Recent Developments in Quorum Sensing-Based Suppression of Intestinal Pathogenic Bacteria

Safir Ullah Khan1,*, Munir Ullah Khan2, Wang Li Chen1

1School of Life Sciences, University of Science and Technology of China, 230027, Hefei, China
2Department of Polymer Science and Engineering, Zhejiang University, 310027, Hangzhou, China
*Corresponding author: safir@mail.ustc.edu.cn

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Abstract
Quorum sensing (QS) is a way for bacteria to communicate with each other. It works by making, releasing, and identifying AIs (autoinducers). It is critical for the growth of microorganisms and is a vital component of the immune system. In the intestinal environment, Salmonella Typhimurium, Vibrio cholera, Clostridium difficile, Escherichia coli and other intestinal pathogens infect the host body, affecting the normal immune metabolism process of the host body, resulting in acute gastroenteritis, dysentery and other diseases. Antibiotics can treat the concurrent infection caused by intestinal pathogens in the traditional treatment. Because of this, antibiotics should be used sparingly. Overuse of antibiotics can lead to the expansion of a wide range of antibiotic resistance in bacteria, which can then spread and evolve through genetic mutation. In recent years, more studies have shown that bacterial biofilm formation, virulence factor production, and drug resistance inhibition can be regulated by manipulating the QS system. Firstly, the working paths of several typical bacterial QS systems were summarized. The therapeutic strategies of QS for several common intestinal pathogens were reviewed to provide some references for developing new therapeutic schemes for intestinal diseases and related inhibitors of intestinal pathogens.

Keywords: quorum sensing, intestinal pathogens, virulence factor, biofilm formation

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1. Introduction

In addition to the material exchange of nutrients between bacteria and the environment, information transmission and exchange also exist in the process of bacterial reproduction in the environment, which is called quorum sensing (QS) [1]. Quorum sensing (QS) is a bacterial communication protocol. Auto inducers (AIs) and quorum receptors work together to allow bacteria to detect population density and adjust the expression of genes accordingly within the population region [2]. With the increase in bacterial population density, AIs accumulate to a threshold concentration in the environment. They are recognized and bound by bacterial QS receptor protein to activate or inhibit the activity of specific target genes, thus regulating the initiation of many biological processes [3], virulence factor secretion [4], biofilm formation [5], bacterial community symbiosis [6], bioluminescence [7], antibiotic synthesis [8], and nucleic acid synthesis [9].

The human intestinal flora is composed of a variety of microorganisms. Pathogenic bacteria secrete toxins to cause diseases, and probiotics treat diseases through probiotics [10,11]. Human intestinal pathogens such as Salmonella, Listeria, Shigella, Escherichia coli, and Clostridium difficile will colonize intestinal epithelial cells through the QS system to regulate toxin secretion and cell colonization, causing intestinal metabolism and immune imbalance, resulting in human acute gastroenteritis, bacterial diarrhea, dysentery, and other diseases. Intestinal probiotics increase globulin secretion (SlgA) in the gut, improve host immunity, antioxidant levels, and reduce intestinal inflammation [12]. Intestinal flora communicates with the host through the QS system and pathogen host communication mechanism. When the balance between bacterial flora is broken, the information exchange between bacteria and the host is interfered with, affecting the human body’s normal body functions and leading to human diseases [13].

Intestinal pathogens work synergistically to infect and injure the host body, and the problems associated with diverse bacterial infections make disease treatment increasingly challenging. The use of antibiotics has greatly solved the problem of intestinal bacterial infection. However, bacterial resistance will arise as a result of genetic movement in intra- and interspecific water levels and mutation under environmental pressure as a result of the extensive use of antibiotics [14,15]. The above factors restrict antibiotics' effectiveness in treating pathogen infection [16,17,18]. Conventional antibiotics inhibit or kill bacteria by inhibiting their metabolic processes and destroying the integrity of their cell membrane. At the same time, microorganisms can resist the effects of
antibiotics through various mechanisms, such as the development of bacterial biofilms that limit the entry of antibiotics into cells to perform a specific role. There are two major functions of the bacterial QS system: virulence factor synthesis and the formation of biofilms. Therefore, inhibiting the QS system of bacteria can effectively weaken the toxicity and invasion ability of pathogenic bacteria and overcome the limitations of biofilm antibiotics. Therefore, based on the important function of the QS system in regulating bacterial virulence and drug resistance, the development of new QS inhibitors can offer new ideas for solving the problem of drug resistance in fine bacteria.

In recent years, with the continuous analysis of various QS regulatory systems, the regulation mechanism and pathway of the quorum-sensing system involved in intestinal imbalance have been further studied. In order to help more researchers have a better understanding of this field, this article from the bacteria in different types of signal molecules mediated QS systems is introduced, summarizes the quorum-sensing system in the latest application of common intestinal pathogenic bacteria, and, based on the development of an inhibitor of QS intestinal pathogenic bacteria, provides a new reference.

2. QS System of Bacteria

Bacterial cell QS systems are diverse. The current research is relatively clear, and the common QS system according to the signal molecule classification mainly includes the following categories: N-acyl-homoserine lactone (AHL) [19], Autoinducer-2 (AI-2) [3], and Autoinduced oligopeptides (AIP) [20].

2.1. AHL Mediated QS System

In gram-negative bacteria, the AHL QS system, also called LuxI/R QS, is the most frequently researched. QS Systems like LuxI/LuxR were initially discovered and understood in Vibrio fischeri, a marine microbe [7,21]. In an AHL-type QS system, AHLs are usually composed of a hydrophilic hyperserine lactone and a hydrophobic acyl side chain. AHL bond saturation based on acyl side chains can be divided into different types; for example, 3-OXOC6-HSL in Vibrio Fischeri [22], 3-OXO-C12-HSL along with C4-HSL in Pseudomonas Aeruginosa [23], and Acinetobacter baumannii Ohe12-HSL in Baumannii [24]. The LuxI gene is highly confirmed in different bacteria [21], indicating that the synthetic AHL molecular structure is similar, but due to the difference in side-chain acyl-ACP, bacteria can synthesize different AHL molecules from one AHL synthase. Ortori et al. [25] found that Yersinia Pseudotuberculosis can jointly produce at least 24 AHL with c4-C15 side chain acyl groups by YtbI and YpsI. LuxR protein transcriptional regulators include self-induced binding domains (ABD domain, N-terminal) and binding DNA helix-turn-helix domains (HTH domain, C-terminal). Compared to luxI, the similarity of the luxR gene between different bacteria was only 18% to 25% [25]. In gram-negative bacteria, the luxR gene is usually adjacent to the luxI gene. A bioinformatics investigation of prokaryotic genomes found that part of the luxR genes in the genome are soloistic, which can respond to endogenous AHL signals generated by non-adjacent LuxI and unknown exogenous signal molecules [26].

In Vibrio fischeri, LuxI catalyzed the acylation of Sadenosyl methionine (SAM) and charged Acyl-ACP to acyl-SAM, which is then esterified, and demethionine is removed to form AHL signaling molecules. AHL binds and activates LuxR, and the AHL-Luxr complex binds a 20 bp DNA fragment in a reverse repeat region called the Lux frame, located about 40 bp upstream of the regulatory gene transcription start site. The transcription level of luxICDABE was lower in low population density. Under conditions of high population density, AHLs accumulate to the threshold concentration and bind to LuxR. Ahl-lux complex binds to DNA in lux frame and recruits RNA polymerase to promoter domain to stimulate the expression of downstream gene luxIABCDE and cause the bioluminescence process of Vibrio fischeri (Figure 1) [27].

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![Figure 1. AHL-mediated QS system model](image-url)
Different from Vibrio fischeri and other bacteria that can synthesize AHLs by themselves, some bacteria that cannot synthesize AHL signal molecules by themselves, such as Escherichia coli and Salmonella, can express SdiA protein to recognize AHL signal molecules produced by other bacteria [28], thus controlling virulence factor generation and biofilm formation of bacteria [29].

2.2. AI-2-mediated QS System

Gram-negative bacteria have ai-2 molecules with the boroyl furan structure in addition to AHL signal molecules. Because LuxS produces ai-2 signal molecules, the AI-2 system is also called the LuxS system. AI-2 receptors are classified into two categories: It was first discovered that the LuxP and LsrB receptors had been identified in Vibrio Harveyi along with Salmonella Typhimurium [30]. ESRB also exists in Escherichia coli [31], Sinorhizobium meliloti [32] and Aggregatibacter actinomycetemcomitans [33]. It starts with LuxS making DBD [(4, S)-4, 5-dihydroxy-2, 3-glutarone]. DBD then combines with other molecules in the cell to make isomers. As a result of the differences in amino acid content at the binding site of the AI-2 molecule between LuxP and LsrB, the two proteins bind to S-ThmF-borate [2S,4S -2-methyl-2,3,3, 4- tetrahydrofuran borate], leading to the formation of two distinct binding substrate structures. ESRB combined with R-ThmF-[2 R, 4 s)-2- methyl-2,3,3, 4-four hydroxyl tetrahydrofuran] [34-35]. After binding with the ai-2 signaling molecule, LuxP regulates the activity of histidine kinase protein across the membrane sensor, thereby modulating the phosphorylated signal transduction cascade, while LsrB interacts synergistically with the LsrACD transporter to regulate the subsequent LSR system [35]. Take the QS system mediated by LuxS-LSRB in Salmonella typhimurium (Figure 2). LuxS produces DBD in the cell, which is isomerized into AI-2 molecules when concentration rises, and the hydrophilic AI-2 is transferred outside the cell membrane by TqsA [36]. When AI-2 reaches a certain concentration in the extracellular environment, LsrK phosphorylates it [37]. As a result, the transcription activator LsrR can no longer suppress the LSR operon, and the LSRABCD gene related gene transcription of bacteria [45]. LuxS synthesizes DBD and isomerizes it into AI-2, which is transferred by TqsA out of the cell and into the environment. After extracellular deposition of AI-2 reaches a specified concentration, LsrK phosphorylates AI-2 to Pi-AI-2, which binds LsrR to eliminate LsrR’s regulation of the LSR operon and increase the translocation of LsrABCD to AI-2. Further isomerization of Pi-AI-2 occurs in E.coli with LsrG catalyzing the formation of P-HPD and P-TPO, while LsrF catalyzes the generation of DHAP and acetyl CoA from P-HPD. Dotted arrow: gene transcription translated into protein; Solid arrow: reaction process flow.

2.3. AIP-mediated QS System

Oligopeptide molecules are known as autoinducer peptides (AIP) to communicate with each other. There are two basic forms of peptide QS in bacteria (Figure 3). The first is a two-part system. In the Aureus AGR-type QS system, AgrD synthesized the propeptide of AIPs, which was processed and matured by the membrane protein AgrB and transported to extracellular accumulation. When AIPs reach the threshold concentration, they will be recognized by histidine-A- grC and transduced into the cell. AIPs transported into the cells activate the regulatory response factor AgrAA-grA and promoted the expression of agrABCD operator-gene and QS downstream genes. AgrC also plays a role in bacteria’s QS behavior in the outer ring of the cell membrane [43]. Pneumonia’s COM system and EnterococcusfaecalisPrgX (Enterococcusfaecalis- subtilisRgg (Streptococcus), NprR (Bacillus cereus), and PlcR (Bacillus cereus) are all named after the receptor protein discovered in distinct species (B. cereus). AIP progenitors are encoded by small Open Reading frames in RRNPP systems (sORFsecretory system (Rap, PlaRPlaPPlaPAB- Eep transport network are activated (PrgXRgg). After accumulating to the threshold concentration, AIP is introduced by the oligopeptidasepermease complex (Oppactivated by receptor proteins) and regulates spore formation and virulence-related gene transcription of bacteria [45].

In Staphylococcus epidermidis, three different AGR type QS systems (I-III) were found, in which AIP signals were different and AgrBCD receptors were also variable. Interestingly, it is worth noting that AIP-I and AIP-III both inhibit AGRC-I, whereas AIP-I and AIP-III both inhibit AGRC-II and III [46].
2.4. Other Types of QS System Microorganisms

In addition to the relatively clear QS regulatory system, some relatively rare QS signal molecules mediate different QS systems. For example, enterohemorrhagic Escherichia coli O157:H7 (Enterogenic Escherichia coli, EHEC) can use suprandin derivatives as signal molecules to regulate virulence gene generation and biofilm formation [47]. In addition to AHL signaling molecules, there are also signal components of Pseudomonas Quinolone Signal (PQS) in Pseudomonas Aeruginosa that participate in forming virulence factors in Pseudomonas Aeruginosa [48]. There was also 3-hydroxymyristate (3-OH MAME) and 3-hydroxypalmitate (3-hydroxypalmitate) in R. solanacearum. Phc-type QS systems with fatty acid derivatives such as 3-OH PAME are QS signal molecules [49].

Zhao et al. [50] found that Bacillus cereus has nine DSFs (Diffusion signal factors) whose structures are cis-2-unsaturated and fatty acids (C8-C15) have been identified, as well as six diketopiperazines (DKPs) - like signaling molecules that regulate the formation of bacterial biofilms.

AgrD synthesizes the AIP precursor in the two-component system and is processed and transported by AgrB to extracellular accumulation. Extracellular AIP is recognized and transduced by AgrC. AgrA is activated to induce autophosphorylation and promote the expression of agrABCD and QS downstream genes. SORF encodes an AIP precursor in the RRNPP system, and it is processed and secreted by the SEC-dependent secretion system (Rap, PlaR, NprR) and the PPTAB-EEP transport system (PrgX, Rgg). After AIP accumulates to threshold concentration in extracellular, Opp transduction is recognized and activated by receptor proteins (Rap, PlaR, NprR, PrgX, Rgg) to regulate downstream gene expression. Dotted line arrows indicate gene transcription into protein; solid arrows indicate reaction process flow.

3. Application of QS System to Suppress Intestinal Pathogens

The emergence of drug-resistant strains and comorbidities caused by various bacterial infections has increasingly become a human health challenge [51]. The QS system controls bacterial infection through target virulence, and interfering with the QS system has become one of the research strategies for treating diseases caused by intestinal pathogen infection [52]. The following is a review on the suppression of infection caused by common intestinal pathogens such as Salmonella typhimurium,
Vibrio cholerae, Clostridium difficile and pathogenic enterobacter based on QS strategies.

3.1. Inhibition of Salmonella Typhi Based on the QS System

Salmonella typhi belongs to gram-negative bacteria, which easily colonize and adhere to the host’s intestinal tract, leading to diarrhea and gastroenteritis. Salmonella communicates with the host through the QS system and regulates pathogenicity, together with biofilm formation, sporogenesis, virulence factor formation, and motility [53]. Birhanu et al. [54] used a combination of pyrogallol (PG) and marbo floxacin (MAR) to suppress Salmonella typhimurium. qPCR showed that the expression levels of hilA (central regulatory factor), invF (virulence island SP-1 transcriptional activator), sipB (adhesive protein) and arca (effector pump) genes were 59.3%, 78.1%, 46.7%, and 63.8%, respectively, when PG and MAR were combined. Salmonella’s invasion and intracellular survival were inhibited by down-regulation of quorum sensing, virulence transport, and efflux pump genes. Mechesso et al. [55] found that ginsenoside Rg3 significantly reduced salmonella motility, adhesion, invasion, and survival. At 50 μmol/L Rg3 down-regulated the expression levels of ompD (adhesion protein), agrK (SPI-1 secreted protein), sigB (invasion channel protein) and AHL QS genes (sdiA and srgE) by 55.3%, 91.1%, 78.8% and 75.0%, respectively. Thus, it affects Salmonella’s adhesion, invasion, and reproduction in host cells.

Bacteria can increase their multi-drug resistance (MDR) to drugs through QS regulation of efflux pump expression and biofilm formation. Shen et al. [56] found that 0.01% ε-polysylne reduced biofilm formation by about 80% in Salmonella Typhimurium. In addition, the expression levels of csgDBAC (curli spion synthesis), lsrKCD (QS manipulation), flbBCDST (flagellin synthase) and cheAWRBZY (chemotaxis egg white) genes were reduced by 2.0 to 8.3 times. According to the results, polysylne suppressed biofilm development by down-regulating the synthesis of genes associated with pil, cilia, and apical adhesion, and by up-regulating the production of genes linked to cilia, QS, flagella, and chemotaxis, and up-regulating the expression of envelope stress response genes, thus inhibiting the proliferation of Salmonella. Seo et al. [57] studied the inhibitory effect of bacteriocins produced by Lactococcus K10 and HW01 on Salmonella. They found that the two bacteriocins reduced the biofilm formation ability by about 60% at a concentration of 2 mg/mL and inhibited the biofilm formation and plankton cell growth of Salmonella on stainless steel, while chicken inhibits Salmonella’s ability to stick.

3.2. Inhibition of Vibrio Cholerae Based on QS System

Gram-negative Vibrio cholerae is a common pathogen that may easily infect the intestines of humans and cause diarrheal cholera. Vibrio cholerae’s adaptation to environmental stress is maintained by regulating virulence component synthesis, biofilm formation, and the VI secretion system. Ethanolamine and CqsR receptor’s binding to the particular d-cache domain of ethanolamine has been discovered, affecting QS gene production and Vibrio cholerae colonization of the host through binding to CqsR, which in turn impacts host colonization by Vibrio cholerae [58]. However, the other three QS effects will offset its inhibitory effect, enabling Vibrio cholerae to colonize the host intestine. Malka et al. [59] found that tryptophol acetate produced by yeast could inhibit the formation of vibrio cholerae biofilm. Furthermore, 200 μmol/L acetate can decrease the ability of QS-related genes like hapR (biological membrane transcription factor), hapa (diarrhea regulatory protein), and ctxA (hopotoxin subunit A). Virulence genes such as vpsTs, APHa, tepHP, and toxF were up-regulated. Bhattacharya et al. [60] tested the effects of ursoic acid (UA), glycyrrhetinic acid (GRA) and betulinic acid (BA) on Vibrio cholerae. It was found that 200 μg/mL GRA, UA, and BA reduced the integrity of biofilms by 33.82%, 21.92%, and 13.98%, respectively, and regulated the activities of EPS related enzymes. GRA and UA can enhance the effect of cephalosporin β-lactam antibiotics, and BA can enhance the effect of fluoroquinolone (ciprofloxacin) antibiotics. The compounds were docked with QS-related egg whites such as VpsT, LuxP, LuxQ, and HapR. The results showed that GRA, UA, and BA mainly bind to the QS receptor protein hydrophobic channel, resulting in the regulation, leading to triterpenoids regulation on biofilm development and virulence gene expression of V. cholerae.

3.3. Inhibiting Clostridium Difficile Based on QS System

Clostridium difficile is a gram-positive spore-producing, obligate anaerobe that causes antibiotic-associated diarrhea and pseudomembranous colitis. Ahmed et al. [20] found in Clostridium difficile that the agr1 system consists of agrB1 and agrD1. When the agrB1 gene is deleted, agrD1 accumulates in the cell, and the transcription level of the tcdABR (Clostridium difficile toxin synthesis protein) gene increases. However, deletion of agrD1 single gene or agrB1/ agrD1 combination genes had little effect on the expression levels of tcdA, tcdB and tcdR. When both AgrB1 and AgrD1 were destroyed, the sporogenesis and motility of C. difficile were reduced. Yang et al. [61] used Bifidobacterium breve (YH68) cell-free supernatant (YH68-CFCs) to inhibit Clostridium difficile, ATCC 9689 (CD), when CD was exposed to a low dose (50 mL, CDL) and a high dose (90 mL, There was a dose-dependent relationship between bacterial growth inhibition and cell membrane integrity in CDH yH68-CFCs. In CDH cells, QS gene expression was inhibited, and genes for virulence synthesis and sporogenesis were improved. In CDL cells, the appearance of genes involved in flagellar assembly and biofilm creation was inhibited, and drug-resistance-related genes were up-regulated. A recent study found that cell extract of Lactobacillus fermentum Lim2 did not affect the growth of Clostridium difficile but affected the intracellular AI-2 molecular level [62]. Lim2 cell extracts induced 19%, 24%, 39%, and 19% decrease in luxS (QS signaling molecule synthase) and virulence genes (tcdA, tcdB, tcdE) expression levels, and a 15% increase in tcdC gene expression levels. The results showed that Lim2 extracts could reduce C. difficile infection by inhibiting QS-related and virulence genes.
3.4. Inhibit pathogenic Escherichia Coli Based on QS System

Escherichia coli bacteria are abundant in the human intestine. Most Escherichia coli strains do not cause any problems. However, a few specific serotypes, like enteropathogenic Escherichia coli, ETPEC, EIEC, and enterohemorrhagic Escherichia coli (EAEC), can control the bacteria’s ability to form biofilms and produce virulence factors through the QS system in Escherichia coli. This system is called QS. In turn, the pathogen is encouraged to overcome the host immune system, anti-microbial stress, and transmission of virulence factors, leading to infectious diarrhea and acute enteritis. Shiva Prasad et al. [63] found that Vitamin C (VitC) inhibited E. coli in a dose-dependent manner. VitC dam-ages 7quorum-sensing (QS), exopolysaccharide (EPS) production and reactive oxygen species (reactive oxygen species, Production of ROS and destruction of cell membranes leads to leakage of biological molecules (reducing sugars and proteins) inside bacterial cells. In addition, the expression levels of luxS, fmA, csgA, malA, and bssSR decreased by 27, 24, 15, 2, and 6 times, respectively. It causes the biofilm formation ability to decline and destroys the cell dynamic balance and survival ability, weakening the E.coli invasion and infection ability. Yuan et al. [64] studied the co-culture of Pseudomonas aeruginosa and Escherichia coli, and Pseudomonas aeruginosa inhibited the growth of Escherichia coli through the synthesis of 4-hydroxy-2, 6-heptylquinoline oxide (HONO) and anthocyanins. The extracellular products of Escherichia coli can enhance the function of the QS system PQS in Pseudomonas to inhibit the growth of Escherichia coli further.

4. Conclusions

When it comes to human health, a healthy gut microbiome has a direct impact on the occurrence and progression of intestinal disease. By suppressing harmful bacteria’s metabolisms or dissolving biofilms, antibiotics have traditionally been used to treat disease. This has led to increased drug resistance and the migration of drug resistance to the genetic level. Therefore, developing new antibacterial directions or new antibacterial drugs is very important. More and more studies have found that the bacterial QS system has played a major role in regulating bacterial virulence and drug resistance in recent years. Quorquerorum sensing enables bacteria to communicate with the same individuals and environment, with different species, and between bacteria and host. Therefore, the development of new methods to block the QS system can not only inhibit the expression of independent genes of bacteria from weakening the invasion ability of bacteria but also effectively inhibit the drug resistance caused by the formation of biofilms, inhibit the production of QS regulatory virulence factors, and reduce the infection of pathogenic bacteria in the host body. This paper firstly summarizes the current common path of the QS regulation of pathogenic intestinal bacteria, and then on the specific range of interference based on QS or inhibit the intestinal pathogenic bacteria virulence strategies were summarized, in order to have help to break through the current antibiotics in the treatment of multiple drug-resistant bacteria limit, based on the QS regulation of intestinal pathogenic bacteria inhibitor. Thus, the pathogenicity and drug resistance of intestinal pathogens can be suppressed efficiently and specifically to solve the health and safety problems of the human body.

Authors Contribution

SUK: conception, drafting, liter-ature search and artwork; MUK, drafting, Supervision and critical revision.

Conflict of Interest

Authors declared no conflict of interest.

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