm

Multiple factors benefit bacterial colonies that adopt a multicellular lifestyle rather than remain planktonic. Bacterial cells embedded within biofilm are protected from detrimental factors, whereas nutrient-deficient conditions and hostile environments are both noted among driver factors for biofilm production [84]. A crucial component of mature *S. aureus* biofilm is the extracellular matrix. This is composed of eDNA, polysaccharide intercellular adhesin, and other proteins. It is the most stable, thus, a problematic stage to treat. To reduce biofilm mass, detachment follows, in which QS as well as nuclease and protease enzymes play a significant part [85–88]. The cell-to-cell signaling of QS pertains to all biofilm formation stages. A key role in the initiation is the communication between bacteria through the detection of AIPs [89]. Chronic

infection of *S. aureus* as well as biofilm formation is linked with low activity of *agr* QS [50]. *In vivo* studies have demonstrated the importance of the *agr* system to disease progression. Although upregulation by *agr* has a role in acute infections, downregulation is involved in biofilm formation [66, 90, 91]. In the dispersal stage, which is directly under-regulation of *agr*, isolation of new cells is ascribed to P3 promoters via the production of proteases and glucose depletion [92]. Hence, there is a direct relation between QS activation and the transition between biofilm and planktonic cell lifestyles. Thus, it remains to be determined whether QS quenching results in biofilm blockage [93, 94].

3. Anti-QS approaches

Because of widespread heightened antimicrobial resistance, the conventional means of treating bacterial infection, antibiotic therapy, is now increasingly impractical, such that alternative approaches are being considered [95]. The presence of biofilm, efflux pumps, and persister cells each exacerbate drug resistance [96]. Targeting QS by disturbing cell-cell communication is a way to combat biofilm [97]. Moreover, the effectiveness of different potential inhibitors against QS has been reported [98]. Various strategies are proposed to disrupt QS, including receptor inactivation, signal inhibition (by natural or synthetic inhibitors), signal degradation by quorum quenching enzymes, blocking QS by antibodies, and applying antibiotics as a cotreatment [98, 99].

Targeting AIPs is a good way of treating QS and considerable effort has been made to date to find inhibitors [100]. A known approach suggested in this context is to cope with RNAIII, due to its key role in QS. Reportedly, RNAIII inhibitory peptides (RIPs) have shown inhibitory effects on *agr* and biofilm. It is believed that targeting this molecule will diminish the production of some virulence factors and toxins [101, 102]. Similarly, based on the inhibition of *agr* of another subgroup [103], natural and synthetic AIPs may be introduced as potential inhibitors. Different inhibitors include nonpeptidic (P3 inhibitor) and synthetic molecules, cyclic dipeptides (from *Lactobacillus*), ambuic acid (a fungal extract), licochalcone A (LicA, a plant extract), antivirulence agents such as naphthalene and biaryl compounds, organic compounds (by interfering with *agr*-DNA binding), and savirin (*S. aureus* virulence inhibitor). Each of these actively inhibits QS in *S. aureus* [104–110]. Monoclonal antibodies, applied as both passive and active immunotherapeutic regimens, have also yielded promising results [49]. Collectively, many approaches that target *agr* and AIPs have been tested. Targeting AIPs via extracellular therapy is advantageous over targeting *agr*, as complications of intercellular therapy such as degradation do not arise.

Another treatment approach for Gram-negative bacteria is based on phenolic compounds. When tested extensively against AHL QS in *P. aeruginosa*, the novel phenolic derivative GM-50 reduces biofilm-related virulence, thereby enhancing antibiotic efficacy [111]. In addition, food-associated bacteria such as lactobacilli can exploit antibiofilm activity by interfering with AHL QS [112]. The efficacy of probiotics against QS has been indicated in previous studies. Presumably, they exert their effects via secretion of metabolites and microencapsulation [113, 114].

Targeting AI-2 lessens the pathogenicity of different bacterial species [115]. Various natural products such as D-galactose and furanocoumarin (reducing AI-2 synthesis), apigenin, hexadecenoic acid, and citral have shown promise at inhibiting *V. harveyi* QS [116–120]. In terms of chemicals, halogenated furanones are effective

against AHL and AI-2, subsequently affecting biofilm formation [121]. In *C. jejuni*, two fatty acids, decanoic acid and lauric acid, were found to be useful against AI-2 at 100 ppm (preventing 90% of AI-2 activity). As a result, biofilm formation and motility of the bacterium were reduced substantially [115]. Similarly, different naturally occurring compounds including monoterpenoid glycosides, emodin, and antimicrobial peptides showed satisfactory inhibition of LuxS/AI-2 in *Streptococcus suis* [122–125].

Currently, there is no drug approved for clinical use, although research and development efforts are continuously making progress toward this goal. As a consequence of administering anti-QS drugs, bacterial virulence (selective pressure will result in no further negative implications) applied should decrease, which is of great importance when seeking novel, effective treatments [111, 126].

4. Conclusions

The complex adaptive regulatory system of QS stands out as the most pivotal mechanism of pathogenicity exhibited by bacteria [127]. Regarding therapy, because of the emergence and widespread prevalence of antibiotic resistance, cotreatment with alternatives as well as surgical removal of infected tissue surrounding implanted medical devices, is being increasingly used. Quenching and inhibitory substances suppress the virulence and pathogenicity of those bacterial pathogens that use QS. Because QS has a critical role in many physiological behaviors such as biofilm formation, exoenzyme secretion, siderophore functioning, membrane vesicle formation, swarming, and sporulation, QQ is becoming a popular strategy [128]. Thus, an in-depth knowledge of biofilm, sensitive antibiotics, penetration, and anti-QS agents will help to inform antimicrobial therapies to overcome biofilm infection [129].

Multiple activities of anti-QS agents have been identified, for instance, QS receptor inactivation, QS signal inhibition, degradation of QS signals, and antibodies to block QS, as well as combination therapies such as flavonoids or immucillin A in *P. aeruginosa,* lactonase in *Acinetobacter baumanni*, AP4-24H11 in *S. aureus,* and farensol with ß-lactamase antibiotics in *S. aureus* [130–134]. Given this premise, a QS inhibitor can modulate gene regulation via either of two strategies: interposition with signal generation and signal reception [135, 136]. Notably, many QS inhibitors, such as furanones and halogenated and acylated furan structures, are improved by competing with the AHL pheromone in *P. aeruginosa* [137, 138]. Furthermore, RIPs have shown promise against *S. aureus* [139].

Negative aspects of disturbing the QS system should be considered. Inadvertent or unregulated modulation of microbiota through the use of QS quenching compounds or inhibitors may cause a disequilibrium of normal microflora. This concept developed as AI-2 molecules resemble bacterial presence to provide microflora [128, 140]. At the same time, pathogenicity tends to increase by applying quenching agents that may contribute to the long-term survival of *S. aureus* [141–144]. In particular, staphylococcal QS *agr* mutant strains tend to develop persister forms as well as raised biofilm production [143, 145]. A possible strategy is to apply QS quenching only in the absence of biofilm. This stems from the observation of applying selective pressure to preserve *agr* as a planktonic form rather than in biofilm [146].

An important clinical consideration is to determine the strain susceptibility and optimal form of treatment, otherwise, the patient's condition may worsen [102]. In addition, limitations and challenges should be carefully weighed. For example, in

S. aureus, the type of condition should be considered, as *agr* performs contrary roles in biofilm and chronic infection. Of note, most studies on QS drugs have been carried out using a single laboratory strain. Although such research models provide valuable information, it is challenging to extrapolate with confidence to clinical settings in, for instance, the case of AIPs in *S. aureus,* as species subgroups are identified. Finally, the selectivity and safety of QS inhibitors, while minimizing disturbance of microflora, are important factors for human usage. Designing a library of QS inhibitors and determining their IC_{50} values is a suggested area for future research.

Conflict of interest

The authors declare no conflict of interest.

Appendices and Nomenclature

AI	Autoinducer.
Agr	Accessory gene regulator
AgrA	Response regulator
AgrB	Membrane-associated export protein, processes AgrD into AIP
AgrC	Membrane-bound histidine kinase receptor
AgrD	Propeptide gene for AIP
AHL	Acyl-homoserine lactone
AIP	Auto-inducing peptide
PIA	Polysaccharide intercellular adhesin
QS	Quorum-sensing
AI-2	Autoinducer-2
RIP	RNAIII inhibitory peptide

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