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Regulatory Mechanisms and Physiological Impacts of Quorum Sensing in Gram-Negative Bacteria

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Abstract: The Quorum sensing (QS) system is a widely existing communication mechanism, which regulates bacterial community behaviors and the expression of specific genes. The most common pathogenic bacteria in clinical infections are gram-negative bacteria, and QS plays an important regulatory role in the production of virulence factors and development of antibiotic resistance. This article reviews the QS systems of gram-negative bacteria and provides an overview of how they regulate their physiological functions.

Keywords: quorum sensing, gram-negative bacteria, physiological impacts

Currently, Gram-negative bacteria are the predominant pathogens responsible for hospital-acquired infections, exceeding the incidence of infections caused by Gram-positive pathogens by 20%.[1] The 2023 China Antimicrobial Surveillance Network data indicate that clinical infections continue to be predominantly caused by gram-negative bacteria, accounting for 70.1% of the cases.[2] The most common pathogens in descending order are *Escherichia coli* (18.02%), *Klebsiella pneumoniae* (14.06%), *Acinetobacter baumannii* (8.76%), and *Pseudomonas aeruginosa* (7.46%).[2] These Gram-negative strains are the most common among carbapenem-resistant gram-negative bacilli and represent drug-resistant bacteria of the greatest concern in clinical settings. In 2019, approximately 4.95 million people died from diseases related to bacterial resistance, with approximately 1.27 million of these deaths directly attributed to bacterial resistance.[3] There are multiple reasons for the development of antibiotic resistance in bacteria, such as biofilm formation, genetic material mutations, latent gene activation, and the transfer of genetic material (for example, horizontal gene transfer mediated by phage transduction or plasmid conjugation).

Quorum sensing (QS) is a mechanism for intra- or intercellular communication and the regulation of gene expression, which is achieved through the production, release, receptor binding, and induction of downstream signals by signaling molecules.[4] Many physiological functions of Gram-negative bacteria are regulated by QS. In terms of virulence regulation, upon invading the human body, pathogens utilize QS systems to sense the population density and develop offensive and defensive strategies. Under low-density conditions, bacteria downregulate the expression of virulence factors to evade the host immune attack. When the population density increases to a level that the human immune system cannot cope with, bacteria express a large number of virulence factors in a short period, thereby delivering a devastating blow to the host's immune system.[5] QS also plays a crucial role in bacterial antibiotic resistance and it has been confirmed that the signaling molecule system regulates bacterial efflux pumps.[6] Under the pressure of antibiotics and host defenses, QS systems can regulate the formation of biofilms, persister cells, and even small colony variants in pathogens.[7] Surface-active agents regulated by QS can enhance the hydrophobicity of cells, thereby facilitating their adhesion to solid substrates.[8] QS is one of the most extensively studied targets in antivirulence therapy research. Since this process enables the coordinated regulation of multiple virulence factors without being essential for bacterial growth, targeting QS can control bacterial pathogenesis while limiting selective pressure for survival and the development of

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antibiotic resistance. The link between QS and pathogen virulence and resistance has led to increasing interest in using QS as a new approach to treat bacterial infections. Therefore, regulation of bacterial physiological functions by QS should be considered. Research on the QS systems of bacteria can aid in gaining a comprehensive understanding of bacterial communities.

An Overview of QS Systems in Gram-Negative Bacterial

The AHL-Based QS System

In Gram-negative bacteria, QS is commonly mediated by N-acyl homoserine lactones (AHLs), also known as auto-inducer-1 (AI-1) (Figure 1A). AHLs were first discovered in the bioluminescence system of the marine bacterium *Vibrio*

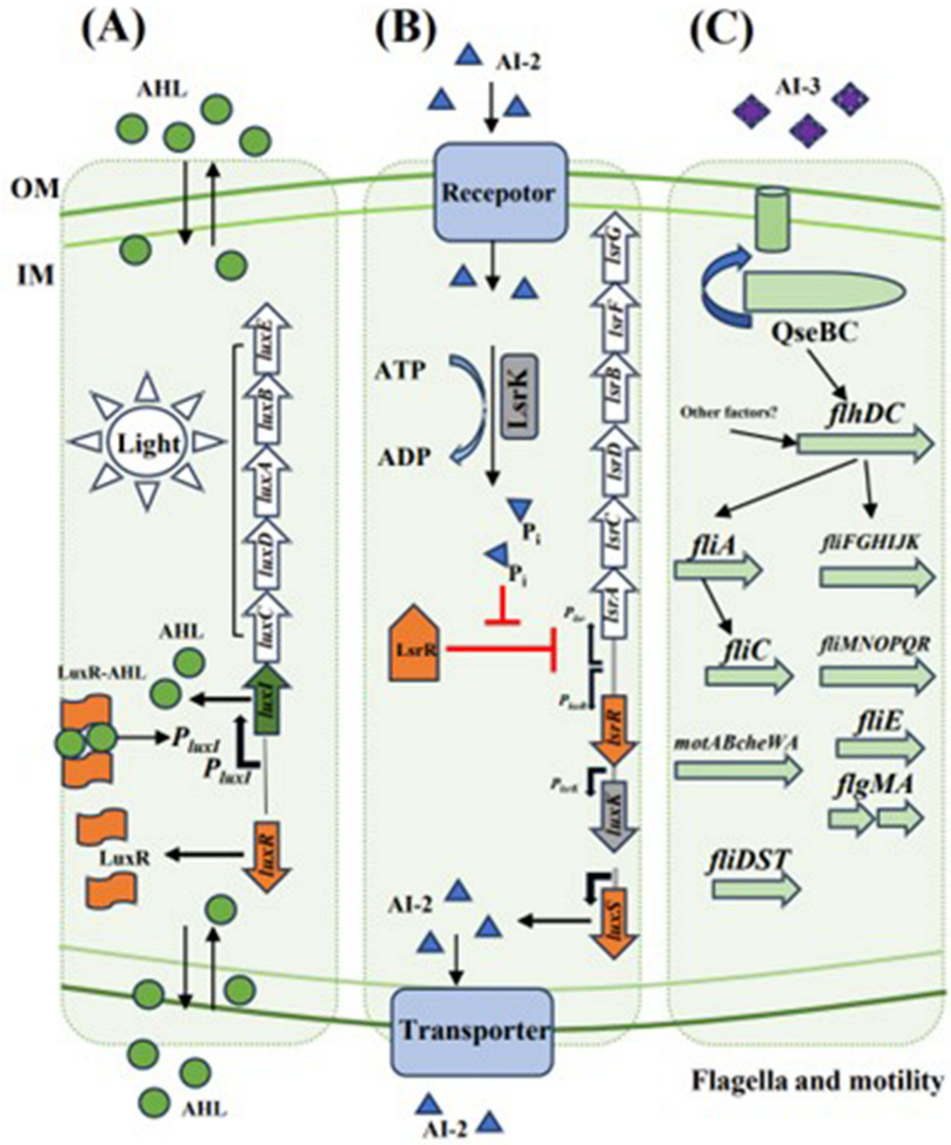

Figure 1 Schematic of three different natural QS systems. (**A**) *V. fischeri's* LuxI/LuxR QS system. AHL is one of the QS signal molecules. LuxI is an AHL synthetase, and LuxR binds to AHL to form the LuxR-AHL complex, which initiates transcription of the *lux* cluster by binding to the plus promoter. The *lux CDABE* in the *Lux* cluster is responsible for bioluminescence. (**B**)AI-2 QS system. AI-2 is one of the QS signaling molecules synthesized by *luxS*. AI-2 is transported into and out of the cell by membrane materials, and *lsrK* can phosphorylate AI-2. In the absence of phosphorylated AI-2, *LsrR* inhibits transcription of P_{lsrR} and P_{lsr} by binding to these promoters. When phosphorylated AI-2 appears and binds to LsrR, transcription is inhibited by the release of LsrR promoter binding. (**C**) The AI - 3 / epinephrine, norepinephrine signaling pathway. AI - 3 and epinephrine/norepinephrine appear to be recognized by the same receptor and interact with sensor kinases located in the periplasm. The adrenergic receptor, QseC, makes uppart of the QseB/C two-component system that regulates the flagellumegulon and thus motility.
Abbreviations: IM, inner membrane; OM, outer membrane.

fischeri, and this phenomenon has been positively correlated with the bacterial population density.[9] The AHL-based QS system comprises three components: (1) AHL signaling molecules, (2) synthase proteins that produce AHL signals, and (3) receptor proteins that perceive and respond to AHLs. AHLs consist of a series of fatty acid side chains of varying lengths that are connected to a homoserine lactone (HSL) ring. Most known AHLs have fatty acid side chains ranging from 4 to 20 carbon atoms in length. Their specificity is primarily determined by the length of the fatty acid side chain, modifications of the carbon atoms (mainly at the C3 position, with some AHLs showing biological activity only after modification), and degree of saturation of the fatty acid side chain.[10,11] The AHL-based QS system exhibits four fundamental characteristics: 1. Autoinducers are typically synthesized from S-adenosylmethionine (SAM) and can traverse the cell membrane, 2. Autoinducers can bind to receptors located in the membrane or cytoplasm, and 3. The AHL-QS pathway activates numerous genes that regulate various cellular processes, 4. Regulation of AHL-QS involves the generation of autoinducers through a positive feedback loop. In gram-negative bacterial species, multiple homologs of AHL-mediated QS system signal-receptor pairs have been identified, including LuxI/R, LasI/R, RhlI/R, AfeI/R, BtaI/R, EsaI/R, and TofI/R.[12] Some organisms, such as *E. coli, K. pneumoniae, Salmonella* spp., and *Shigella* spp., lack AHL synthase enzymes, and thus do not produce AHLs. However, they possess a LuxR homolog known as SdiA, which can bind to AHLs produced by other microorganisms and influence gene expression.[13,14]

In Gram-negative bacteria that utilize AHL as QS signals, signal transduction pathways are diverse. Among these, *P. aeruginosa*, which is the most extensively researched species, primarily comprises four QS systems: *lasR/lasI, rhlR/rhlI, pqs*, and *iqs*. The first system is the *lasR/lasI* system, which is composed of the transcriptional activator LasR and acyl-homoserine lactone synthase LasI. *LasI* guides the synthesis of N-3-oxo-dodecanoyl-homoserine lactone (3-oxo-C12-HSL) and secretes it into the extracellular environment during active transport. At a certain threshold concentration, it binds to LasR, activating the transcription of virulence factors including alkaline protease, exotoxin A, and elastase, thereby enhancing the expression of virulence genes in *P. aeruginos*a.[15] The second system is the *rhlR/rhlI* system, in which RhlR acts as a transcriptional regulatory factor, and *RhlI* encodes an AHL synthase. This system produces homoserine lactones with a C4-HSL structure that can freely traverse the cell membrane and regulate the expression of numerous genes such as chitinase, cyanide, and pyocyanin.[16] In addition to typical AHLs, *P. aeruginosa* produces 2-heptyl-3-hydroxy-4(1H)-quinolone [Pseudomonas quinolone signal (PQS)] as a QS signal. PQS belongs to the 2-alkyl-4-quinolone (AQs) family[17] and represents the third recently discovered QS system specific to *P. aeruginosa*. The signaling molecules of the quinolone system possess antimicrobial activity and are insoluble in water.[18] The *pqs* system primarily functions through two signalling molecules, PQS and 2-heptyl-4-hydroxyquinoline (HHQ), both of which can bind to the LysR-type transcriptional regulator PqsR to form a PqsR-PQS (or PqsR-HHQ) complex, activating the expression of various virulence genes.[19,20] In addition to its role in QS regulation through binding to PqsR, PQS can independently regulate gene expression in a manner that does not rely on PqsR.[21] The PQS can link two systems: *lasR/lasI* and *rhlR/rhlI*. On the one hand, *lasR/lasI* and *rhlR/rhlI* control PQS production. In contrast, PQS influenced *lasR/lasI* and *rhlR/rhlI*. The *iqs* system utilizes IQS as a QS signal molecule, and its structure has been identified as that of 2-(2-hydroxyphenyl)-thiazole-4-ethanal. The genes involved in *iqs* synthesis belong to the non-ribosomal peptide synthetase gene cluster, *ambBCDE*. Under low-phosphate conditions, mutations in *ambBCDE* lead to reduced production of PQS and C4-HSL signals, as well as decreased expression of virulence factors such as pyocyanin, rhamnolipids, and elastase.[22] In addition to the aforementioned four QS systems, another *P. aeruginosa* QS auxiliary system, namely the GacS/GacA system, plays a significant role in enhancing bacterial motility, releasing rhamnolipids, and promoting biofilm formation, among other functions[23]

AI-2 QS System

Synthesis of AI-2

The AI-2 QS system utilizes furanone borate diester compounds as signaling molecules, and this QS system is present in both Gram-negative and Gram-positive bacteria. The classical biosynthetic pathway of AI-2 is a part of the activated methyl cycle, where AI-2 is generated from methionine. It goes through four enzymatic reactions to produce AI-2. Methionine is converted into S-adenosylmethionine (SAM) by S-adenosylmethionine synthase (MetK). SAM served as a methyl donor to generate S-adenosylhomocysteine (SAH). The synthesis of AI-2 involves the conversion of SAH to

homocysteine, which can be accomplished through a one-step reaction using SAH hydrolase (SahH), or a two-step reaction that requires SAH nucleosidase (Pfs) and LuxS. LuxS catalyzes the cleavage of the sulfur-ether bond in SRH, yielding homocysteine and 4,5-dihydroxy-2,3-pentanedione (DPD). The former generates methionine to enter the methyl cycle, whereas the latter can be rearranged to produce two different conformations, (2S,4S)-2-methyl-2,3,3,4-tetrahydroxytetrahydrofuran (S-THMF) and (2R,4S)-2-methyl-2,3,3,4-tetrahydroxytetrahydrofuran (R-THMF), which can interconvert and serve as ligands for *Vibrio* Harveyi LuxP-type receptors and *Salmonella enterica* LsrB-type receptors.[24]

The Perception of AI-2

The AI-2 mediated QS system exists in over 60 bacterial species, including *V. fischeri, E. coli, K. pneumoniae, Salmonella* Typhi, *Bacillus subtilis, Staphylococcus aureus*, and *Yersinia* Pestis.[25] To date, four types of AI-2 receptors have been discovered: periplasmic binding proteins homologous to LuxP and LsrB,[26] CahR-type receptors containing the dCache_1 domain[27] and YeaJ-type AI-2 receptors containing the GAPES1 domain.[28]

LuxP and LsrB are two homologs of periplasmic binding proteins (PBPs), with only 11% nucleotide similarity. These two receptors bind to different chemical properties of AI-2 precursor molecules derived from DPD.[29] The LuxP receptor is only found in Vibrio species and belongs to the high-affinity substrate-binding protein family. It regulates the activity of the membrane-bound sensor histidine kinases (HKs) protein using AI-2, effectively modulating the transmission of phosphorylation signals and impacting downstream gene expression. When AI-2 is present at low concentrations, LuxQ undergoes phosphorylation and transmits a phosphorylation signal through LuxU to LuxO. Phosphorylated LuxO cooperates with the alternative sigma factor σ^{54} to activate sRNA transcription. sRNA forms a complex with the partner protein Hfq, leading to the disruption of LuxR, a transcriptional regulator protein that controls the transcription of the *lux* operon. This inhibition suppressed transcription of the *lux* operon. However, when AI-2 is present at high concentrations, it binds to the LuxP receptor protein and activates its phosphatase activity. This leads to the dephosphorylation of the phosphotransferase LuxU and the transcriptional regulator LuxO. Dephosphorylated LuxO relieves its inhibitory effect on the transcription activator LuxR, initiating the transcription of the bioluminescence operon and resulting in bioluminescence phenomenon.[25]

Unlike the LuxP receptor, which is found only in *S. enterica*, the LsrB receptor was initially identified in *Vibrio* species. It has also been found in members of other *Enterobacteriaceae, Rhizobiaceae, Bacillaceae*, and *Clostridi*a.[30,31] The LsrB receptor, a high-affinity substrate-binding periplasmic protein and component of the ATP-binding cassette (ABC) transport system, can internalize AI-2.[32,33] When the extracellular accumulation of AI-2 reaches a threshold, AI-2 is recognized, binds to the LsrB receptor, and enters the cytoplasm through a heterodimeric transmembrane channel composed of LsrC and LsrD, a process energized by ATP hydrolysis by LsrA. Once in the cytoplasm, AI-2 is phosphorylated by the kinase LsrK, and is further processed AI-2 by LsrF, which can bind to the inhibitory protein LsrR of the *lsrACDBFGE* operon, releasing it from the *Plsr* promoter and enhancing the expression of the *lsr* operon, facilitating the rapid transport of extracellular AI-2[34](Figure 1B).

Studies have shown that many bacteria lacking LuxP or LsrB receptors respond to AI-2, indicating the presence of unidentified AI-2 receptors. In recent years, two new types of AI-2 receptors, the CahR-type[27,35] and YeaJ-type,[28] have been discovered.

The CahR-type receptor is a newly discovered sensor of extracellular signal transduction proteins, in which AI-2 recognizes the dCache_1 domain of the CahR-type receptor, thus activating downstream gene expression. Studies have shown that CahR-type AI-2 receptors are widely present in prokaryotes and regulate chemotaxis and biofilm formation in *P. aeruginosa* PAO1.[27]

The YeaJ-type AI-2 receptor is characterized by the presence of a GAPES1 domain and GGDEF domain responsible for the synthesis of cyclic di-GMP (c-di-GMP). The interaction of YeaJ and YedQ with AI-2 and host-derived bile components taurocholate and taurodeoxycholate leads to an increase in intracellular concentrations of c-di-GMP. This elevation in c-di-GMP levels subsequently enhances the abundance of the T3SS chaperone SicA. The binding of SicA to InvF, SipB, and SipC was diminished, leading to a decrease in the transcription levels of T3SS-1 genes, including *sopB, sopE2, sicA, sipB*, and *sipC*. Specifically, in *S.* Typhi, binding of AI-2 to the GAPES1 domain of the YeaJ-type receptor

induces c-di-GMP synthesis, thereby inhibiting the expression of T3SS-1 genes. Studies indicate that homologs of YeaJ are present in many species of the *Enterobacteriaceae* family.[28]

AI-3 QS System

In recent years, research has shown that in *E. coli* mutants lacking the LuxS protein, which is incapable of synthesizing the AI-2 signaling molecule, a novel signaling molecule distinct from AI-2, termed AI-3, is produced to maintain interspecies communication (Figure 1C). However, the structure of AI-3 remains elusive. However, epinephrine (Epi) and norepinephrine (NE) can promote toxin secretion by enterohemorrhagic *E. coli*, indicating that the AI-3 type QS system regulates bacterial virulence through AI-3, epinephrine, and norepinephrine.[36] In 2020, AI-3 was identified as 3.6-dimethylpyrazin-2-ol (3,6-DPO), a small molecule derived from threonine metabolism. This discovery underscores the complexity of the QS system in bacteria and highlights the sophisticated mechanisms by which bacteria interact with their hosts and regulate virulence factors.[37]

Other Signaling Molecules in Gram-Negative Bacteria

Diffusible Signal Factors

The diffusible signal factor (DSF) family is an intriguing group of QS signals found in various Gram-negative bacteria. The first identified DSF was cis-11-methyl-dodecenoic acid (XcDSF), discovered in the plant pathogen *Xanthomonas campestris* pv. *campestris* (*Xcc*). Subsequently, other DSFs were discovered. DSF-mediated interspecies communication pathways typically fall into three distinct groups, represented by *Xcc, B. cenocepacia*, and *P. aeruginos*a.[38] In addition, DSF can mediate interspecies communication. DSF plays a crucial role in regulating biofilm formation, virulence, motility, toxin production, exopolysaccharide synthesis, and extracellular enzyme activity.

α-Hydroxyketones

In recent years, a novel class of signaling molecules known as AHKs has been identified in human pathogens such as *Legionella pneumophila* and *Vibrio cholerae. V. cholerae* synthesizes cholera autoinducer (CAI)-1 (3-hydroxytridecan-4-one) through the *cqs* gene, while *L. pneumophila* produces autoinducer (LAI)-1 (3-hydroxypentadecan-4-one) via the *lqs* gene cluster. Both CAI-1 and LAI-1 are diffusible and volatile autoinducers that play crucial roles in regulating biofilm formation, motility, and pathogenicity.[39]

Indole

Various bacteria and some plants produce significant amounts of indole, leading to its widespread presence in both prokaryotic and eukaryotic communities. Recently, indole has been demonstrated to function as an intercellular, interspecies, and interkingdom signaling molecule. Indole is stable in indole-producing bacteria, but many non-indole-producing bacteria and eukaryotes can modify or degrade indole through various oxygenases. Recently, indole has been shown to regulate antibiotic resistance and persistence formation in *E. coli*.[40] Indole stimulates biofilm formation in *P. aeruginosa* and alters gene expression in a manner opposite to that of AHL, downregulating virulence and QS-regulated phenotypes in *P. aeruginosa*. Numerous studies have reported that indole controls various bacterial phenotypes and exhibits anti-virulence properties against non-indole-producing pathogens. Possible anti-virulence mechanisms include the inhibition of bacterial QS, biofilm formation, toxin production, and various bacterial adhesion factors.[41]

An Overview of Physiological Functions Mediated by QS Systems

The fact that QS can be perceived by a wide range of receptors from different species demonstrates its extensive involvement in the regulation of various physiological functions of bacteria, such as bioluminescence, motility, aggregation, biofilm formation, expression of virulence factors, bacterial escape, competition, antibiotic resistance, plasmid conjugation, spore formation, and colonization.(Figure 2 and Table 1)

Regulation of Bacterial Motility, Chemotaxis, and Autoaggregation by QS Systems

In nature, bacteria exist in two primary life forms: a planktonic state and an attached state that forms biofilms on surfaces. Biofilm formation aids bacteria in resisting adverse external factors, and supports their growth and proliferation. *E. coli*

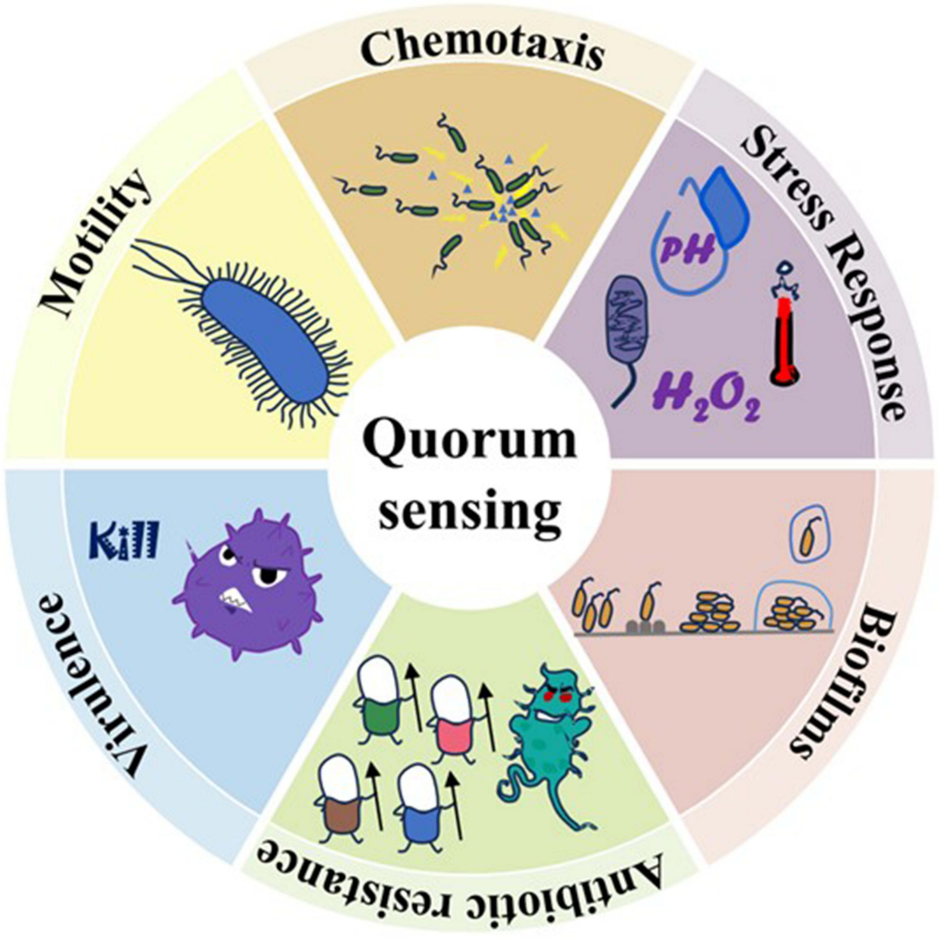

Figure 2 Physiological Functions Mediated by QS System.

utilizes AI-2 as its sole QS signal, which mediates aggregation of *E. coli* through the induction of chemotactic responses. This process can be divided into three stages. Stage One does not rely on the chemotactic ability of the cells. *E. coli* expressing Ag43 initially form "seeding" aggregates through random collisions. Ag43 belongs to the autotransporter protein family, in which adjacent cells Ag43 can interact to form dimers. Since the physiological density of the cells is not high at this time, relying solely on random collisions for further growth is inefficient. Stage Two: The "seeding" aggregates formed in the initial stage secrete sufficient concentrations of AI-2, thereby gradient-mediated chemotaxis of individual cells towards the aggregate. The increase in the growth rate of the aggregates may be due to the increase in local cell density mediated by chemotaxis, which slows as the aggregates and motile cells reach equilibrium. Stage Three: As the concentration of AI-2 further increased, the high levels of AI-2 in the external environment gradually disrupted the chemotaxis of *E. coli* towards the aggregates, resulting in more separated cells within the aggregates than those connecting them, leading to the dissolution of the aggregates. Curli fibers are a major protein component of the *E. coli* biofilm matrix. Research indicates that AI-2 induced chemotaxis promotes early stage autoaggregation of *E. coli* mediated by curli fibers during low-temperature growth. This aggregation enhances the AI-2-mediated signal transduction, biofilm formation, and resistance to adverse conditions.[105]

Regulation of Bacterial Environmental Stress Response by QS Systems

The ability of bacteria to resist stress is a crucial determinant of their survival in natural environments and represents a significant marker of their adaptability. Extensive research has shown that the QS system plays a vital role in regulating bacterial stress resistance. Studies have found that after the deletion of the*luxS* gene in *Porphyromonas gingivalis*, its survival rate significantly increased under conditions of 50°C, pH 9.0, and exposure to 0.35 mm hydrogen peroxide.[106]

Table 1 Informative Table of Different Gram-Negative Bacterial QS Systems and Function

Bacterium	QS systems	Virulence-related phenotypes	Resistance phenotypes	Reference
Pseudomonas aeruginosa	(1) LasI (S)-LasR (R)-HSL (s)	Expression of several virulence factors including: LasA protease, LasB elastase, Apr alkaline protease	Regulating biofilm formation influences resistance to most antibiotics	[42–44]
	(2) RhlI(S)-RhlR(R)-HSL(s)	Expression of several virulence factors including: LasB elastase, RhlAB rhamnolipids, Phz pyocyanin, Hen hydrogen cyanid	Regulating biofilm formation influences resistance to most antibiotics	[45,46]
	(3)PqsABCD(S)-PqsR (R)-Alkyl quinolones (PQS)	Expression of several virulence factors including: Phz pyocyanin, Hian hydrogen cyanidel, LecA lectin PQS may exert cytotoxicity on cells by targeting the inhibition of the cellular respiratory chain	Regulating biofilm formation influences resistance to most antibiotics	[47]
	(4)AmbBCDE(S)-IqsR (R)- integrated quorum sensing system(IQS)	Expression of several virulence factors including: pyocyanin, rhamnolipids and elastase	Regulating biofilm formation influences resistance to most antibiotics	[15]
Enterohemorrhagic *Escherichia coli*	(1) Unknown (S)-SdiA (R)-3OC8HSL (s)	Growth and division, Colonization, Adhesion and subversion of epithelial intestinal cells	Regulating biofilm formation influences resistance to most antibiotics Regulating the arcAB pathway of the efflux pump through SdiA affects Resistance to nalidixic acid, Chloramphenicol, Quinolones (ciprofloxacin, Norfloxacin)	[48–50]
	(2) LuxS (S)-LsrB (R)-AI-2 (s)	Motility, Adhesion and subversion of epithelial intestinal cells, Exotoxin, Persistent infection, Stress survival	Regulating biofilm formation influences resistance to most antibiotics	[51–54]
	(3) Unknown (S)-QseC (R)-AI-3 (s)	Motility, Adhesion and subversion of epithelial intestinal cells		[55,56]
	(4) Indole	Adhesion and subversion of epithelial intestinal cells, Persistent infection	Regulating biofilm formation influences resistance to most antibiotics	[57–59]
Klebsiella pneumoniae	(1) Unknown (S)-SdiA (R)- HSL (s)	Controlling fimbriae expression, biofilm formation		[60]
	(2) LuxS (S)-LsrB (R)-AI-2 (s)	Regulating the synthesis of LPS and PNAG and the structure of biofilms		[61]
	(3) QseB(S)-QseC (R)-AI-3 (s)	Biofilm formation, serum resistance		[62]
Salmonella.Typhi	(1) Unknown (S)-SdiA (R)-3OC8HSL (s)	Competitive advantage, Motility, Adhesion, Invasion, Resistance to complement, Persistent infection	Regulating biofilm formation influences resistance to most antibiotics Influencing resistance to Nisin through PhoPQ and PmrAB	[63–66]
	(2) LuxS (S)-LsrB (R)-AI-2 (s)	Stress survival (oxidative stress), Motility, Adhesion, Invasion		[67–69]
	(3) Unknown (S)-QseC (R)-AI-3 (s)	Motility, Invasion, Intracellular survival, Persistent infection	Regulating biofilm formation influences resistance to most antibiotics	[70,71]
	(4) Indole	Motility, Invasion	Influencing resistance to multi-antibiotics through the Phage-shock response and oxidative stress pathway mediated by OxyR	[72,73]
	(5) DSF	Invasion		[74,75]
Burkhordelia cepacea	(1) Cep1 (S)-CepR (R)-C8HSL, C6HSL (s)	Expression of swarm motility genes and several virulence factors including: proteases, siderophores, toxins, antifungal agents and biofilm formation		[76]
	(2) CciI (S)-CciR (R)-C8HSL, C6HSL (s)	Expression of swarm motility genes and several virulence factors including: proteases, siderophores, toxins, antifungal agents and biofilm formation		[77]
Vibrio Harveyi	(1) LuxM (S)-LuxN (R)- 3OHC4HSL (s)	Expression of bioluminescence genes		[78]
	(2) LuxS (S)-LuxP (R)-AI-2 (s)	Expression of several virulence factors including: extracellular protease; swimming and swarming abilities		[79]
	(3) CqsA (S)-CqsS (R)-CAI-1 (s)	Expression of bioluminescence genes, metalloprotease production, and type III secretion		[80]

(*Continued*)

Table 1 (Continued).

Bacterium	QS systems	Virulence-related phenotypes	Resistance phenotypes	Reference
Vibrio Cholerae	(1) LuxS (S)-LuxP (R)-AI-2 (s)	Expression of several virulence factors including: Biofilm formation and EPS production, host colonization	Aminoglycosides	[81,82]
	(2) CqsA(S)-CqsS (R)-CAI-1 (s)	Expression of several virulence factors including: Biofilm formation and EPS production, host colonization		[83]
Acinetobacter spp	(1) AbaI (S)-AbaR (R)-3OHC12HSL (s)	Expression of virulence factors including biofilm formation		[84]
Haemophilus influenzae	(1) LuxS (S)-RbsB (R)-AI-2 (s)	Invasion, lipooligosaccharide composition, Persistent infection		[85–87]
Campylobacter jejuni	(1) AHL QS	Transmission ability		[88]
	(2) LuxS (S)-unknown (R)-AI-2 (s)	Motility, Adhesion and invasion, Stress survival, Transmission ability, Exotoxin	Influencing resistance to most antibiotics through Biofilm formation and VBNC formation	[89–92]
Yersinia Pestis	(1) YspI(S)- YspR(R)-3OC6HSL, 3OC8HSL (2) YpeI(S)-YpeIR(R)-unknown	Survival ability in fleas, Stress survival (Starvation stress), Growth and division Invasion		[93–95]
	(2) LuxS (S)-unknown-AI-2 (s)	Survival ability during host infection, Survival ability in fleas, Adhesion, Invasion, Membrane modeling		[96,97]
Yersinia Enterocolitica	(1) YenI(S)- YenR(R)-HSL(s)	Swarming motility and cell aggregation, Host cell attachment, Virulence Plasmid Maintenance (pYVe)		[98,99]
Yersinia Pseudotuberculosis	(1) YpsI(S)-YpsR(R)-HSL(s) (2) YtbI(S)-YtbR(R)-HSL(s)	Swarming motility and cell aggregation, Survival ability, Damage host cells		[100,101]
Brucella melitensis	(1) Unknown (S)-vjbR (R)- C12-HSL (2) Unknown (S)-BlxR(R)-	Motility, Survival ability in Brucella containing vacuoles (BCV), Adhesion, Intracellular replication, Immune evasion	Influencing rifampin resistance through the virB operon (virB7–11)	[102–104]

Regulation of Bacterial Biofilms by QS Systems

The formation of biofilms is a result of cell density-dependent gene expression and provides an appropriate microenvironment for intercellular communication. The main events involved in biofilm formation include the initial attachment of planktonic cells to a surface, followed by cell differentiation, EPS secretion, maturation, and dispersal.[107] QS plays a significant regulatory role in coordinating biofilm formation across multiple species, although it may not be the primary regulatory factor, with varying effects from initial attachment to maturation. QS-induced alterations in cell surface characteristics contribute to biofilm phenotypic variation, cell aggregation, and the synthesis of extracellular polysaccharides or adhesins. As a component of biofilms, EPS offers microorganisms a stable environment to withstand environmental stresses such as high temperatures, elevated alcohol levels, and acidity. Additionally, the polysaccharides and proteins in EPS serve as nutritional sources for microbial growth and metabolism. Firstly, QS affects the physicochemical properties of cells and enhances biofilm formation in the biofilm lifestyle. QS-regulated surfactants can increase cell hydrophobicity, promoting their adhesion to solid substrates.[8] Further findings indicate a direct correlation between QS and EPS production. In wastewater treatment, the exogenous addition of 5 nmol/L C6-HSL significantly boosted EPS secretion.[108] Other AHL molecules, such as 3-O-C6-HSL, C8-HSL, and C12-HSL, are also significantly related to EPS formation.[109] Therefore, microbial communities can be regulated by QS through EPS and biofilm formation.

The majority of bacterial infections in the human body are associated with biofilms, and the formation of biofilms is a critical factor contributing to the difficulty in treating and preventing the recurrence of clinical bacterial infections; AI-2 plays a crucial regulatory role during biofilm formation.[6] When the *luxS* gene in *Haemophilus influenzae*, responsible for the QS system, is lacking, its ability to form biofilms is significantly enhanced.[85,110] In *K. pneumoniae, luxS* mutants can form mature biofilms but with a reduced capacity for microcolony development, primarily during the early stages of

biofilm formation.[61] The regulation of biofilms by QS varies considerably among bacterial strains and potentially exhibits strain-specific characteristics.

The Regulation of Bacterial Antibiotic Resistance by QS Systems

QS Systems Collaborate with Biofilm to Mediate Antibiotic Resistance

The collective QS in conjunction with biofilms mediates the dissemination of antibiotic resistance. Studies have demonstrated that obstructing the QS system within biofilms further elucidates the interplay between QS resistance and QS.[111] Protective polymers on the surfaces of biofilms attenuate bacterial growth and respiration rates within biofilms, rendering natural and artificial antibiotics insufficient to completely eradicate infectious biofilm communities.[112] When mature bacterial biofilms are formed, the bacteria within the biofilm exhibit significantly increased resistance, with cells showing antibiotic resistance levels 10–1000 times higher than those of planktonic bacteria of the same species at similar growth stages.[113] Pathogenic bacteria within biofilms use QS mechanisms to activate virulence factors and to develop antibiotic resistance. Additionally, antibiotic-degrading enzymes produced within the bacterial biofilms and certain gene products contribute to bacterial resistance. Antibiotic-degrading enzymes acquire antibiotic resistance via QS as a stress response. Studies have shown that the β-lactamases produced by bacteria are critical factors in conferring resistance to β-lactam antibiotics in biofilms. The reduced permeability of antibiotics through biofilms is attributed to the potential binding of antibiotics to the structural components within the biofilm matrix, rather than a decrease in antibiotic diffusion within the biofilm matrix.[114]

QS Systems Regulate the Active Efflux of Antibiotics

In addition to preventing drugs from entering the cell, bacteria can also actively pump drugs. Efflux pumps are transmembrane proteins that transport various toxic compounds, including antibiotics, in an energy-dependent manner across the bacterial membranes. Although all bacteria contain multiple efflux pumps, they are particularly important as mechanisms of antimicrobial resistance (AMR) in gram-negative bacteria. Efflux transport proteins are classified into six families, including members of the resistance-nodulation-division (RND) family, which exhibit the most clinically relevant levels of resistance in gram-negative bacteria. In Gram-negative bacteria, the signaling molecule AHL actively translocates through the cell membrane via the MexAB-OprM efflux pump. Some researchers have found that auto-inducer molecules can upregulate the expression of the multidrug resistance pump MexAB-OprM, leading to multidrug resistance in *P. aeruginos*a.[115] Overexpression of the QS regulator SdiA leads to increased expression of the AcrAB efflux pump, which also plays a role in the multidrug resistance efflux pump system in *E. col*i.[116] However, the expression levels of efflux pumps can also affect the signaling molecules. Some researchers have found that over-expression of the MexCD-OprJ multidrug resistance efflux pump can reduce the signaling molecule response in *P. aeruginos*a.[117] Furthermore, a previous study demonstrated that chemical induction of the MexEF-oprN efflux pump can inhibit QS in *P. aeruginos*a.[118] The notable contribution of RND efflux pumps to multidrug resistance, especially in clinically relevant gram-negative pathogens, offers a distinct opportunity to restore drug sensitivity by targeting the structure, function, and regulation of these transport proteins.

QS Systems Regulate the Formation of Persistent Bacteria

Persistent bacteria represent a specific subset of bacterial cells that display transient antibiotic tolerance, are often characterized by reduced growth or growth arrest, and can resume growth after exposure to lethal stress. The presence of these persistent cells significantly contributes to the persistent and recurrent nature of stubborn bacterial infections and is closely linked to an increased risk of developing antibiotic resistance during the course of treatment. In *E. coli*, the *hipB* gene, which is associated with the toxin-antitoxin system, is involved in the formation of persisters related to exposure to nanoaluminum, triggering antibiotic persistence in *E. coli* through the quorum-sensing regulators LrsF and QseB.[119] Research has also found that substances secreted by *E. coli*, which can serve as QS signal molecules, such as indole, can lead to an increase in the persistence of *S.*Typhi.[120]

The Regulation of Antibiotic Resistance Genes (ARGs) Expression by QS Systems

A study found that in *P. aeruginosa*, cis-2-unsaturated fatty acid signaling molecules are involved in inter-species communication, which can lead to biofilm formation and alterations in susceptibility to various antibiotics.[121] The LasI/R circuit in *P. aeruginosa* regulates the expression of ampC β-lactamase. After three days of exposure to imipenem, the expression of *ampC* in the *ΔlasI* strain was reduced by one-fourth compared to that in the wild-type strain.[122] Study also discovered that under antibiotic induction, the activity of AHLs signaling molecules can promote the expression of resistance genes, potentially leading to the gradual development of multidrug resistance in *A. baumannii*, causing bacteria to evolve into multidrug-resistant strains[123] Further comprehensive investigation is warranted to elucidate the influence of QS on the expression of ARGs.

The Regulation of Horizontal Gene Transfer by QS Systems

In the process of bacterial biofilm formation involving QS, bacteria in biofilms can also transfer and spread antibiotic resistance genes through the conjugative transfer of plasmids.[124] The bonding efficiency of plasmids in the biofilm was 700 times that of suspended cells.[125] When *Licht* et al[126] studied the conjugational transfer of plasmids, they found that the conjugational transfer frequency between suspended cells was much lower than that in the biofilm system (4–50 times), and the conjugational transfer frequency of plasmids in the biofilm system peaked in a short time. In addition, the frequency of plasmid conjugative transfer was high when bacteria containing anti-plasmids were introduced into bacteria that formed biofilms. A study also demonstrated that bacterial QS facilitates conjugative transfer of the multidrug-resistant plasmid RP4 within bacterial biofilms, significantly affecting the dissemination and spread of antibiotic resistance genes [127].

Furthermore, in a study by *Wang Ting* et al [128], it was found that AI-2 acts as a self-inducer and enhances conjugation frequency by regulating the expression levels of conjugative transfer-related genes, thereby promoting conjugative transfer of tetracycline resistance genes in *Vibrio* Parahaemolyticus. Exogenous AI-2 can upregulate the expression of TEM-type enzymes in a *LsrR*-dependent manner, increasing antibiotic resistance in *E. coli* strains [129].2.5 The Regulation of Bacterial Virulence by QS Systems.

QS Systems Regulate Virulence Through the Secretion Systems

The bacterial secretion system is a macromolecular complex that exists in the bacterial cell membrane. It is a complex transmembrane molecular machine that can provide a secretion pathway for a variety of bacterial effectors. Nine bacterial secretory systems, T1SS~T9SS, have been found to play important roles in bacterial survival and pathogenicity. Transcriptomic analysis of *P. aeruginosa* reveals that the Type 1 secretion System (T1SS) is positively regulated by the QS system, as the expression of its effector alkaline protease AprA depends on QS. The Type 2 secretion System (T2SS) is responsible for secreting folded proteins from the periplasm of Gram-negative bacteria [130]. The Xcp system in *P. aeruginosa* secretes QS-regulated virulence factors including elastase and exotoxins. Interestingly, the Xcp system itself is positively regulated by QS [131]. The QS system is directly associated with Type IV Secretion System (T4SS) in *Brucella*. In *Brucella*, the LuxR-type QS system is responsible for the virulence characteristics regulated by the *virB* operon, which encodes the T4SS controlled by *VjbR* [132].

QS Systems Regulate Virulence Phenotypes

A study revealed that deletion of the *luxS* gene in *Actinobacillus pleuropneumoniae* significantly reduced the transcription level of the virulence gene *apxIIA*. Mouse experiments confirmed a 96-fold decrease in LD50 for the *luxS* deletion strain, and bacterial loads in the peritoneal lavage fluid, spleen, and lung tissues of mice were also significantly reduced. These findings indicate that QS positively regulates the virulence of *A. pleuropneumoniae* [133]. However, the opposite experimental results were found in *H. influenzae*, where the *luxS* deletion strain exhibited enhanced invasiveness in NCI-H292 cells. Infection experiments in chinchillas demonstrated that the luxS deletion strain of *H. influenzae* displayed increased pathogenicity in chinchillas, with significantly higher levels isolated from the middle ear than the wild-type strain. Additionally, histopathological results showed stronger inflammation and increased goblet cell hyperplasia in mice infected with the *luxS* deletion strain of *H. influenzae* 10 d post-infection [86]. This indicated that the QS system regulates virulence differently in different bacterial strains.

Discussion and Prospects

In summary, in recent decades, there has been a significant advancement in our understanding of QS. The regulation of physiological functions by QS in Gram-negative bacteria has been studied extensively. This review provides a brief overview of QS systems in gram-negative bacteria and summarizes the regulation of chemotaxis, biofilm formation, resistance, virulence, and other QS aspects. This helps us to understand the role of the QS system in the physiological regulation of gram-negative bacteria.

Currently, research on QS systems of gram-negative bacteria has mainly focused on AHL signaling molecules, and *P. aeruginosa* has become a model strain. In contrast, relatively little research has been conducted on the AI-2 QS system in Gram-negative bacteria, and many aspects of AI-2 regulation remain unclear, posing numerous questions worthy of further investigation: 1) There is limited research on the interaction of AI-2 with the host, and the role of AI-2 signaling molecules in the microbial-host interaction process remains unclear. 2) Existing studies on the interaction of AI-2 with the host are mainly confined to in vitro cell culture experiments, and there is an urgent need for animal experiments to understand whether AI-2 can exert harmful biological effects by coordinating microbial behavior and regulating microbial networks or individual bacteria. 3) As an inter-species signaling molecule, there is currently limited research on the role of AI-2 in bacterial–bacterial interactions. 4) With the development of advanced technologies, AI-2-related research should focus on the combined use of metagenomics, transcriptomics, proteomics, metabolomics, and other multiomics technologies to elucidate the regulatory role of AI-2. Addressing these issues can help researchers gain a better understanding of the microbial world and provide a theoretical basis for the prevention and control of related pathogenic bacteria as well as the development of antimicrobial drugs.

This article focuses on the regulatory role of QS in Gram-negative bacteria, but QS, as a ubiquitous form of communication in microbial communities, also exerts significant effects on Gram-positive bacteria and fungi. Gram-positive bacteria, for instance, regulate the production of toxins and extracellular enzymes through QS. *S. aureus*, for example, utilizes a QS system known as the Agr system to regulate the expression of toxins (such as α-hemolysin) and other virulence factors. This enables the bacteria to coordinate the expression of virulence in response to population density during host infection, thereby enhancing their infectivity. In fungi, such as *Candida albicans*, virulence often depends on QS signals. When the population density increases, QS activates virulence-related genes, promoting the transition of the fungus from a yeast form to a filamentous form, thus enhancing its invasiveness. Furthermore, QS also plays a regulatory role in biofilm formation and antimicrobial resistance in both Gram-positive bacteria and fungi. Through QS, microorganisms can more efficiently regulate gene expression, cooperate in attacking the host, and improve their competitive survival. In the context of antibiotic and antifungal treatments, QS mechanisms may serve as new therapeutic targets. Therefore, a deeper understanding of the mechanisms of QS could help develop new strategies for combating bacterial and fungal infections, especially in the face of growing antimicrobial resistance.

Author Contributions

All authors have made significant contributions to the work reported. Xiaobing Chu completed the conception of the article, data acquisition, initial drafting, and figure drawing, while Qiwen Yang completed the conception of the article, as well as the review and revision work. All authors have no objections to the current version of the manuscript, agree to submit the article to this journal, and take full responsibility for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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