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Targeting quorum sensing for manipulation of commensal microbiota

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Abstract

Bacteria communicate through the accumulation of autoinducer (AI) molecules that regulate gene expression at critical densities in a process called *quorum sensing* (QS). Extensive work using simple systems and single strains of bacteria have revealed a role for QS in the regulation of virulence factors and biofilm formation; however, less is known about QS dynamics among communities, especially in vivo. In this review, we summarize the diversity of QS signals as well as their ability to influence "non-target" behaviors among species that have receptors but not synthases for those signals. We highlight host-microbe interactions facilitated by QS and describe cross-talk between QS and the mammalian endocrine and immune systems, as well as host surveillance of QS. Further, we describe emerging evidence for the role of QS in non-infectious, chronic, microbially associated diseases including inflammatory bowel diseases and cancers. Finally, we describe potential therapeutic approaches that involve leveraging QS signals as well as quorum quenching approaches to block signaling in vivo to mitigate deleterious consequences to the host. Ultimately, QS offers a previously underexplored target that may be leveraged for precision modification of the microbiota without deleterious bactericidal consequences.

Keywords Bacterial communication, Gut microbiota, Microbiota therapeutics, Quorum sensing, Quorum quenching, Signaling

Introduction

Many bacteria communicate using diffusible, small molecules that regulate gene expression in a density-dependent manner in a process called *quorum sensing* (QS; Fig. 1) [1]. Accumulation of autoinducer (AI) molecules, *e.g. N*-acyl-homoserine lactones (AHLs; autoinducer-I (AI-1)), by Gram-negative bacteria is a sensitive and effective way to regulate gene expression and plays a significant role in intra- and inter-species, as well as inter-kingdom, interactions [2]. In addition to AHLs, produced predominantly by Gram-negative Proteobacteria and some Bacteroidetes, Cyanobacteria, and Archaea [3–5], Gram-positive bacteria produce autoinducing peptides (AIPs), and the autoinducer-2 (AI-2), a furanosyl borate diester, described as a universal signal of interspecies communication [6]. Moreover, discovery and characterization of new classes of QS compounds remains an active area of research [7–9]. While some molecules, like AI-2, may be used for "signaling," or the induction of an evolved behavior in the presence of QS molecules, they may also be "cues", or used to manipulate or coerce specific behaviors from other species [10].

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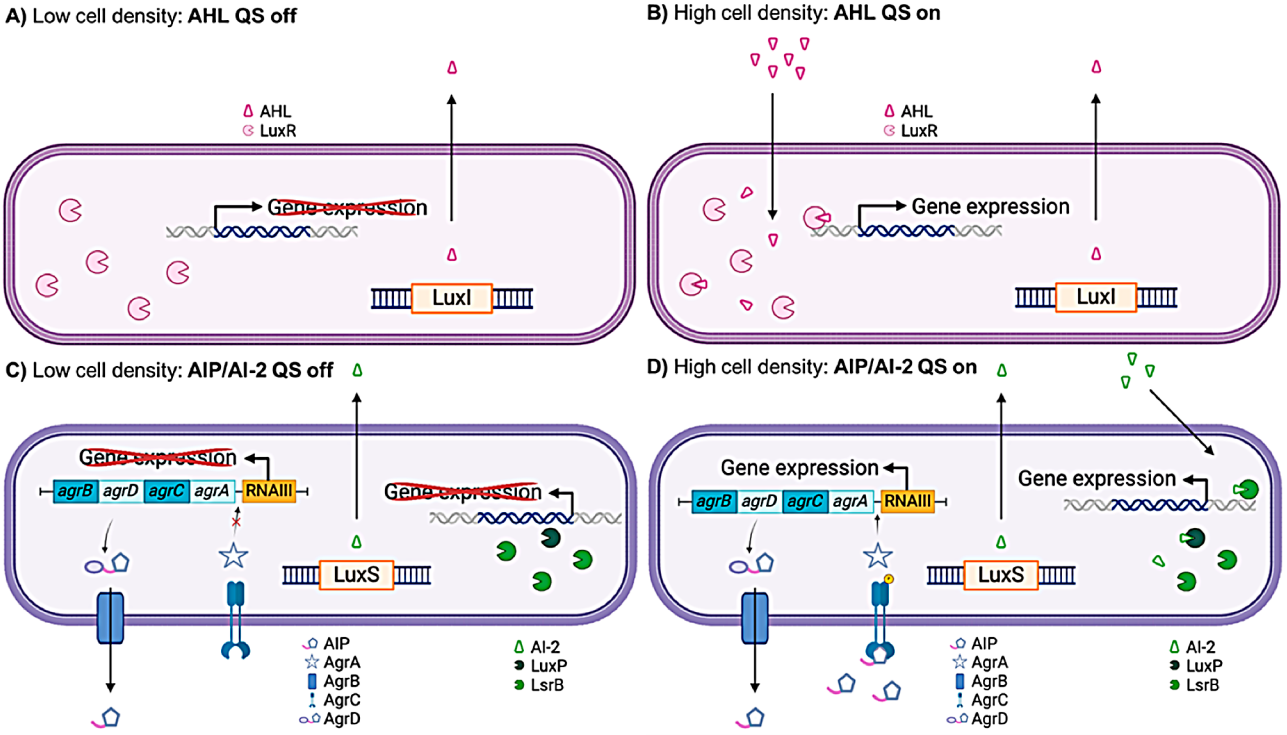

Fig. 1 Representations of *N*-acyl homoserine lactone (AHL), autoinducer-2 (AI-2), and autoinducing peptide (AIP) mediated quorum sensing (QS). **A** Bacteria produce AHLs via the LuxI synthase, which are released into the extracellular environment. At low cell density, AHL concentrations outside the cell remain low, leading to inactive QS. **B** As bacterial density increases, the concentration of AHLs increases, causing entry into the cell. AHLs bind to their corresponding cytoplasmic LuxR receptors, which initiates the expression of target genes, including the production of additional AHLs. **C** Similarly, AI-2 is produced via the LuxS synthase and is released into the extracellular space. At low cell density, AI-2 does not activate gene expression. Pre-AIPs, which are encoded by *agrD*, leave the bacteria through AgrB, a membrane receptor. Without sufficient concentration, gene expression will not be activated. **D** Increased bacterial density leads to AI-2 entry into the cell, where it binds LuxP and LsrB receptors, which initiate the expression of target genes. As the concentration of extracellular AIPs increases, more binding with AgrC occurs, which initiates the phosphorylation of AgrA and subsequent activation of target genes. Figures created using BioRender

Autoinducer systems not only regulate the release of communication signals, but they may also directly or indirectly affect expression of genes related to the ability to withstand changes in environmental conditions (e.g., pH) [8]. Increasing a population of cells may increase their efficiency at reducing harmful environmental substances [11–13]; conversely, cells may sense an impending environmental threat and use AI systems to prevent further deleterious change to the environment resulting from cellular metabolism [14, 15]. AI systems may also serve as master regulators, affecting the expression of hundreds of genes, allowing large shifts in phenotype [8]. Importantly, once a critical AI concentration is reached, a majority of cells in a population act in a homogenously coordinated way, sometimes with a reduction in non-cooperative traits [16], to carry out a function that could not be done effectively without a large population of cells [8]. However, some heterogeneity in function has been observed within a population, where subpopulations carry out specific, directed tasks (e.g. cannibalism of toxins, production of surfactin) in service to a larger function (e.g. virulence, biofilm production), regulated by multiple AI systems [17, 18].

As suggested above, QS signals are involved in more than QS activities and may exert antibiotic pressures and induce responses in both bacteria and eukaryotes that do not produce them [19, 20]. *Quorum quenching* (QQ) refers to any process that interferes with QS [21]. QQ molecules vary in their chemical nature, target, and mode of action and may affect any part of the QS process from production, release, accumulation, or detection of QS signaling molecules. Enzymes that inactivate QS signals are termed *QQ enzymes*, while chemicals that disrupt QS pathways are called *quorum sensing inhibitors* [20]. In addition, environmental conditions like temperature and pH may also limit the longevity of QS signals [22, 23]. Over the last decade, research into QQ molecules has intensified, driven by the need to find complementary or alternative approaches to antibiotics and other potentially harmful agricultural compounds [20]. In this review, we describe the current state of the literature related to the function of QS/QQ signaling in host-microbe interactions, with a focus on mammalian cells

and hosts, and we propose future directions to leverage QQ as a novel therapeutic.

AHLs have diverse effects across kingdoms

In addition to their role in bacterial communication, AHLs are able to modify interactions with AHL-producing cells via different biological properties. Long-chain AHLs (≥C12) may be used as biosurfactants or for antibiotic applications [24, 25]. Inter-kingdom competition and communication mediated by AHLs has also been reported for *Candida albicans-Pseudomonas aeruginosa* [26, 27], as well as the algal genera *Enteromorpha* and *Ulva* with AHL-producing biofilms of *Vibrio anguillarum* [28, 29], Similarly, single species biofilms of *V. anguillarum*, *Aeromonas hydrophila*, and *Sulfitobacter* sp. BR1 expressing AHLs were attractive to the barnacle species *Balanus improvises*, but not biofilms in which AHL production was not conserved [30]. In plants, *Medicago truncatula* and *Arabidopsis thaliana* showed changes in their transcriptome when exposed to AHLs [31, 32], while the tomato plant *Solanum lycopersicum* showed increased resistance to infection when colonized with AHL-producing *Serratia liquifaciens* [33].

Different bacterial species produce unique AHLs with modifications in length and composition of the acyl side chains, and these features confer specificity for the corresponding receptor [34]. While each AHL synthase normally produces only one type of AHL, multiple AHL synthase-receptor pairs (*luxI/luxR* homologues; Fig. 1A-B) have been reported in single species throughout the Proteobacteria [35]. Moreover, AHL receptors may have different levels of substrate affinity allowing them to eavesdrop on similar signals produced by other species [35, 36]. A recently developed high-sensitivity, ultra-high performance liquid chromatography-mass spectrometry (UPLC-MS)/MS-based assay was able to detect 27 AHLs in cecal, serum, and liver samples from conventionalized mice [37], and a previous method found 14 different AHLs in human fecal samples from healthy controls and those with inflammatory bowel disease (IBD) [38]. These results suggest that the intestinal commensal microbiota is utilizing AI-1 QS, although work to determine which species are producing which AHLs is needed. There is also recent evidence that the host can sense AHLs [39], although the consequences of this remain to be explored.

The capacity to enzymatically degrade AHLs is widespread amongst bacteria [9, 21, 40], archaea [41], and eukaryotes [31, 42]. The classes of enzymes that degrade AHLs include lactonases that open the lactone ring of AHLs [41, 43], amidases or acylases that hydrolyze the amide bond [44], or oxidoreductases that either reduce acyl chains of AHLs or reduce 3-oxo-AHLs [45, 46]. Some bacteria are limited to cleaving AHLs of specific side chain length [40, 47], while others act on a broader range of substrates [21, 40]. We highlight lactonases as potentially tunable enzymes to target specific types of AHLs produced by specific taxa (Fig. 2; Table 1).

AI-2

Based on a genomic survey, approximately 80% of Firmicutes encode a homolog of the *luxS* gene, an AI-2 synthase (Fig. 1C-D), while < 20% of the Bacteroidetes were similarly predicted to be producers of AI-2 [48]. However, sequencing of new members of the families *Muribaculaceae* and *Barnesiellaceae* in the phylum Bacteroidetes is revealing a wider distribution of AI-2 in this phylum [49]. The functional effects of AI-2 also differ by species: it acts as an activator of biofilm formation in *Clostridioides difficile*, but as a repressor of biofilm formation in *V. cholera* [50]. AI-2 may also play a role in niche competition; for example, *luxS*, the AI-2 synthase, of *Bifidobacterium breve* was found to be essential for murine colonization and promoted iron acquisition [51]. Notably, the increased iron availability may enhance the pathogenic potential of opportunistic pathogens amongst the commensal microbiota. Additionally, AI-2 has been associated with other functions including antibiotic resistance, hemolytic activity, motility, and virulence factor production [52]. The host may also sense AI-2, stimulating immunomodulatory and inflammatory pathways [53]. An AI-2 mimic produced by colon, lung, and cervical cells in mammals in response to bacterial metabolites and impairment in tight junctions also activates bacterial QS behaviors [54], although the functional reasons underlying this remain to be explored. The hormones epinephrine and dynorphin have also been shown to stimulate QS in *Escherichia coli* and *P. aeruginosa*, respectively [55, 56]. These studies highlight the bidirectional role of QS in host-microbe communication.

Autoinducing peptides (AIPs)

Gram-positive bacteria utilize short, typically cyclical peptides called autoinducing peptides (AIPs) to communicate [9]. AIPs are bound by transmembrane histidine kinases, which results in the downstream phosphorylation of regulators of gene expression [57]. AIP QS systems are well-defined in numerous bacteria, including *Staphylococcus aureus* [58], *Enterococcus faecalis* [59], and *Bacillus cereus* [60]. Like all QS circuits, Gram-positive QS relies on production, detection, and response to AIs [57]; however, unlike Gram-negative QS systems in which AHLs can freely diffuse across the cell membrane, Gram-positive QS requires active transport for passage of AIPs across the membrane [61, 62]. *Agr* is regarded as the model QS regulatory system in Gram-positive bacteria [63]. The agr system relies on four genes—*agrB*, *agrD*, *agrC* and *agrA*—which code for transmembrane endopeptidase AgrB, pre-AIP AgrD, transmembrane protein

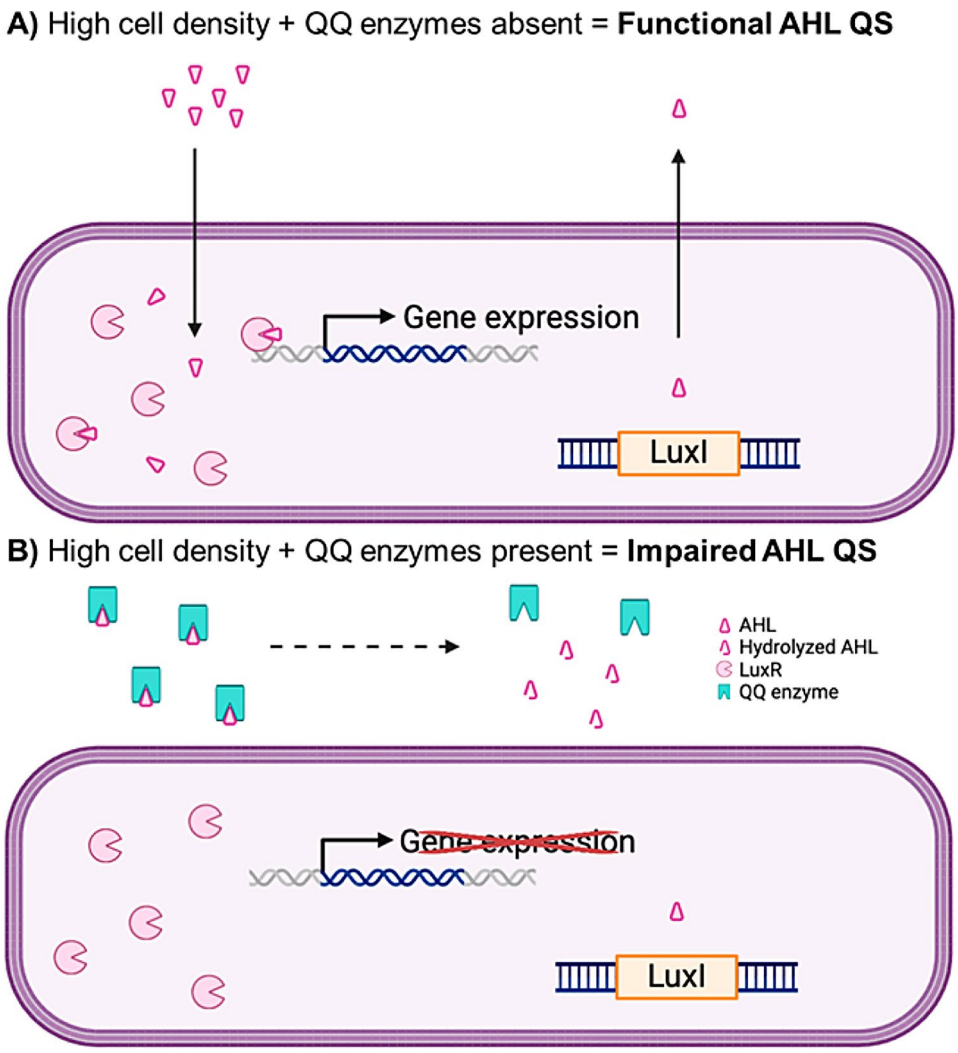

Fig. 2 Depiction of AHL-mediated QS and enzymatic QQ. **A** Bacteria produce AHLs via the LuxI synthase, which are released into the extracellular environment. AHLs bind to their corresponding cytoplasmic LuxR receptors, which initiates the expression of target genes, including the production of additional AHLs. **B** Quorum quenching enzymes degrade extracellular AHLs, thus preventing them from reaching the threshold required to activate QS. Figures created using BioRender

AgrC, and transcriptional activator AgrA, respectively (Fig. 1C-D) [64].

The relationship between AIPs and phenotypic changes, particularly in virulence, has been investigated. A recent study reported the removal of extracellular AIP-I during early-stage cell culture inhibits the *S. aureus* QS *agr* system [65]. Interestingly, in a skin abscess model, co-injection of non-cognate native AIP alongside *S. aureus* was reported to hinder *agr* activity [66]. This interference occurred due to non-cognate AIPs competing with their cognate counterparts, thus minimizing abscess formation [66]. Specifically, the *agr* locus in *S. aureus* is highly responsive to other staphylococcal species, such as dog pathogen *S. schleiferi*, suggesting a degree of inter-species cross-talk within this QS system [67]. Furthermore, the sustained release of a peptide-based QS inhibitor, as opposed to a single-dose bolus, significantly improved outcomes in a murine model of methicillin-resistant *S. aureus* (MRSA) skin infections in vivo [68]. These results present an attractive approach to controlling virulence in vivo.

Quorum sensing among intestinal commensal microbiota

Quorum sensing may play a role in the spatial distribution of bacteria throughout the gastrointestinal tract [69]. Studies indicate that the size and density of microbial aggregates can affect both the population size required for successful QS signaling as well as the distance over which that signaling may affect other species [70, 71]. The AI-2 synthase *luxS* has been demonstrated to be critical for gastrointestinal transit and biofilm formation in

Table 1 Representative quorum quenching lactonases previously described

Genus	Species	AHL lactonase	Target	Reference
Agrobacterium	*tumefaciens* C58, M103	AttM (AiiB)	C4-HSL, C6-HSL, C7-HSL, C8-HSL, C10-HSL, 3OC6-HSL, 3OC8-HSL	[157, 158]
Arthrobacter	sp. IBN110	AhlD	C6-HSL, C8-HSL, C10-HSL, 3OC6-HSL, 3OC12-HSL	[159]
Bacillus	sp. 240B1, *thuringiensis*	AiiA	3OC6-HSL, 3OC8-HSL, 3OC10-HSL	[160]
Chryseobacterium	sp. StRB126	AidC	C6-, C8-, C10-, C12-HSL; 3OC6-, 3OC8-, 3OC10-, 3OC12-HSL	[161]
Klebsiella	*pneumoniae* KCTC2241	AhlK	C6-HSL, 3OC6-HSL	[159]
Microbacterium	*testaceum* StLB037	AiiM	C6-, C8-, C10, C12-HSL; 3OC6-, 3OC8-, 3OC10, 3OC12-HSL	[162]
Mycobacterium	*avium* ssp. *paratuberculosis* K-10	MCP (MAP3668c)	C6-, C7-, C8-, C10-, C12-HSL; 3-oxo-C8-HSL	[163]
Mycobacterium	*tuberculosis*	PPH	C4-, C10-HSL; 3OC8-HSL	[163, 164]
Ochrobactrum	sp. T63	AidH	C4-, C6-, C10-HSL; 3OCC6-, 3OC8-HSL; 3-OH-C6-HSL	[165]
Parageobacillus	*caldoxylosilyticus*	GcL	C4-, C6, C8, C10, 3OC8, C10, 3OC12-HSL	[166, 167]
Pseudoalteromonas	*byunsanensis* 1A01261	QsdH	C4-, C6-, C8-, C10-, C12-, C14-HSLs; 3OC6-, 3OC8-HSL	[168]
Rhizobium	sp. NGR234	QsdR1	3OC8-HSL	[169]
Rhizobium	sp. NGR234	DhlR	3OC8-HSL	[169]
Rhodococcus	*erythropolis* W2, SQ1, Mic1, MP50, CECT3008	QsdA (AhlA)	C4-HSL, C6- to C14-HSLs	[43, 164, 170]
Solibacillus	*silvestris* StLB046	AhlS	C10-HSL	[171]
Sulfolobus	*solfataricus* P2	*SsoPox*	C4-HSL, C6-HSL, C8-HSL, C12-HSL; 3OC6-HSL, 3OC8-HSL, 3OC10-HSL, 2OC12-HSL	[172]
Sulfolobus	*Islandicus* M.16.4	*SisLac*	C4-HSL, C8-HSL, C12-HSL, 3OC8-HSL, 3OC10-HSL, 3OC12-HSL	[172, 173]

Table adapted from Fetzner, S. (2015) [156]

[1]C4-HSL: *N*-butanoyl-L-homoserine lactone; C6-HSL: *N*-hexanoyl-Lhomoserine lactone; C7-HSL: *N*-heptanoyl-L-homoserine lactone; C8-HSL: *N*-octanoyl-L-homoserine lactone; C10-HSL: *N*-decanoyl-L-homoserine lactone; C12-HSL: *N*-dodecanoyl-L-homoserine lactone; C14-HSL: *N*-tetradecanoyl-L-homoserine lactone; 3OC6-HSL: *N*-(3-oxohexanoyl)-L-homoserine; lactone; 3OC8-HSL: *N*-(3-oxooctanoyl)-L-homoserine lactone; 3OC10-HSL: *N*-(3-oxodecanoyl)-L-homoserine lactone; 3OC12-HSL: *N*-(3-oxododecanoyl)-L-homoserine lactone; 3OC14-HSL: *N*-(3-oxotetradecanoyl)-L-homoserine lactone

Lactobacillus rhamnosus GG [72], leading to a suggestion that the members of the Bacteroidetes, a minority of which have this system [48], may be at a competitive disadvantage [69]. AI-2 has also been demonstrated to affect biofilm formation and adhesion to the mucosa as well as the regulation of iron accumulation in *Bifidobacteria* and *Lactobacillus* [51, 73], *Actinobacillus* [74, 75], and *Vibrio* genera [76]. It was further suggested that similar dynamics under the control of AI-2 modulate the selective proliferation of *E. coli* in the mucus layer vs. in the luminal space [69]. Furthermore, enterohemorrhagic *E. coli* (EHEC) O157:H7 was suggested to respond to surrounding AHLs to activate gene expression related to acid resistance to survive transit through the acidic stomach environment [77].

While inter-species competitive dynamics may rely more heavily on AI-2, AI-1 has also been shown to effect host phenotype [78], and the LuxI/LuxR synthase/receptor pair for AI-1 have been found in a variety of human pathogens [79]. This system is critical to successful colonization and infection, virulence factor production, biofilm formation, and antimicrobial resistance [80]. Several bacteria, including *E. coli*, *Salmonella enterica*, *Enterobacter* spp., and *Klebsiella pneumonia* are known to encode SdiA, a QS regulator and homologue to the LuxR receptor for AI-1, but lack an AHL synthase gene, suggesting they do not produce AHLs but can respond to those produced from other taxa [81]. Despite a paucity of evidence that commensal intestinal microbiota produce AHLs, they have been detected in sputum, saliva, wounds, and feces of both infected patients and healthy individuals, suggesting they play a role in community function [79].

Due to the widespread and frequent use of antibiotics, the problem of antibiotic resistance has become a pressing global concern [82]. As a result, interference of QS systems may become a novel therapeutic strategy to achieve control of potential pathogens without deleterious bystander effects [83]. The majority of QQ compounds identified to date have targeted AHLs (AI-1), although newer reports describe enzymes that may be able to degrade AI-2 [9]. Below, we review the interactions between bacterially produced QS signals and mammalian physiology.

Interaction between QS and host endocrine signaling

The field of microbial endocrinology was born in 1992 when Lyte and Ernst observed that stress-induced neuroendocrine hormones could influence bacterial growth [84]. Subsequent research within the field uncovered the presence of hormone receptors in microorganisms, which suggested the existence of a microbial intercellular communication system [85]. Moreover, neurohormones implicated in host metabolism (e.g. dopamine,

epinephrine, norepinephrine, melatonin, and serotonin) may be the result of bacterial horizontal gene transfer [86]. Suspicions of bacterial-endocrine system crosstalk were hypothesized by early observations of bacterial QS in *V. fischeri* by 3OC6-HSL [87].

In addition to modulating gene expression, some AI molecules interact with host hormones to activate various signaling pathways. Catecholamines (e.g. dopamine, epinephrine, norepinephrine), for example, improve bacterial attachment to host tissues as well as influence bacterial growth and virulence [88, 89]. Sperandio, et al. investigated the QS interactions in EHEC with host hormones. It was found that although EHEC with a *luxS* mutantion was unable to produce AI-2 molecules, the bacteria's ability to activate virulence genes was conserved [90]. Epinephrine and norepinephrine were recognized as integral signals in this process, as evidenced by α- and β-adrenergic antagonists blocking the bacterial response, which suggests an element of cross-communication between bacteria and host cells [90]. Moreover, Yang, et al. found the presence of norepinephrine and dopamine to increase the expression of genes related to virulence and biofilm production in *V. harveyi* [91]. It was later demonstrated that epinephrine enhances adhesion, biofilm formation, and virulence in *P. aeruginosa* H103 [92].

Human sex hormones, such as estradiol and estriol, also play a role in QS regulation. Vidaillac, et al. explored the effect of sex steroid hormones on membrane stress and virulence responses in *P. aeruginosa* [93]. This study sought to expand on the earlier findings of Beury, et al. [94], which reported, at supra-physiological concentrations, the human hormones estradiol, estrone, and estriol led to a decrease in C4-HSL and 3OC12-HSL concentrations in cell cultures, suggesting an influence on QS signal synthesis and signaling. However, Vidaillac, et al. reported, at nanomolar (physiological) concentrations, sex steroids testosterone and estriol promote *P. aeruginosa* PAO1 virulence in vitro and in vivo [93]. Taken together, these two studies suggest a dose-dependent effect of sex steroids on *P. aeruginosa* and could suggest competition between QS and endocrine signaling.

There is a clear parallel between quorum sensing and endocrine signaling; however, notable differences exist in terms of function, scope and scale, and the nature of signaling molecules and their detection. Endocrine signaling involves hormone secretion by endocrine glands into the bloodstream, which allows these hormones to travel to distant target organs and tissues to regulate various physiological processes [95], whereas QS primarily functions within microbial communities [96]. Furthermore, AIs in QS are typically small molecules like AHLs or oligopeptides [6], while hormones in endocrine signaling include a diverse range of molecules like steroids, peptides, and amino acid derivatives [97]. The extent to which these systems are competitive or complementary (or both, under differing conditions) is an area that requires extensive further study.

Interaction between QS and host immunity

Quorum sensing has been proposed to be a mechanism by which bacteria induce apoptosis in host cells to create an anti-inflammatory environment to facilitate infection [98]. Elaborated study of *P. aeruginosa* has revealed interactions between AHLs and the immune system. It was reported that in *P. aeruginosa*, 3OC12-HSL increased transcript abundances of interleukin (IL)-1α, IL-6, IL-8/KC, and COX-2 in a dose-dependent manner, but expression was unaffected by C4-HSL [99]. 3OC12-HSL can induce apoptosis in Jurkat T lymphocytes, neutrophils, macrophages, fibroblasts, and breast cancer cells [98, 100–102]. Interestingly, six other AHLs, including C4-HSL, C6-HSL, 3OC6-HSL, C8-HSL, 3OC8-HSL, C10-HSL, failed to induce apoptosis in Jurkat cells [98]. Moreover, 3OC12-HSL was found not to induce activation of established immune modulators TNF, interferon (IFN)-β, and macrophage inflammatory protein 2, although concentrations as low as 10μM induced biochemical changes in macrophages and significantly reduced the viability of mammalian cells at 25μM [103]. The authors noted that canonical pattern recognition receptors were not required for 3OC12-HSL signaling, suggesting a novel mechanism through which *P. aeruginosa* establishes persistent infection.

Host detection of QS

The host also responds to a subset of QS molecules, primarily mediated through the aryl hydrocarbon receptor (AhR). AhR is highly polymorphic, thought to be controlled by a small number of loci (or possibly just one), with different AhR variants presenting varied binding affinities [104, 105]. While a complete list of QS molecules that act as AhR ligands has not been described, it is known that AHLs; quinolones; phenazines, such as pyocyanin, 1-hydroxyphenazine, phenazine-1-carboxylic acid, and phenazine-1-carboxamide; and naphthoquinone phthiocol, as well as various metabolites, are all AhR ligands [39, 106–108]. The main role of AhR in the body is to modulate the host's response into xenobiotics [109, 110]. It primarily accomplishes this by acting as a transcriptional modulator, binding to a large variety of exogenous ligands before dimerizing with the aryl hydrocarbon receptor nuclear translocator to activate the transcription of several metabolic enzymes and other genes encoding CYP1A1 and IL-22, with CYP1A1 inducing the metabolism of unwanted xenobiotic chemicals [110].

The relationship between AhR and the microbiota is complex, as a variety of microbially produced metabolites

can act as substrates. AhR-mediated IL-22 production aids in protecting the host from fungal infection and reducing intestinal inflammation, and is often triggered by indole-3-aldehyde, a metabolite of tryptophan [111, 112]. While not primarily used for QS signaling, germ-free mice fail to metabolize tryptophan into indole-3-aldehyde and suffer from increased intestinal inflammation [112, 113]. Other tryptophan ligands have a range of AhR-affinity, from the no or very low affinity seen with indole-3-propionate or indole-3-lactate to the high affinity seen with indole-3-pyruvate or indole-3-acetamide, with preliminary studies even demonstrating possible synergistic effects of multiple indoles on AhR in vitro [114]. It should be noted, though, that a low AhR-affinity does not mean a lack of physiological effects: indole-3-propionate has been shown to inhibit cancer cell proliferation, movement, and metastasis through the AhR pathway. Moreover, early stage breast cancer patients have been shown to have suppressed indole-3-propionate biosynthesis, indicating indole-3-propionate plays a key role in disease initiation and progression [115].

Similar to germ-free mice failing to metabolize tryptophan into indole-3-aldehyde, rats with IBD showed excessive serotonin availability [116]. Serotonin is a key host metabolite of tryptophan, with an excess indicating a likely decrease of tryptophan metabolism through the bacterial indole pathway and a decrease in AhR activation [116]. In both the germ-free mice and rats with IBD, the introduction of an AhR agonist or one of several strains of *Lactobacillus* capable of metabolizing tryptophan through the indole pathway significantly reduced inflammation and alleviated some or all symptoms [112, 113, 116]. This is also seen in human trials, where IBD patients have lowered AhR activation compared to healthy controls and IBD patients have lower levels of tryptophan and indole-3-acetic acid [112].

This host-microbe interaction through AhR is not limited to IBD. In a previous study, all mice with AhR knockout genes developed severe inflammation and in many cases developed colonic tumors due to aberrant β-catenin [117, 118]. However, germ-free AhR knockout mice had significantly reduced cecal tumor development compared to AhR knockout mice with unaltered gut microbiomes. Although these germ-free mice still displayed the abnormal accumulation of β-catenin seen in their microbially unaltered peers, a bacteria-triggered inflammation signaling pathway was required for intestinal tumorigenesis [117, 118].

AhR is not solely anti-inflammatory and plays a key role in maintaining homeostasis in host-microbe interactions. *P. aeruginosa* is a common Gram-negative opportunistic pathogen responsible for many nosocomial infections whose QS signaling is regulated by four interconnected pathways the expression of which vary over the course of infection [39]. The early and exponential stages of *P. aeruginosa* infection are dominated by 3OC12-HSL, while the stationary phase has C4-HSL, which does not effectively bind AhR, as the predominant QS molecules. AhR has demonstrated an ability both in vitro and in vivo to detect changes in the ratios of these molecules and modulate downstream responses to tune host immune defenses according to the severity of infection. Moreover, in a recent mouse study, it was found that *L. bulgaricus* could activate the AhR pathway to increase CYP1A1 expression and ameliorate dextran sodium sulfate-induced colitis, although the specific substrate produced by *L. bulgaricus* has yet to be determined [119]. Taken together, these studies highlight the role of QS-AhR signaling to regulate host physiology.

Probiotics

Probiotic approaches are now being considered where genetically engineered probiotic strains are used to promote a diverse microbial community. These strains carry vectors, which upon entry to gut environment, allow delivery of signaling molecules that engage in QS [9]. Lactic acid bacteria are the most widely studied probiotic group, and QS inhibition by this group and others has been recently reviewed [120]. Subspecies of *Lactobacillus* have different mechanisms of causing interference in QS with pathogenic bacteria. *L. acidophilus* demonstrated inhibition of QS against *C. difficile*, *P. aeruginosa*, and *E. coli* [121–126]. *C. difficile* AI-2 production was inhibited when exposed to cell extracts from *L. acidophilus* GP1B resulting from a significant decrease in expression of the AI-2 synthase [121]. The cell extract also suppressed virulence factors encoded by *tcdA*, *tcdB*, and *tcdE*. *L. acidophilus* induced an inhibitory growth effect on *C. difficile*, which is likely due to the production of lactic acids from *L. acidophilus*. *Staph. aureus* was inhibited via the AI-2 pathway in pigs and decreased the activity of AI-2 as well as hindered the ability of the pathogen to form biofilms within the gut [122]. In *E. coli*, the addition of the probiotic strain decreased adhesion and biofilm formation to HeLa cells (active molecules were unidentified) [124, 125]. *L. acidophilus* has further shown the ability to inhibit the formation of *P. aeruginosa* biofilms, as well as its virulence through application of probiotic cell extracts [126]. The bioactive molecules found were four active diketopiperazines such as cyclo-Phe-Pro diketopiperazine. This molecule prevents binding of effector molecules to DNA, it also exhibits anti-biofilm and anti-QS activity [127]. *L. acidophilus* degrades elastase, a virulence factor, by up to 74%, limiting the virulence potential of *P. aeruginosa*. Unfortunately, the actual molecules that caused the QQ were not well identified. In addition, it appears that the cell extracts described do not act in a dose-dependent manner.

Reuterin, an antimicrobial agent produced by *L. reuteri*, was observed to inhibit biofilm formation, motility, and virulence gene expression of *C. perfringens* [128]. Another group found that *L. reuteri* can also produce small signaling molecules cyclo l-Tyr-l-Pro and l-Tyr-d-Pro that interfere with *S. aureus* via the AIP QS system (Fig. 1C-D) [129]. These molecules were added in a dose-dependent manner to measure effectiveness against *S. aureus* and were able to reduce transcription of virulence genes. Similarly, when *C. perfringens* and *L. fermentum* were co-cultured, similar results were observed reducing the adhesion of the pathogen to chicken intestinal epithelial cells in vitro [130]. The highly virulent *C. difficile* ribotype 027 was also inhibited by cell extracts from *L. fermentum* Lim2 through the reduction of AI-2 activity [131]. Quorum sensing genes such as the AI-2 synthase *luxS*, virulence factors (*tcdA*, t*cdB*, and *tcdE*), and a negative regulator gene (*tcdC*) were up-regulated, indicating that the potential of a probiotic cocktail to affect multiple aspects of pathogenicity.

Bacillus spp. have also been shown to prevent colonization by *Staph. aureus* through AIP inhibition in a rural Thai population [132]. Lipoproteins β-OH-C17-fengycin A and β-OH-C16-fengycin B produced by *Bacillus* compete with AIP of *S. aureus* and inhibited QS. Similarly, subtilosin A produced by *B. subtilis* was found to have a QQ effect, by inhibition of AI-2 production, on pathogens such as *Gardnerella vaginalis*, *E. coli*, and *Listeria monocytogenes* and significantly reduced biofilm formation [133]. Violacein produced by bacilli was also used to examine biofilm inhibition in *E. coli* and found a 60% reduction. *Salmonella* is also thought to be affected by the same molecule [134].

A health promoting AHL

3-oxo-C12:2-HSL was first described in the context of IBD when it was found that this AHL was present significantly more frequently in healthy controls (65.4%) than IBD flare (16%) and remission (37.5%) patients, and controls had significantly greater fecal concentrations of 3-oxo-C12:2 than IBD patients [38]. Furthermore, this molecule was reported to provide a protective effect on human gut epithelial Caco-2/TC7 cells, as evidenced by significantly decreased IL-1β—induced IL-8 secretion in its presence [38]. It was later found 3-oxo-C12:2-HSL-treated RAW264.7 murine macrophage cells exhibited reduced secretion of pro-inflammatory TNFα and IL-1β compared to controls [135]. Consistent with findings for proteins, mRNA levels of TNFα and IL-1β were lower in 3-oxo-C12:2-HSL-exposed macrophages than controls [135]. Conversely, IL-10, an anti-inflammatory cytokine, expression was enhanced in cells exposed to the AHL [135]. These results were confirmed using peripheral blood mononuclear cells in which inflammation was triggered by lipopolysaccharides [135]. Peripheral blood mononuclear cells exposed to 3-oxo-C12:2-HSL demonstrated decreased TNFα secretion [135]. Together, these results demonstrate an anti-inflammatory role of 3-oxo-C12:2-HSL.

Therapeutic applications of QS/QQ

Evidence for QS systems in chronic microbially associated conditions has recently been described [79]. Dysbiosis in IBD is both a cause and consequence of inflammation [136, 137]. The presence of 3-oxo-C12:2-HSL (described in detail above) can modulate this balance and is associated with increases in Firmicutes and decreases in pathogenic bacteria [38]. Mammalian blood typically contains AHL-degrading paraoxonase enzymes (PONs) that are hypothesized to relate to innate immunity [138, 139] and which were found at lower concentrations in IBD patients relative to controls [140, 141]. The combination of decreased PONs with increased intestinal permeability typical of IBD is expected to result in higher concentrations of AHL in the bloodstream, which was observed in a study of serum samples from Crohn's disease patients and healthy controls [142]. This suggests QS molecules could be used as an efficient and accurate method of diagnosing IBD [143], which would enable more rapid therapeutic intervention.

Similar to IBD, concentrations of AI-2 were significantly greater in tissue and stool of colorectal cancer (CRC) patients relative to patients with colorectal adenoma or normal colon mucosa [144]. Further, AI-2 of *F. nucleatum* was found in this study to stimulate macrophage polarization via modulation of expression of tumor necrosis factor ligand superfamily member 9 in macrophages in the tumor microenvironment. In an orthotopic murine model of CRC, EntF*, a metabolite of the EntF QS peptide produced by *Ent. faecium*, promoted metastasis to the liver and lungs [145]. Further in vitro experimentation suggested a mechanism for this was via reduction of E-cadherin expression. Moreover, pro-inflammatory effects of AI-2 from *E. coli* were induced in vitro through induction of IL-8 in HCT-8 colon cancer cells [53].

Early cystic fibrosis (CF) QS/QQ work centered on *P. aeruginosa*, finding furanone C-30, a QS molecule, partially or completely suppressed virulence factor production in vitro [146]. Interestingly, when mice lungs were infected with *P. aeruginosa* and treated with furanone C-30 in vivo, QS-regulated gene expression was significantly repressed. In a more recent study, outbred (NMRI) and inbred BALB/c mice with wild-type-colonized implants were administered furanone C-30 interperitoneally [147]. The results demonstrated that mice treated with C-30 exhibited significantly lower levels of adherent bacteria upon implant removal than the control group. Further investigation into *P. aeruginosa* QS

utilized isolates from CF patients at various stages of lung infections [148]. It was found the ability of *P. aeruginosa* to produce 3OC12-HSL and C4-HSL signal molecules are lost at different times, suggesting distinct regulatory mechanisms of two hierarchically-organized AI-1 systems encoded by *las* and *rhl* genes, respectively [148], which are reviewed extensively elsewhere [149]. A recent study using a three dimensional lung epithelium cell model reported CF isolates without LasR remain capable of inducing cell death through RhlR (the C4-HSL receptor), thus underscoring the adaptability of *P. aeruginosa* and positioning C4-HSL as a possible therapeutic target in CF [150].

Methicillin-resistant *Staphylococcus aureus* infections are also of particular interest in the context of QS/QQ therapies. Treatment of MRSA-infected wounds with biaryl hydroxyketone compounds resulted in a significant increase in wound healing percentage compared to untreated controls in a murine model, thus demonstrating the feasibility of QQ agents as topical therapeutics [151]. Interestingly, metabolites isolated from the cell-free supernatant of *Ent. faecium* strain 30,616 and *L. lactis* strain 11,454 enhance the susceptibility of two clinical strains of MRSA to cefoxitin, an antibiotic not currently effective against MRSA infections, highlighting that probiotic metabolites may be effectively used in conjunction with beta-lactam antibiotics to restore MRSA sensitivity to cefoxitin and potentially other therapeutics [152].

Future perspectives

There is growing evidence that bacterial signaling via QS plays a role in the establishment, severity, and persistence of both infections and non-infectious microbially associated diseases [79]. While host-microbe interactions surrounding QS have been well studied for a few model genera, e.g., *Vibrio* and *Pseudomonas*, we are only beginning to appreciate the diversity of QS signals and the species able to produce and react to them [9, 153]. Difficulty in detection remains a critical challenge to characterizing QS signals from complex matrices, e.g., stool or serum [37], in preclinical, in vivo models and human clinical trials. Moreover, the larger concentrations and amounts of compound needed to study the effects of QS signals in vivo present further barriers of cost and labor [154]. Nevertheless, evidence in IBD [143], cancer [144, 145], and cystic fibrosis [146] highlight the necessity of understanding the relationship between QS and disease progression and outcomes. Importantly, QS/QQ may be a critical avenue to better understand, predict, and manipulate the microbiota without unintended harm to protective and/or beneficial commensal microbiota [155]. Multidisciplinary, team science-based approaches will be critical to bringing this work into clinical translation.

Conclusion

Quorum sensing through the production of autoinducer molecules is a widespread phenomenon among a broad distribution of bacteria, the extent of which continues to grow as novel methods of detection are developed [37] and bioinformatics databases and annotations improve [153]. QS signaling has been shown to impact the expression of virulence factors and biofilm formation, in addition to establishment and persistence of infection. Furthermore, QS signaling extends beyond interspecies communication among the microbiota and is detected by the host [39], interacts with endocrine signaling [93, 94], and can drive immunological responses [78]. Emerging evidence suggests a role for QS signals in chronic diseases such as IBD and cancers [79], positioning these signaling pathways as potential targets for emerging therapies targeting the microbiota. Future work is necessary to describe the effects of QS/QQ signals in preclinical, in vivo models to understand complex host-microbe interactions. However, further development and optimization of QQ strategies to "turn off" pathogenic signaling presents an exciting frontier in the growing field of personalized medicine [79, 155].

Abbreviations

3OC6-HSL	N-(3-oxohexanoyl)-L-homoserine lactone
3OC8-HSL	N-(3-oxooctanoyl)-L-homoserine lactone
3OC10-HSL	N-(3-oxodecanoyl)-L-homoserine lactone
3OC12-HSL	N-(3-oxododecanoyl)-L-homoserine lactone
3OC14-HSL	N-(3-oxotetradecanoyl)-L-homoserine lactone
AI	Autoinducer
AHL	N-acyl-homoserine lactone
AhR	aryl hydrocarbon receptor
C4-HSL	N-butanoyl-L-homoserine lactone
C6-HSL	N-hexanoyl-L-homoserine lactone
C7-HSL	N-heptanoyl-L-homoserine lactone
C8-HSL	N-octanoyl-L-homoserine lactone
C10-HSL	N-decanoyl-L-homoserine lactone
C12-HSL	N-dodecanoyl-L-homoserine lactone
C14-HSL	N-tetradecanoyl-L-homoserine lactone
CF	Cystic fibrosis
CRC	Colorectal cancer
EHEC	Enterohemorrhagic Escherichia coli
IBD	Inflammatory bowel disease
IFN	Interferon
IL	Interleukin
Ig	Immunoglobulin
MMP	Matrix metalloprotease
MRSA	Methicillin-resistant Staphylococcus aureus
OdDHL	N-(3-oxododecanoyl)-L-homoserine lactone,3OC12-HSL
OHHL	N-(3-oxohexanoyl)-L-homoserine lactone,3OC6-HSL
PON	Paraoxonase
PPAR	Peroxisome proliferator-activated receptor
QS	Quorum sensing
QQ	Quorum quenching
TJ	Tight junction
TNF	Tumor necrosis factor

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Data availability
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Declarations

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