Journal of Genetic Engineering and Biotechnology 16 (2018) 239–252

HOSTED BY

Contents lists available at ScienceDirect

Journal of Genetic Engineering and Biotechnology

journal homepage: www.elsevier.com/locate/jgeb

Quorum sensing intervened bacterial signaling: Pursuit of its cognizance and repression

Kayeen Vadakkan [a], Abbas Alam Choudhury [a], Ramya Gunasekaran [a], Janarthanam Hemapriya [b], Selvaraj Vijayanand [a,*]

[a] Bioresource Technology Lab, Department of Biotechnology, Thiruvalluvar University, Vellore, TN 632115, India
[b] Department of Microbiology, DKM College for Women, Vellore, TN 632001, India

ARTICLE INFO

Article history:
Received 11 March 2018
Received in revised form 9 June 2018
Accepted 3 July 2018
Available online 7 July 2018

Keywords:
Antibacterial agents
Autoinducers
Quorum quenching
Quorum sensing

ABSTRACT

Bacteria communicate within a system by means of a density dependent mechanism known as quorum sensing which regulate the metabolic and behavioral activities of a bacterial community. This sort of interaction occurs through a dialect of chemical signals called as autoinducers synthesized by bacteria. Bacterial quorum sensing occurs through various complex pathways depending upon specious diversity. Therefore the cognizance of quorum sensing mechanism will enable the regulation and thereby constrain bacterial communication. Inhibition strategies of quorum sensing are collectively called as quorum quenching; through which bacteria are incapacitated of its interaction with each other. Many virulence mechanism such as sporulation, biofilm formation, toxin production can be blocked by quorum quenching. Usually quorum quenching mechanisms can be broadly classified into enzymatic methods and non-enzymatic methods. Substantial understanding of bacterial communication and its inhibition enhances the development of novel antibacterial therapeutic drugs. In this review we have discussed the types and mechanisms of quorum sensing and various methods to inhibit and regulate density dependent bacterial communication.

Contents

Peer review under responsibility of National Research Center, Egypt.

* Corresponding author.
E-mail address: selvarajvijayanand76@gmail.com (S. Vijayanand).

https://doi.org/10.1016/j.jgeb.2018.07.001
1687-157X/

1. Introduction

Communication stands crucial in progress of a fraternity and it's observed that bacteria too communicate with each, which is collectively called as Quorum sensing. This is a density dependent mechanism where communication is mediated by signaling molecules termed as autoinducers; it assists bacterial community to coordinate and work as a single unit in a population [1–3]. Numerous bacterial functions such as secondary metabolite production, sporulation, biofilm formation and symbiosis are regulated by quorum sensing mechanism [4,5]. All bacterial quorum sensing systems fulfills three basic precepts i. Concentration dependent response to autoinducers; where autoinducers are secreted outside the cell and later inflexed depending on autoinducer concentration [6,7], ii. Bacteria consists specialized receptors in its cell membrane or in cytoplasm that sense and respond to concentration of autoinducer, iii. Detection of autoinducers by receptors recommence quorum sensing loop thereby bacterial virulence [8,9]. Quorum sensing was first observed in a gram negative marine bacteria *Vibrio fischeri* [10] as studies showed that phenotype bioluminescence was regulated by quorum sensing machinery [11,12]. Since then many bacteria have been successfully scrutinized for their quorum sensing ability. Understanding of quorum sensing open up possibilities of regulating bacterial virulence as far as the immense role of quorum sensing upon it is concerned [13]. Recently many studies have been carried out to down regulate bacterial quorum sensing and this strategy is collectively called quorum quenching [14,15]. Inhibiting communication of a bacterial population disables them to initiate most of its virulence activity which help host for an effective immunological clearance. In this review we discus about the types and mechanisms of quorum sensing and different approaches of quorum quenching through which bacterial communication can be inhibited.

2. Autoinducers: alphabets of bacterial dialect

Specialized signaling molecule; autoinducers play a key role in quorum sensing and consequently considered as alphabets of bacterial language. Autoinducers are studied under three different classes based on their structure and specific function; they are AHLs (Acyl Homoserine Lactones), AIP (Autoinducing Peptides) and Autoinducer-2 (AI-2) [16]. AHLs are small diffusible molecules with a core lactone ring and acyl side chain which is responsible for facilitating signaling in gram negative bacteria [17]. Quorum sensing in gram positive bacteria are found to be mediated by AIPs which are short peptide chains synthesized in cell. AIP lack free transportation across the cell membrane hence requires specialized membrane transport proteins [18,19]. AI-2 are furonone derived signaling molecules found functioning in both gram negative and gram positive bacteria [20] also exhibit features of both AHLs and AIPs [21]. Signaling molecules are produced inside the bacterial cells which will be processed internally or externally hinge upon the organism. Despite of their functional and structural differences, autoinducers possess certain common characteristics such as high degree of receptor specificity and transport across cell membrane which may be active or passive.

3. AHL mediated bacterial communication

AHL mediated quorum sensing is intensely studied in gram negative bacteria that constitutes maximum pathogenic strains in it. Numerous virulence factors in gram negative bacteria such as bacterial adhesion, biofilm formation, exozyme secretion, pigment production are regulated by N- Acyl homoserine lactone(AHL) dependent quorum sensing [22,23]. Typical quorum sensing system in gram negative bacteria contains two integrant; an autoinducer synthase which is responsible to synthesize AHLs [24,25] and an autoinducer receptor cum transcriptional activator [26]. AHL mediated signaling is highly intra-specious specific due to peculiar receptor binding sites that recognize only precise AHLs [27–29] thus signals produced by one specious will not disturb the communication mechanism of other [30,31]. Modification in AHL structure is accomplished by varying number of Carbon and modification upon R- group [32] which gives advantage to bacteria in an endosymbiont environment. Some important signaling systems mediated by AHLs are discussed here.

3.1. LuxIR: typical gram negative bacterial quorum sensing system

LuxIR quorum sensing circuit stands archetypal of gram negative bacterial communication (Fig. 1) as over hundred gram negative bacterial strains communicate by the engagement of LuxIR homologues genes [33]. SmaIR in *Serratia marcescens* [34,35], CviIR in *Chromobacterium violaceum* [36,37], hanIR in *Halomonas anticariensis* [38]and TraIR of *Agrobacterium tumefaciens* [39] all work based on the principle of LuxIR but with slight variations in AHLs. This is the first studied bacterial linguistics model and was discovered in marine bioluminescent bacteria *Vibrio harveyi* which is capable to lead a free and symbiotic lifestyle [40].

This system is based in the reactions mediated by LuxI and LuxR. LuxI is an autoinducer synthase that catalyze the interaction between S-adenosylmethionine and acyl carrier protein which leads into the formation of N-(3-Oxohexanoyl)-L-homoserine lactone which subsequently functions as autoinducer [25,41,42]. AHL will be dispersed out of cell until a specific threshold level is attained. In high external concentrations, AHL will be taken back into the cell which sequentially interact with LuxR. If not bound with AHL, in free state LuxR will be degraded inside bacterial cell, whereas after forming LuxR-AHL complex it will be capped from degrading [43]. LuxR-AHL complex binds upon Lux promoter region that initiate bioluminescence and other quorum sensing regulated functions [44,45].

3.2. LasIR-RhlIR: overlapping quorum sensing system

LasIR-RhlIR is serially arranged overlapping quorum sensing circuits observed in *Pseudomonas aeruginosa* where LasIR and RhlIR are arranged one after other in a series (Fig. 2) [46,47]. *Pseudomonas aeruginosa* is a widely observed human opportunistic pathogen which is mainly concerned with nosocomial infections upon patients suffering from Cancer, AIDS and cystic fibrosis [48,49]. It produces virulent factors such as elastase, protease, exotoxin A that collectively cause serious tissue damage in mammals

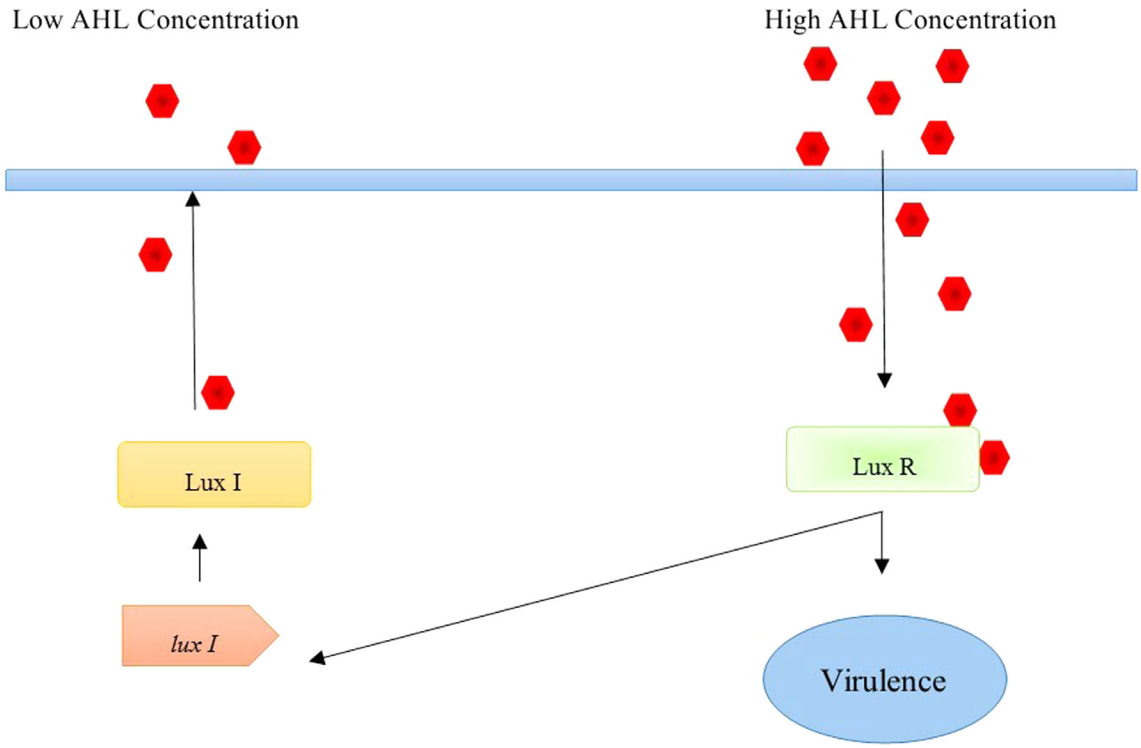

Fig. 1. LuxIR signaling Circuit. Red hexagons indicate the autoinducer produced by LuxI.

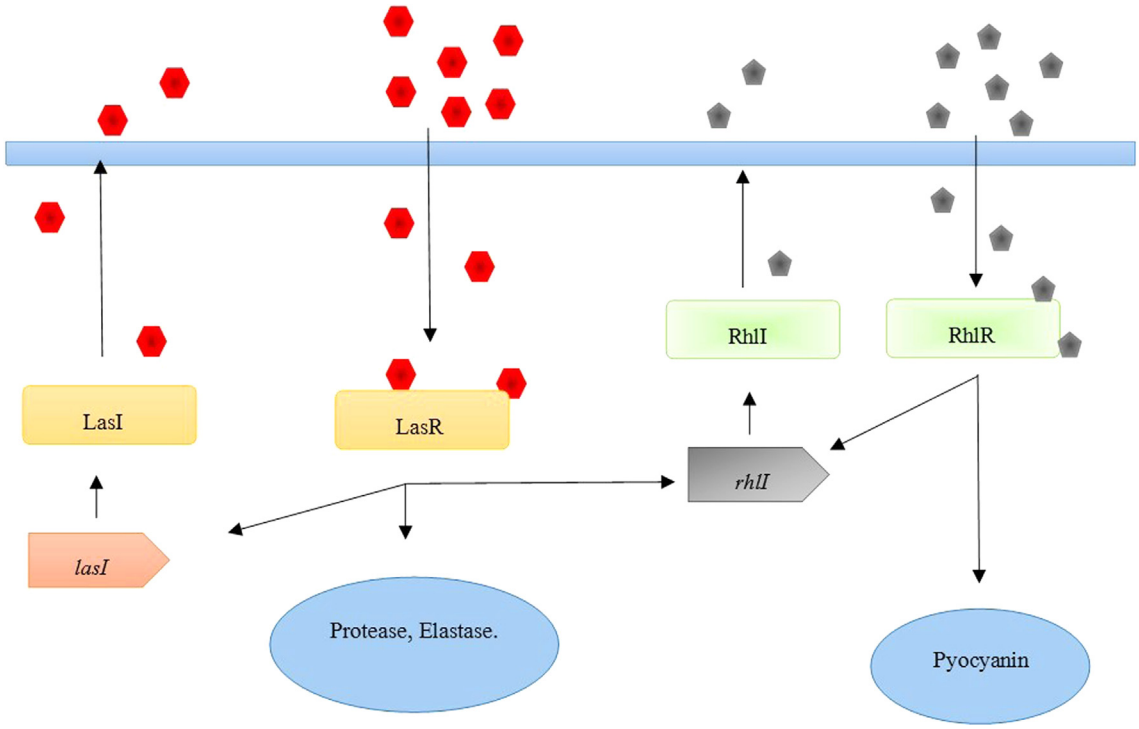

Fig. 2. LasIR signaling system, Red hexagons indicate the signaling molecules involved in LasIR circuit and grey pentagons denotes RhlIR signaling system.

[50]. Such mechanisms are found to be controlled by Quorum sensing circuits [51].

Signaling is initiated by the production of AHL (3OC12-homoserine lactone) by LasI which act as a homologous of LuxI [52]. AHL will be diffused out of the cell and in high concentration it will be in taken and binds with LasR. Numerous activities such as production of elastase, protease and exotoxins are triggered by LasR-AHL complex [53]. Other than triggering this virulence factor production LasR-AHL also initiate the second system RhlIR. [54]. As a result RhlI produce a secondary AHL (C4-homoserine lactone) that binds with RhlR resulting in the production of subsequent products such as sidophores and pyocyanin [55,56]. All Quorum

sensing controlled mechanism in *Pseudomonas aeruginosa* is regulated by any one circuit but immense overlap between this systems are noted [57,58] which enables to carry on virulence by any one system [59].

3.3. ExpIR: virulence down regulating quorum sensing system

ExpIR mediated quorum sensing is observed in opportunistic plant pathogen *Erwinia carotovora* (Fig. 3) that frequently causes soft rot in plants [60]. Study of Exp IR system have lot of economic importance on it as soft rot disease affect lot of economic crop plants such as potato, carrot, pineapple, cucumber, onion. It is also observed that Exp IR also regulate synthesis of antibiotics such as carbapenem ß-lactum which give dominance to the bacteria to survive in a high bacterial diverse rhizosphere [61].

Exp circuit is initiated by the production of OHHL by Exp I. Unlike other QS systems the virulence factors of bacteria *Erwina carotovora* is such as pectate lyase, pectin lyases, cellulases and proteases are positively influenced by the OHHL alone [62] OHHL also triggers the action of Exp R by forming conjugated complex but Exp R have no significant role in bacterial virulence in fact it is found decreasing exozyme production by bacteria [63]. This stand in contrast to many other bacterial virulence mechanism whereas virulence is triggered by regulatory protein not directly by AHL. The difference possessed by Exp IR system found to help bacteria against host defense mechanism [64], Exp R bind with low density of AHL would produce only less exozyme hence low level of effect; this indeed provokes host defense mechanism which challenges the existence of bacteria. Where as in *Erwina carotovora* ExpR neutralizes the low AHL density which inhibits the production of exozyme. Therefore exozymes will be produced only in high level of OHHL

4. Peptide mediated bacterial communication

The signaling in gram positive bacteria are controlled by Oligopeptide which is commonly referred as autoinducer peptides [AIPs] [65]. AIPs are produced inside the bacterial cell as pro-AIP which will be processed and modified inside or outside the cell hinge upon the organism [66]. Unlike AHL signaling molecule AIP's are impermeable to cell membrane hence requires specialized transport proteins for the inward and outward carriage of AIP's [67]. This transport of AIP's are generally accomplished by cell membrane bound sensor kinases [68]. Competence mechanism such as sporulation in *Bacillus subtilis* virulence initiation by *Staphylococcus aureus*, *Listeria monocytogenes*, *Clostridium perfringens*, *Enterococcus faecalis* are regulated by Quorum sensing systems [69–73]. Even though gram positive Quorum sensing circuits have a general resemblance some small variation in mechanism is observed depending on specious and living environment which is discussed here

4.1. Two component system in gram positive bacteria

Most of the gram positive bacterial linguistics are depending upon membrane bound two component system that identify signaling molecule autoinducer peptides (Fig. 4) [74,75]. A classic example for two component quorum sensing system is found in *Staphylococcus aureus* [76]. This is a nosocomial pathogen which is normally concerned with skin infection if neglected leads to bacteremia and sepsis [77].

Virulence and communication of this bacteria is regulated by Arg locus which is a combination of two transcripts RNA II and RNA III [78]. Pro-AIP will be produced by ArgD one among the four component of Quorum sensing system. Pro-AIP will be processed and modified by Arg B after which it will be transported out by

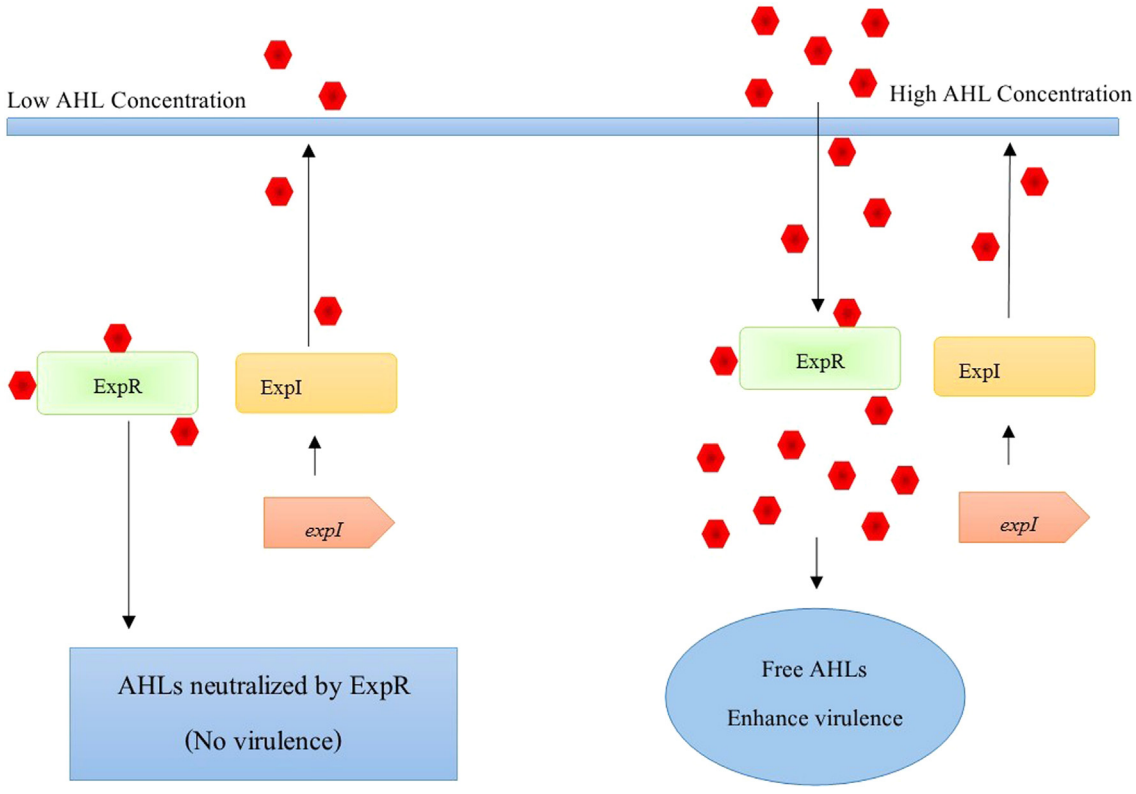

Fig. 3. ExpIR mediated signaling in *Erwinia carotovora* which is homologues to LuxIR signaling circuit.

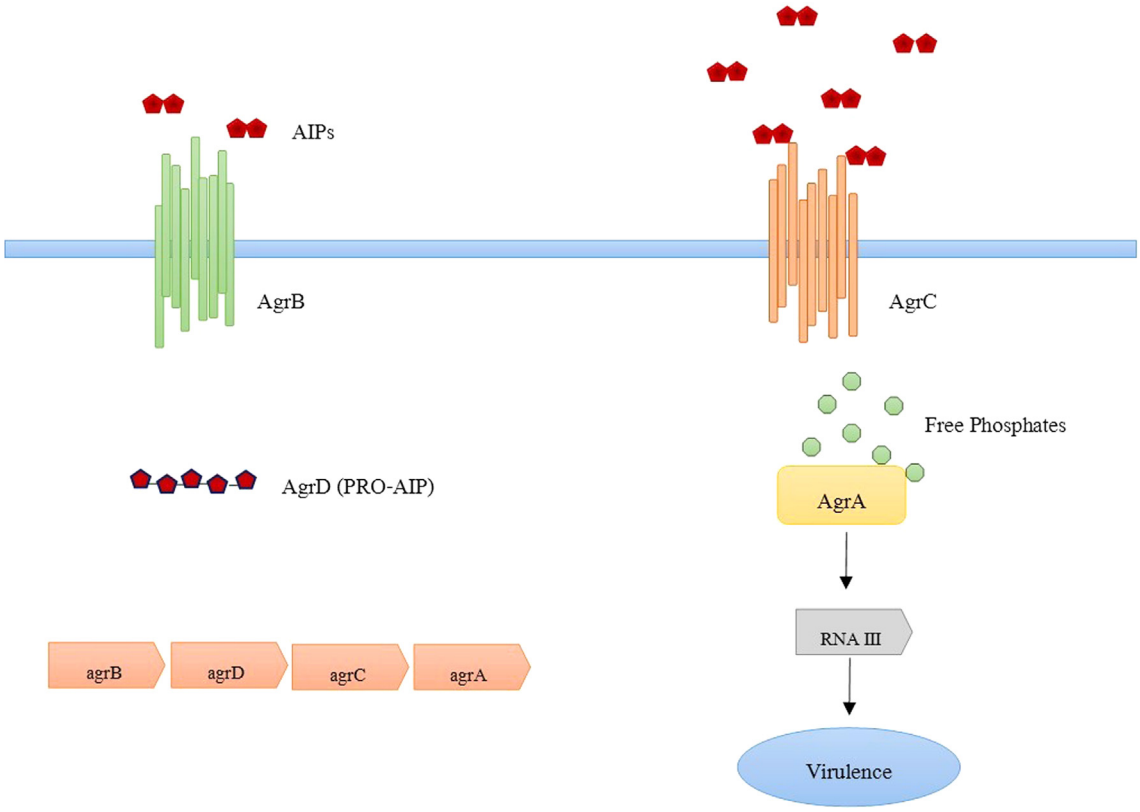

Fig. 4. Agr circuit depended two component quorum sensing system is found in *Staphylococcus aureus.*

the same. [79]. During the course of modification pro-AIP that of 47 amino acid residue will be derived to 9 residue peptide. In high bacterial density, AIP will accumulate extra cellular environment and attain a certain threshold level. In this stage Arg C; a trans membrane protein will get activated which in turn bind with AIP [80]. Agr C is a histidine kinase which phosphorylate by the combination of AIP. Hence available phosphate group interacts with Agr A which is the response regulator [81]. Agr C and Agr A together constitute two component system. Activation of Agr C - Agr A activates the transportation of RNA II which continues the quorum sensing circuit and RNA III that is responsible for virulence [82].

4.2. Extracellular protease processed AIP quorum sensing circuit

In some gram positive bacteria processing of pro AIP is done in the external environment of bacterial cell by extracellular protease enzymes after which AIP will be transported back to cell for regulating transcription (Fig. 5) [83]. Many virulent factors like sporulation and enzyme production in *Bacillus cereus*, plasmid transfer in *Enterococcus faecalis* are regulated by such mechanism [84,85]. Quorum sensing circuit in *Bacillus cereus* is a significant example for extracellular protease processed AIPs. A 48 amino acid long pap R intercellular pro-AIP is been produced by pap R gene. An amino terminal signaling peptide present in pro-AIP will initiate a secretory pathway due to which PRO-AIP is been taken out of bacterial cells and will be processed by an extracellular protease into an active AIP [86,87]. Once the concentration of processed AIP reach a threshold level it will be transported inside bacterial cell by oligopeptide permease trans membrane protein [88]. It is observed that only processed pap R could interact with oligopeptide permease system whereas during the process pro -AIP will be degraded into peptides of 5, 7, 8 and 11. This is because of the specific activity of Intercellular transcription regulator plc R upon pentapeptide and heptapeptide [89]. Interaction of AIP on transcription factor plc R brings conformational changes and initiate plc R oligomerization which subsequently induces production of virulence factors [90].

4.3. Competitive quorum-sensing system

In this type of Quorum sensing; network of different phenotype would antagonize each other based upon the desired lifestyle of bacteria [46]. This is moreover a combination of other two above mentioned systems. *Bacillus subtilis* stands as a perfect example of such signaling circuits (Fig. 6). In this bacteria signaling system of competence and sporulation influence each other based on necessity. Competence in bacteria is controlled by Com X peptide which is a ten amino acid [91] sized and processed and secreted by Com Q [92]. In high density: Com X is identified by an histidine kinase Com P that initiate formation of Com X - Com P complex which eventually trigger autophosphorylation that enable Com A to consume a phosphate group [93]. Com A is a DNA binding response regulator that initiate numerous competence mechanism [94].

In other hand this bacteria also produce another oligopeptide by gene phr C and called as CSF (competence and sporulation factor). From cytoplasm CSF is effluxed out by transmembrane proteins [95]. In optimum threshold level CSF is taken back into the bacterial cell by by oligopeptide permease [96]. Internalized CSF have two positive fates depending upon its internal concentrations. In low concentrations CSF bind with cytoplasmic protein Rap C and promote bacterial competence [97]. Rap C protein in free state disturbs Com A hence bacterial competence. Therefore CFS-Rap C complex leads to smooth regulation of bacterial competence. In the high internal concentration level CSF form a complex with

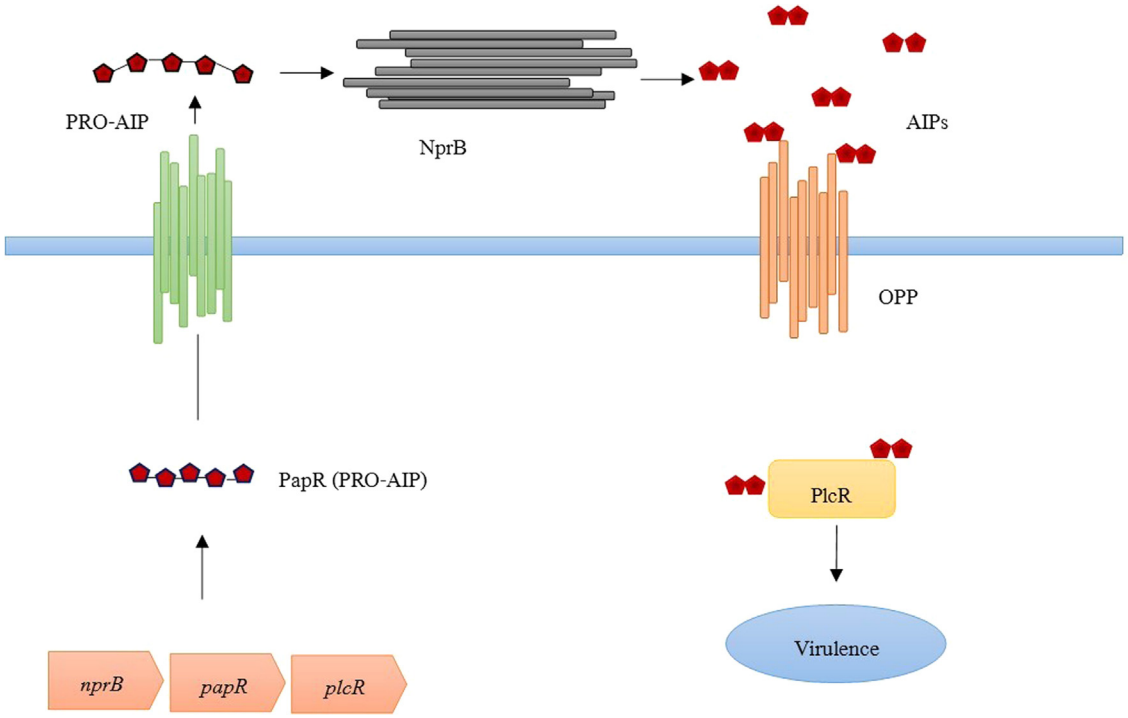

Fig. 5. Extracellular protease processed AIP Quorum sensing circuit in *Bacillus cereus.*

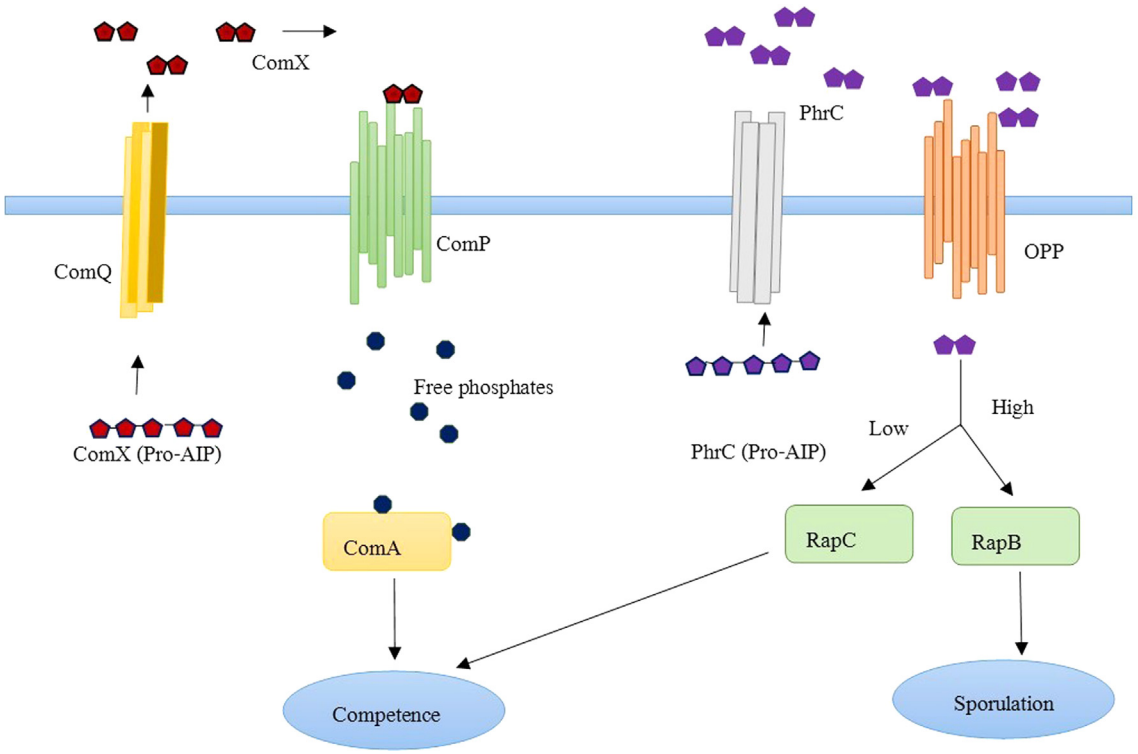

Fig. 6. Competitive quorum-sensing system in *Bacillus subtilis.*

Rap B protein hence induce sporulation [98]. In free State Rap B block sporulation by phosphorylation of SPOOF gene which is responsible for sporulation [99]. Complex formation between CSF-Rap B also ensures the availability of Rap C to inhibit competence.

5. Bacterial silencing: taking antibacterial strategy to a new dimension

The mechanism through which bacteria are made "*silent*" by blocking quorum sensing system is called as quorum quenching.

In this era of antibiotic depletion world is searching for new remedies against bacterial infections. Quorum sensing targeted antibacterial therapy has evolved new revolution in this field. Suppression of Quorum quenching have immense value in clearing bacterial infections such as chronic lung infections in CF patients, severe wound infection [100,101]. Quorum sensing targeting drugs basically does not killing the bacteria but it is only attenuating bacterial virulence [102] and offers additional time to host defense mechanism that effect in better immunological clearance of pathogen. Quorum sensing circuit targeted treatment against *Staphylococcus aureus* [103], *Pseudomonas aeruginosa* [104], *Vibrio cholera* [105] were successful and comprehensive. Not only in pharmacological field but agriculture, aqua culture, industries are also found benefited by quorum quenching. There are many strategies which can be relied for blocking bacterial communication which is generally classified as enzymatic and non-enzymatic quorum quenching methods. There are many techniques to find appropriate quorum quencher such as cross streak assay, disc diffusion method, overlay assay, metagenomic analysis, microarray based screening. The choice of technique vary with the requirement. In this part we discuss some important quorum quenching methods and its applications.

6. Enzymatic quorum quenching

Enzymatic quorum quenching is concerned with altering conformation and structure of signaling molecule which eventually block bacterial communication. These quorum quenching enzymes are mostly derived from microorganisms which is found to give benefit to the producer in a competitive environment [106,107]. This hypothesis of bacterial benefit by producing quorum quenching enzymes are based on the discovery co-existence between quorum sensing and quorum quenching bacteria [108,109]. Four different types of chemical reactions are observed behind enzymatic quorum sensing they are decarboxylation, deaminisation acylase and lactonase activity [110]. So far enzymes those found degrading signal molecules are studied under three categories which is constituted by lactonase enzymes, acylase enzymes and oxydoreductase enzymes.

6.1. Lactonase mediated quorum quenching

AHL lactonanses hydrolyze lactonase ring of the signaling molecules due to which opened ring structure will be formed (Fig. 7). It is also observed that lactonase enzyme doesn't disturb anything other than lactone ring. [111,112]. It was believed that enzyme hydrolyze amide linkage between lactone and acyl side chain but recent studies on structure and function proved that ester link is affected. Based on phylogeny lactonase belongs to metallo-beta-lactonase superfamily and phosphotriesterase family among which maximum candidates belong to metallo-beta-lactamase superfamily [113,114]. AHL lactonase are extensively produced by bacteria those have no phylogenetic relation suggests that enzyme production is not dependent upon taxonomic classification. First analyzed bacterial AHL-lactonase is AiiA $_{24B1}$, A product of aiiA gene possessed by *Bacillus* sp. 24B1 [115]. Since then many bacteria were found producing AHL lactonases which is homologous of AiiA [116]. A thermostable lactonase enzyme namely GKL was obtained from *Geobacillus kaustophilus* which belonged to phosphotriesterase family and showed relatively low *paraoxonase activity* suggesting its non-involvement of phosphate ester as substrate [117]. *Geobacillus stearothermophilus* was observed to produce low

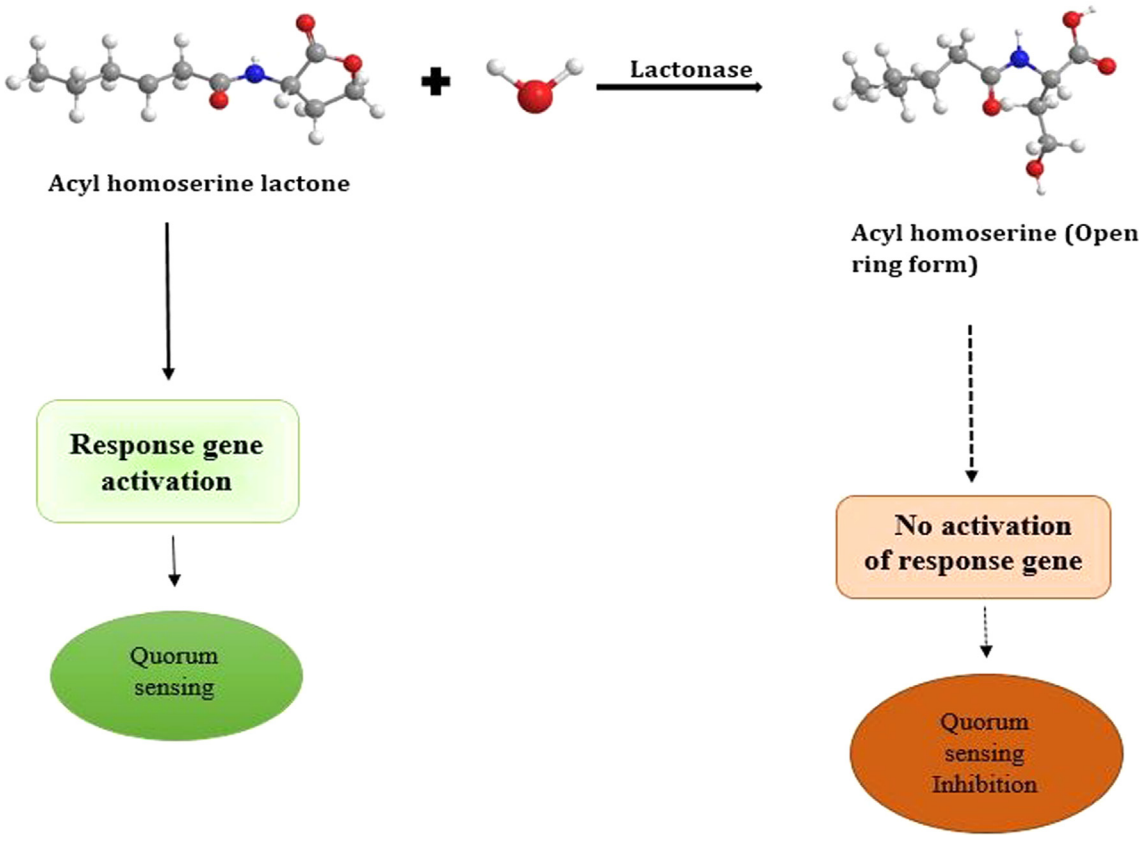

Fig. 7. Structural modification by the hydrolase action of lactonase which disables bacterial signaling.

catalytic enzyme but with high thermo stability [118]. Thermostable lactonase enzyme were also produced by *Geobacillus caldoxylosilyticus* YS-8 and *Geobacilius kaustophilus* HTA426 [119,120].

It was also evident that some bacterial strains produce lactonase enzyme that show major deviation from aiiA gene product. For instance, AiiM lactonase enzyme was obtained from *Agrobacterium tumefaciens* [121] AhiD of *Arthrobacter*, *Ochrobactrum* produced Aid H Aiim of *Microbacterium testaceum*, Qsd A of *Rhodococcus* [122–125] all were examples of lactonases that showed deviation from aiiA. It was believed that AiiA hydrolyze amide linkage between lactone and acyl side chain but recent studies on structure and function of AiiA proved that ester link is the one got attacked by enzyme. Crystal structure of AiiA suggested that there are two Zn^{2+} ions present in active center and these metal ions are very much essential for the catalytic activity and folding of enzyme [126]. Analysis on lactonase from *Bacillus thuringiensis* indicated that Zn1 binds to His 104, HiS 106 and HiS 109 however Z2 binds up on Asp 108, His 109 and His 235 [127] substitution of di-zinc by di-cobalt, di-manganese and di-cadmium suppressed the lactonase activity which proves the role of Zn ion in enzyme activity [128].

6.2. Acylase mediated quorum quenching

Acylase are the group of quorum sensing enzyme that hydrolyze amide bond between homoserine lactone and acyl side chain (Fig. 8) [129]. Major number of identified AHL acylases belong to Ntn Hydrolase superfamily and are classified into two clusters referred as AAC and Qui P cluster [130]. These two cluster differ in their substrate specificity whereas AAC specifically degrade AHL's longer than C8-HSL however Qui P cluster have a varying range of catalytic activity [131] initial reports of acylase enzyme was by gram negative bacterium *Variovorax paradoxus* that efficiently degraded AHL in growth media [129]. Till date many bacterial strains have been studied for its production of acylase enzyme. Gram positive *Streptomyces Sp.* was found producing acylase enzyme. This stand first such example for gram positive bacteria [132] AiiD from *Ralstonia* sp. XJ12B effectively degraded short and long AHLs. *Actinoplanes utahensis* and *Brevundimonas diminuta* produced acylase those with high similarities to *Ralstonia* acylase [133] acylase in substrate selection. Bacterial strain *Pseudomonas syringae* strain B728a were immensely studied for the ability to produce two acylase namely Hac A and Hac B [134]. Many other bacteria such as *Shewanella* sp. [135] *Tenacibaculum maritimum* [136], *Comamonas testosterone* [137] were also able to produce acylase. From the structural analysis it was observed that acylase enzyme is composed of two or more sub units. Amino acid sequence usually consists of four domains those are signal peptide, Alpha-subunit, Linear spacer and Beta-subunit [138]. Pro acylase enzyme is not functional and it will be converted to activate enzyme by proteolysis.

6.3. Oxidoreductase mediated quorum quenching

Oxidreducatase mediated Quorum quenching is targeting signal receptor specificity towards AHL signals. This enzymes modify the chemical structure of AHLs that disable them to interact with receptor and hence blocking signaling pathway (Fig. 9) such reports were first observed in *Rhodococcus erythropolis* [139]. AHL oxydoreductase obtained from *Bacillus megaterium* found oxidising ω-1,2,3 carbons of acyl chain [140]. There are not much reports obtained about oxydoreductases but NADH-dependent BpiBoa enzyme [141] obtained from *Burkholderia* GG4 give great hope to carry on more intense study in the possibility of structural remodeling of AHL signal molecules

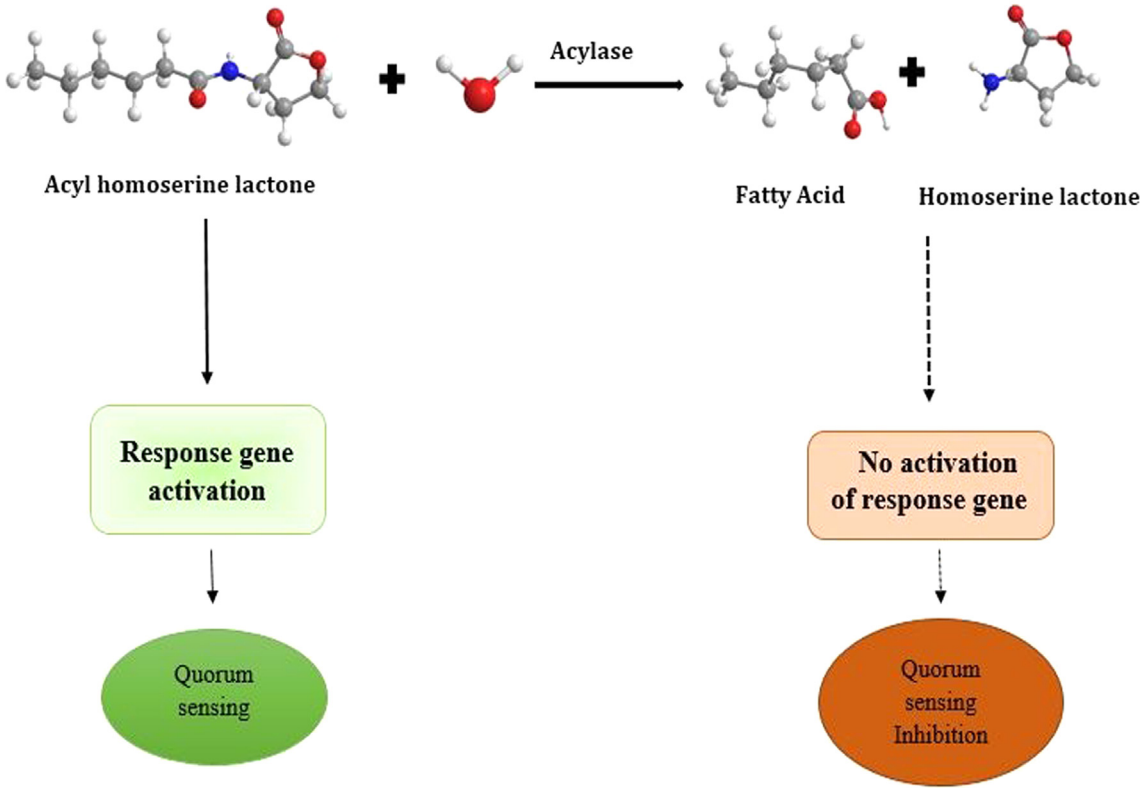

Fig. 8. Structural modification by the hydrolase action of acylase because of which quorum sensing circuit is compromised.

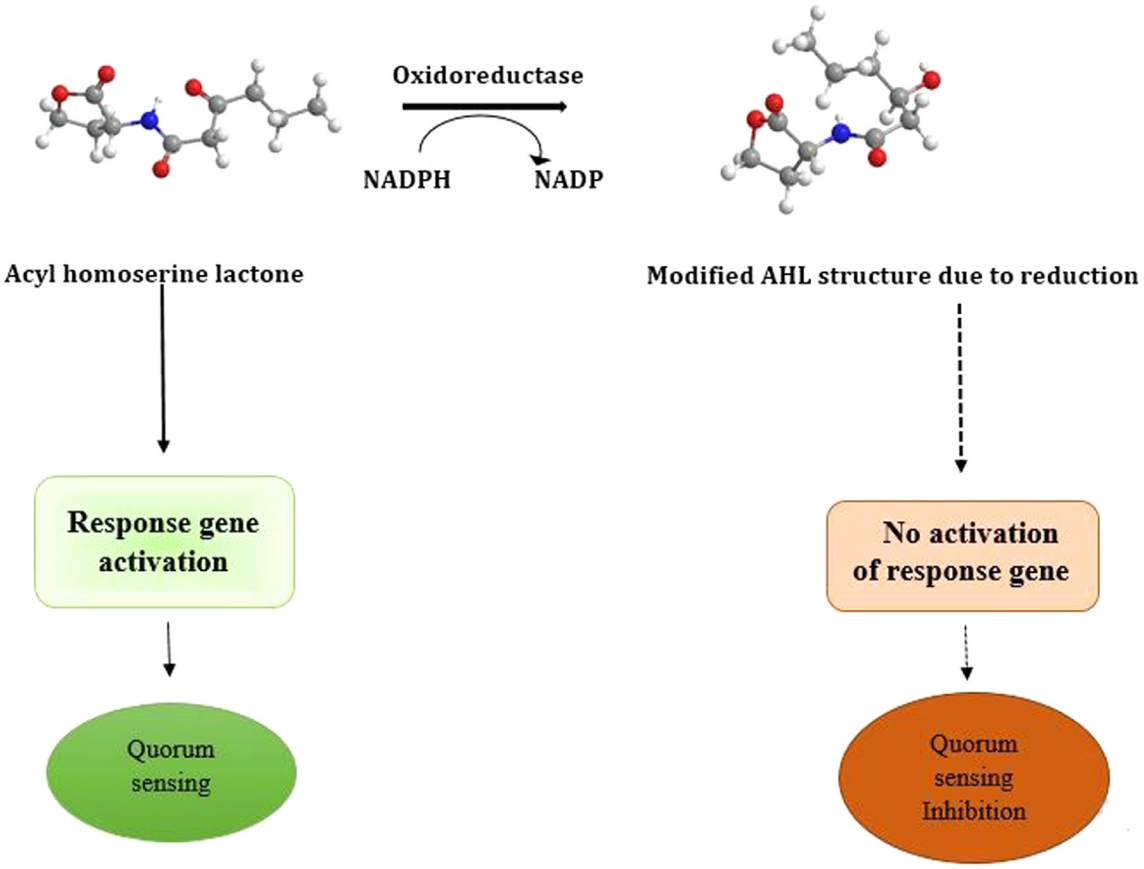

Fig. 9. Structural modification of AHL due to reduction by oxydoreductase enzyme which in turn mediate quorum quenching.

7. Non enzymatic quorum quenching

This is a widely used quorum quenching method now a day. Basic principle of this mechanism is to block communication signals rather than degrading it. Blocking of signaling molecules are generally done by competitive inhibition or by structural modification [142]. However quorum sensing antagonistic molecules either bind with signal receptors which enable the interaction of receptor-signal molecule or bind with signaling molecule which disable them to interact with receptors. In the present study, some of the non-enzymatic quorum quenching components have been discussed.

One among the popular strategy is using prokaryotic byproducts to regulate the quorum se mechanism in a quorum sensing bacterial strain. Numerous reports of bacterial byproducts to be a quorum quencher have been postulated. Isobutyramide and 3-methyl-N-(2-phenylethl)-butyramide produced by *Halobacillus salinus* was able to target Lux system of *Vibrio harveyi* [143] in the same way *Bacillus cereus* strain D28 effectively inhibited AHL mediated quorum sensing in *Chromobacterium violaceum* [144]. Toxin production in *Staphylococcus* Sp. found successfully reduced by cyclic dipeptides produced by *Lactobacillus reuteri* [145]. Yayurea A and B purified from gram positive bacteria *Staphylococcus delphini* showed its action against QS mediated mechanisms such as pigment production, bioluminance and biofilm formation [146]. CviR gene found inhibited by Cis-9-octadecenoic acid produced by unusual bacteria *Stenotrophomonas maltophilia* BJ01 which was isolated from rhizosphere [147]. In the same way many reports of Cynobacterial products inhibited bacterial quorum sensing. One well studied blue green algae for quorum quenching is *Blennothrix cantharidosmum* due to its abundance production of tumonic acids (E, F, G and G). These compounds were effective in regulating bioluminescence in *Vibrio harveyi* [148]. *Lyngbya majuscula* has evolved a strong individual and it was found that chemical components like lyngbic acid, lyngbyoic acid, Malyngolide, Pitinoic acid and peptides as microcolins which was produced by them have shown quorum sensing antagonistic action [149–151]. *Leptolyngbya crosbyana* found producing Honaucins that showed inhibition of quorum sensing mediated bacterial communication [152].

In this post antibiotic era fungal metabolites have evolved as important quorum quenching tools. An early report of fungal metabolites that block bacterial communication was by patulin and penicillic acid which were produced by *Penicillium coprobium* and *Penicillium radicicola* respectively. This extracts found very effective in blocking quorum sensing of *Pseudomonas* aeruginosa. *In vivo* studies conducted in mouse models indicated that there were rapid clearance of pathogens which was treated with patulin compared with the placebo group [153]. Later the quorum quenching antagonistic action of a sesquiterpine farnesol extracted from *Candida albicans* was reported. Addition of farnesol as well as co-culture with fungul strain decreased the pyocyanin production, a quorum sensing controlled system in *Pseudomonas aeruginosa.* This report suggests the advantage of quorum quenching organism in an ecosystem [154]. A secondary fungal metabolic ambuic acid purified from fungal strain KAP-21 was reported very efficient against quorum sensing in gram positive bacterial strains where it inhibited the quorum-sensing-mediated gelatinase production without influencing the growth of *Enterococcus faecalis* also targeted the biosynthesis of a cyclic peptide quormone called gelatinase biosynthesis-activating pheromone. Furthermore, ambuic acid also inhibited the biosynthesis of the cyclic peptide quormones of *Staphylococcus aureus* and *Listeria innocua.* These results

suggest the potential use of ambuic acid as a lead compound of anti-pathogenic drugs that target the quorum sensing- mediated virulence expression of gram-positive bacteria [155].

Aspergillus sp produced Kojic acid that inhibited quorum sensing dependent biofilm formation by regulating Lux system. Kojic acid inhibited formation of microbial communities on glass slides, decreasing the densities of bacteria this study suggests that natural products with quorum sensing inhibitory properties can be used for controlling biofouling communities [156]. Polyhydroxyanthraquinones purified from distinct red guttates of the endophytic fungus *Penicillium restrictum* efficiently inhibited quorum sensing in clinical isolate of Methicillin-resistant *Staphylococcus aureus* (MRSA) [157]. Recent studies on marine endosymbiotic fungi revealed the quorum quenching activity of four different genera *Sarocladium, Fusarium*, *Epicoccum*, and *Khuskia.* These strains proved an abundant source of novel secondary metabolites against bacterial quorum sensing [158].

There have been some reports of quorum quenching by some invertebrate animals such as Molluscs, Arthropods and Annelida. First among them is honey a product by honey bee that efficiently reduced bacterial communication. Honey was found antagonizing LasR and RhIR quorum sensing systems [159,160]. Another report says the efficacy of solenopsin A produced by fire ant that effectively regulated rhI circuits [161]. LuxR signaling was greatly influenced by byproducts of Annelids and Molluscs as cembranoids from *Pseudoplexaura flagellosa* and exadates from *Caenorhabditis elegans* showed anti quorum sensing action [162,163]. Add on to these Poriferans also had some great deal in neutralizing bacterial quorum sensing. *Luffaria variabilis* inhibited the action of Lux regulatory proteins by its metabolite secomanoalide [164] and hymenialdisin an alkaloid produced by *Hymeniacidon aldis* also had inhibitory effect on LuxI and LasR proteins [156].

Since the ancient medical era plants and plant products have contributed a lot against disease and infections. In the same way many plant products were found antagonizing bacterial communication. L-Canavanine obtained from *Medicago sativa* influenced ExpR and CviR [165] and thereby suppressed the biofilm formation of pathogens. 2,5-di-O-galloyl-d-Hamamelose obtained from *Hamamamelis virginiana* which is commonly called as witch hazel and obacunone from grapes possessed ability to inhibit quorum sensing [166]. CviR and RhiR controlled quorum sensing was inhibited by plant derivatives Benzopyran and Catachin [167]. Malabaricone C purified from *Myrstica cinnamomea* as well as Curcumin from *Curcuma longa* regulated quorum sensing dependent biofilm development [168,169]. Along with this, many other several macromolecules such as chitosan is also found to have high degree of quorum quenching ability [170,171]. This recent observation could open up new dimensions of quorum quenching studies.

8. Significance and future aspects of quorum quenching mediated bacterial silencing

Strategy of quorum quenching is widely employed in various fields as a powerful weapon against bacterial caused misfortunes. In agricultural field a great loss is being occurred due to the pathogenic action of bacteria. Quorum quenching is been effectively applied to remediate such issues, among them a major breakthrough have been reported against soft rot disease [172,173]. The disease can be controlled either by introducing a gene into plants whose products block AHL synthesis or by the employment of AHL degrading bacteria [174,175]. Transgenic plants that express AiiA lactonase were pretty much effective against infection by *Pectobacterium carotovorum* [111]. Despite achieving this successful hypothesis, the less acceptability of transgenic food around the globe limits this method. Biofouling has grown as a major concern over years which accumulates the microorganisms on the surfaces those are in contact with water [176]. Quorum quenching agents can be successfully employed to reduce bacterial reduce biofouling [177].

In pharmacology, quorum quenching compounds have initialized a new aeon of antibacterial treatment. The main principle behind this strategy is the down regulation of quorum sensing which mediates virulence factor production by quorum quenching [178]. Many Quorum quenching compounds have been experimented for its pharmacological activity either by blocking AHL signal or by degrading AHL signals. It is observed that enzymatic quorum quencher could be of great significance in antibacterial therapy as they inactivate signaling molecule without messing with bacterial metabolism [179]. It is also observed that database of quorum quenching molecules for different bacteria are available which could aid the future research in this field. Databases such as Quorumpeps [180] which deliberately explains about quorum quenching peptides and Sigmol [181] that contains data of prokaryotic are perfect examples of quorum quenching databases. Even though numerous studies are emerging about quorum quenching molecules as antibacterial drugs, much of the components haven't reached clinical level due to their low biocompatibility. Thus the discovery of novel quorum quenching component without toxic effects could pave the way towards new pastures of antibacterial therapy.

9. Conclusions

Quorum sensing is a bacterial density depended mechanism which regulate virulence. It is controlled by signalling molecules termed as autoinducers. It is evident that by manipulating the signalling circuit of bacterial communication it is possible to attenuate pathogen.

Conflict of interest

We declare 'no conflict of interest'.

Acknowledgement

We would like to thank Mr. Suresh Lingam of Yaazh Xenomics for his supports.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or Not-for-profit sectors.

References

[1] Fuqua WC, Winans SC, Greenberg EP. Quorum sensing in bacteria: the LuxR-LuxI family of cell density- responsive transcriptional regulators. J Bacteriol 1994;176:269–75. https://doi.org/10.1128/jb.176.2.269-275.1994.
[2] Parker CT, Sperandio V. Cell-to-cell signalling during pathogenesis. Cell Microbiol 2009;11:363–9. https://doi.org/10.1111/j.1462-5822.2008.01272.x.Cell-to-cell.
[3] Whiteley M, Diggle S, Greenberg E. Progress in and promise of bacterial quorum sensing research. Nature 2017;551:313–20.
[4] Whitehead NA, Barnard AML, Slater H, Simpson NJL, Salmond GPC. Quorum-sensing in Gram-negative bacteria. FEMS Microbiol Rev 2001;25:365–404. https://doi.org/10.1111/j.1574-6976.2001.tb00583.x.
[5] Papenfort K, Bassler BL. Quorum sensing signal–response systems in Gram-negative bacteria. Nat Rev Microbiol 2016;14:576–88.
[6] Kaplan HB, Greenberg EP. Diffusion of autoinducer is involved in regulation of the *Vibrio fischeri* luminescence system. Microbiology 1985;163:1210–4.
[7] Hawver LA, Jung SA, Ng W. Specificity and complexity in bacterial quorum-sensing systems. FEMS Microbiol Rev 2018;40:738–52. https://doi.org/10.1093/femsre/fuw014.

[8] Novick R, Projan S, Kornblum J, Ross H, Ji G, Kreiswirth B, et al. The agr P2 operon: an autocatalytic sensory transduction system in *Staphylococcus aureus*. Mol Gen Genet 1995:446–58.
[9] Seed P, Passador L, Iglewski B. Activation of the *Pseudomonas aeruginosa* lasI gene by LasR and the Pseudomonas autoinducer PAI: an autoinduction regulatory hierarchy. J Bacteriol 1995:654–9.
[10] Shadel GS, Baldwin TO. Positive autoregulation of the *Vibrio fischeri* luxR gene. J Biol Chem 1992;267:7696–702.
[11] Egland K, Greenberg EP. Quorum sensing in *Vibrio fischeri*: elements of the luxI promoter. Mol Microbiol 1999:1197–204. https://doi.org/10.1046/j.1365-2958.1999.01261.x.
[12] Pérez P, Hagen S. Heterogeneous response to a quorum-sensing signal in the luminescence of individual *Vibrio fischeri*. PLoS One 2010;5:e15473. https://doi.org/10.1371/journal.pone.0015473.
[13] Hartman G, Richard W. Quorum sensing: potential means of treating gram-negative infections? Lancet 1998;351:848–9. https://doi.org/10.1016/S0140-6736(05)70282-.
[14] Manefield M, Rasmussen TB, Henzter M, Andersen JB, Steinberg P, Kjelleberg S, et al. Halogenated furanones inhibit quorum sensing through accelerated LuxR turnover. Microbiology 2002;148:1119–27. https://doi.org/10.1099/00221287-148-4-1119.
[15] Tannières M, Lang J, Barnier C, Shykoff JA, Faure D. Quorum-quenching limits quorum- sensing exploitation by signal- negative invaders. Sci Rep 2017;6:1–10. https://doi.org/10.1038/srep40126.
[16] Hense B, Schuster M. Core principles of bacterial autoinducer systems. Microbiol Mol Biol Rev 2015;79:153–69. https://doi.org/10.1128/MMBR.00024-14.
[17] Manefield M, Turner S. Quorum sensing in context: out of molecular biology and into microbial ecology. Microbiology 2002:3762–4.
[18] Kolibachuk D, Greenberg E. The *Vibrio fischeri* luminescence gene activator LuxR is a membrane-associated protein. J Bacteriol 1993;175:7307–12.
[19] Sturme M, Kleerebezem M, Nakayama J, Akkermans A, Vaugha E, de Vos W. Cell to cell communication by autoinducing peptides in gram-positive bacteria. Antonie Van Leeuwenhoek 2002;81:233–43.
[20] Coulthurst S, Kurz C, Salmond G. luxS mutants of Serratia defective in autoinducer-2-dependent 'quorum sensing' show strain-dependent impacts on virulence and production of carbapenem and prodigiosin. Microbiology 2004;150:1901–10.
[21] Xavier K, Bassler B. LuxS quorum sensing: more than just a numbers gameLuxS quorum sensing: more than just a numbers game. Curr Opin Microbiol 2003;6:191–7.
[22] Rutherford ST, Bassler BL. Bacterial quorum sensing: its role in virulence and possibilities for its control. Cold Spring Harb Perspect Med 2012;2. https://doi.org/10.1101/cshperspect.a012427.
[23] Schuster M, Sexton D, Diggle S, Greenberg E. Acyl-homoserine lactone quorum sensing: from evolution to application. Annu Rev Microbiol 2013;67:43–63. https://doi.org/10.1146/annurev-micro-092412-155635.
[24] Eberhard A, Burlingame A, Eberhard C, Kenyon G, Nealson KH, Oppenheimer N. Structural identification of autoinducer of *Photobacterium fischeri* luciferase. Biochemistry 1981;20:2444–9.
[25] Engebrecht J, Silverman M. Identification of genes and gene products necessary for bacterial bioluminescence. Proc Natl Acad Sci USA 1984;81:4154–8.
[26] Engebrecht J, Nealson K, Silverman M. Bacterial bioluminescence: isolation and genetic analysis of functions from *Vibrio fischeri*. Cell 1983;32:773–81.
[27] Yao Y, Martinez-Yamout M, Dickerson T, Brogan A, Wright P, Dyson H. Structure of the *Escherichia coli* quorum sensing protein SdiA: activation of the folding switch by acyl homoserine lactones. J Mol Biol 2006:262–73.
[28] Bottomley M, Muraglia E, Bazzo R, Carfi A. Molecular insights into quorum sensing in the human pathogen *Pseudomonas aeruginosa* from the structure of the virulence regulator LasR bound to its autoinducer. J Biol Chem 2007;282:13592–600.
[29] Chen G, Swem L, Swem D, Stauff D, O'Loughlin C, Jeffrey P, et al. A strategy for antagonizing quorum sensing. Mol Cell 2011;42:199–209.
[30] Watson W, Minogue T, Val D, von Bodman S, Churchill M. Structural basis and specificity of acyl-homoserine lactone signal production in bacterial quorum sensing. Mol Cell 2002;9:685–94.
[31] Gould T, Schweizer H, Churchill M. Structure of the *Pseudomonas aeruginosa* acyl-homoserinelactone synthase LasI. Mol Microbiol 2004;53:1135–46.
[32] Fuqua C, Parsek M, Greenberg E. Regulation of gene expression by cell-to-cell communication: acyl-homoserine lactone quorum sensing. Annu Rev Genet 2001;35:439–68.
[33] Case R, Labbate M, Kjelleberg S. AHL-driven quorum- sensing circuits: their frequency and function among the Proteobacteria. Isme J 2008;2:345–9.
[34] Thomson N, Crow M, McGowan S, Cox A, Salmond G. Biosynthesis of carbapenem antibiotic and prodigiosin pigment in Serratia is under quorum sensing control. Mol Microbiol 2000;36:539–56.
[35] Salini R, Pandian SK. Interference of quorum sensing in urinary pathogen *Serratia marcescens* by *Anethum graveolens*. FEMS Pathog Dis 2015;73:1–8. https://doi.org/10.1093/femspd/ftv038.
[36] McClean K, Winson M, Fish L, Taylor A, Chhabra S, Camara M, et al. Quorum sensing and *Chromobacterium violaceum*: exploitation of violacein production and inhibition for the detection of N-acylhomoserine lactones. Microbiology 1997;143:3703–11.
[37] Deryabin D, Inchagova KS. Inhibitory effect of aminoglycosides and tetracyclines on quorum sensing in *Chromobacterium violaceum*. Microbiology 2018;87:1–8.
[38] Tahrioui A, Quesada E, Llamas I. The hanR/hanI quorum-sensing system of *Halomonas anticariensis*, a moderately halophilic bacterium. Microbiology 2011;157:3378–87. https://doi.org/10.1099/mic.0.052167-0.
[39] Zhu J, Winans S. Autoinducer binding by the quorum- sensing regulator TraR increases affinity for target promoters in vitro and decreases TraR turnover rates in whole cells. Proc Natl Acad Sci 1999;96:4832–7.
[40] Meighen E. Genetics of bacterial bioluminescence. Annu Rev Genet 1994;28:117–39.
[41] More M, Finger L, Stryker J, Fuqua C, Eberhard A, Winans S. Enzymatic synthesis of a quorum-sensing autoinducer through use of defined substrates. Science (80-) 1996;272:1655–8.
[42] Schaefer A, Val D, Hanzelka B, Cronan JJ, Greenberg E. Generation of cell-to-cell signals in quorum sensing: acyl homoserine lactone synthase activity of a purified *Vibrio fischeri* LuxI protein. Proc Natl Acad Sci 1996;93:9505–9.
[43] Zhu J, Winans S. The quorum-sensing transcriptional regulator TraR requires its cognate signaling ligand for protein folding, protease resistance, and dimerization. Proc Natl Acad Sci 2001;98:1507–12.
[44] Stevens A, Dolan K, Greenberg E. Synergistic binding of the *Vibrio fischeri* LuxR transcriptional activator domain and RNA polymerase to the lux promoter region. Proc Natl Acad Sci 1994;91:12619–23.
[45] Devine J, Shadel G, Baldwin T. Identification of the operator of the lux regulon from the Vibrio fisheri strain ATCC7744. Proc Natl Acad Sci USA 1989;86:5688–92.
[46] Waters C, Bassler B. Quorum sensing: cell-to-cell communication in bacteria. Annu Rev Cell Dev Biol 2005;21:319–46.
[47] Mukherjee S, Moustafa D, Smith CD, Goldberg JB, Bassler L. The RhlR quorum-sensing receptor controls *Pseudomonas aeruginosa* pathogenesis and biofilm development independently of its canonical homoserine lactone autoinducer. PLOS Pathog 2017;13:e1006504. https://doi.org/10.1371/journal.ppat.1006504.
[48] Bodey G, Bolivar R, Fainstein V, Jadeja L. Infections caused by *Pseudomonas aeruginosa*. Rev Infect Dis 1983;5:279–313.
[49] Smith R, Harris S, Phipps R, Iglewski B. The *Pseudomonas aeruginosa* Quorum sensing molecule N-(3- Oxododeconoyl) homoserine lactone contributes to virulence and induces inflammation in vivo. J Bacteriol 2002;184:1132–9.
[50] Gambello M, Iglewski B. Cloning and characterisation of *Pseudomonas aeruginosa* lasR gene, a transcriptional activator of elastase expression. J Bacteriol 1991;173:3000–9.
[51] Latifi A, Winson M, Foglino M, Bycroft B, Stewart G, Lazdunski A, et al. Multiple homologues of LuxR and LuxI control expression of virulence determinants and secondary metabolites through quorum sensing in *Pseudomonas aeruginosa* POA1. Mol Microbiol 1995;17:333–43.
[52] Pearson J, Gray K, Passador L, Tucker K, Eberhard A, Iglewski B, et al. Structure of the autoinducer required for expression of *Pseudomonas aeruginosa* virulence genes. Proc Natl Acad Sci USA 1994;91:197–201.
[53] Gambello M, Kaye S, Iglewski B. LasR of *Pseudomonas aeruginosa* is a transcriptional activator of the alkaline protease gene (apr) and an enhancer of exotoxin A expression. Infect Immun 1993;61:1180–4.
[54] Pesci E, Pearson J, Seed P, Iglewski B. Regulation of las and rhl quorum sensing in *Pseudomonas aeruginosa*. J Bacteriol 1997;179:3127–32.
[55] Ochsner U, Koch A, Fiechter A, Reiser J. Isolation and characterisation of a regulatory gene affecting rhamnolipid biosurfactant synthesis in *Pseudomonas aeruginosa*. J Bacteriol 1994;176:2044–54.
[56] Schuster M, Urbanowski M, Greenberg E. Promoter specificity in *Pseudomonas aeruginosa* quorum sensing revealed by DNA binding of purified LasR. Proc Natl Acad Sci 2004;101:15833–9.
[57] Whiteley M, Lee K, Greenberg E. Identification of genes controlled by quorum sensing in *Pseudomonas aeruginosa*. Proc Natl Acad Sci 1999;96:13904–9.
[58] Lee J, Zhang L. The hierarchy quorum sensing network in *Pseudomonas aeruginosa*. Protein Cell 2015;6:26–41. https://doi.org/10.1007/s13238-014-0100-x.
[59] Dekimpe V, Deziel E. Revisiting the quorum-sensing hierarchy in *Pseudomonas aeruginosa*: the transcriptional regulator RhlR regulates LasR-specific factors. Microbiology 2009;155:712–23.
[60] Perombelon M, Kelman A. Ecology of the soft rot erwinias. Ann Rev Phytopathol 1980;18:361–87.
[61] Andersson RA, Eriksson ARB, Heikinheimo R, Mäe A, Pirhonen M, Kõiv V, et al. Quorum sensing in the plant pathogen *Erwinia carotovora* subsp. carotovora: the role of expR Ecc. MPM 2014;13:384–93. https://doi.org/10.1094/MPMI.2000.13.4.384.
[62] Jones S, Yu B, Bainton N, Birdsall M, Bycroft B, Chhabra S, et al. The lux autoinducer regulates the production of exoenzyme virulence determinants in Erwinia carotovora and *Pseudomonas aeruginosa*. EMBO J 1993;12:2477–82.
[63] McGowan S, Sebaihia M, Porter L, Stewart G, Williams P, Bycroft B, et al. Analysis of bacterial carbapenem antibiotic production genes reveals a novel b-lactam biosynthesis pathway. Mol Microbiol 1996;22:415–26.
[64] Barnard AML, Bowden SD, Burr T, Coulthurst SJ, Monson RE, Salmond GPC. Quorum sensing, virulence and secondary metabolite production in plant soft-rotting bacteria. Phil Trans R Soc B 2007;362:1165–83. https://doi.org/10.1098/rstb.2007.2042.

[65] Ji G, Beavis R, Novick R. Cell density control of staphylococcal virulence mediated by an octapeptide pheromone. Proc Natl Acad Sci USA 1995;92:12055–9.
[66] Okada M, Sato I, Cho S, Iwata H, Nishio T, Dubnau D, et al. Structure of the *Bacillus subtilis* quorum- sensing peptide pheromone ComX. Nat Chem Biol 2005;1:23–4.
[67] Bouillaut L, Perchat S, Arold S, Zorrilla S, Slamti L, Henry C, et al. Molecular basis for group-specific activation of the virulence regulator PlcR by PapR heptapeptides. Nucleic Acids Res 2008;36:3791–801.
[68] Lyon G, Wright J, Muir T, Key RPN. Determinants of receptor activation in the agr autoinducing peptides of staphylococcus aureus. Biochemistry 2002;41:10095–104.
[69] Kleerebezem M, Quadri L, Kuipers O, de Vos W. Quorum sensing by peptide pheromones and two-component signal-transduction systems in Gram-positive bacteria. Mol Microbiol 1997;24:895–904.
[70] Autret N, Raynaud C, Dubail I, Berche P, Charbit A. Identification of the agr locus of Listeria monocytogenes: role in bacterial virulence. Infect Immun 2003;71:4463–71.
[71] Podbielski A, Kreikemeyer B. Cell density-dependent regulation: Basic principles and effects on the virulence of Gram-positive cocci. Int J Infect Dis 2004;8:81–95.
[72] Ohtani K, Yuan Y, Hassan S, Wang R, Wang Y, Shimizu T. Virulence gene regulation by the agr system in *Clostridium perfringens*. J Bacteriol 2009;191:3919–27.
[73] Thoendel M, Kavanaugh J, Flack C, Horswill A. Peptide signaling in the staphylococci. Chem Rev 2011;111:117–51.
[74] Havarstein L, Coomaraswamy G, Morrison D. An unmodified heptadecapeptide pheromone induces competence for genetic transformation in *Streptococcus pneumoniae*. Proc Natl Acad Sci 1995;92:11140–4.
[75] Olson ME, Todd DA, Schaeffer CR, Paharik AE, Van Dyke MJ, Büttner H, et al. *Staphylococcus epidermidis* agr quorum-sensing system: signal identification, cross talk, and importance in colonization. J Bacteriol 2014;196:3482–93. https://doi.org/10.1128/JB.01882-14.
[76] Thoendel M, Horswill A. Biosynthesis of peptide signals in gram-positive bacteria. Adv Appl Microbiol 2010;71:91–112.
[77] Massey R, Horsburgh M, Lina G, Hook M, Recker M. The evolution and maintenance of virulence in *Staphylococcus aureus*: a role for host-to-host transmission? Nat Rev Microbiol 2006;4:953–8.
[78] Yarwood JM, Schlievert PM. Quorum sensing in Staphylococcus infections. J Clin Invest 2003;112. https://doi.org/10.1172/JCI200320442.Staphylococcus.
[79] Saenz H, Augsburger V, Vuong C, Jack R, Gotz F, Otto M. Inducible expression and cellular location of AgrB, a protein involved in the maturation of the staphylococcal quorum-sensing pheromone. Arch Microbiol 2000;174:452–5.
[80] Le KY, Otto M. Quorum-sensing regulation in staphylococci—an overview. Front Microbiol 2015;6:1–8. https://doi.org/10.3389/fmicb.2015.01174.
[81] Lina G, Jarraud S, Ji G, Greenland T, Pedraza A, Etienne J, et al. Transmembrane topology and histidine protein kinase activity of AgrC, the agr signal receptor in *Staphylococcus aureus*. Mol Microbiol 1998;28:655–62.
[82] Queck S, Jameson-Lee M, Villaruz A, Bach T, Khan BA, Sturdevant D. RNAIII-independent target gene control by the agr quorum-sensing system: insight into the evolution of virulence regulation in *Staphylococcus aureus*. MolCell 2008;32:150–8. https://doi.org/10.1016/j.molcel.2008. 08.005.
[83] Slamti L, Lereclus D. Specificity and polymorphism of the PlcR-PapR quorum-sensing system in the *Bacillus cereus* group. J Bacteriol 2005;187:1182–7.
[84] Pottathil M, Lazazzera B. The extracellular Phr peptide-Rap phosphatase signaling circuit of *Bacillus subtilis*. Front Biosci 2003;8:d32–45.
[85] Dunny G. The peptide pheromone-inducible conjugation system of *Enterococcus faecalis* plasmid pCF10: cell-cell signalling, gene transfer, complexity and evolution. Philos Trans R Soc L B Biol Sci 2007;362:1185–93.
[86] Okstad O, Gominet M, Purnelle B, Rose M, Lereclus D, Kolsto A. Sequence analysis of three *Bacillus cereus* loci carrying PlcR-regulated genes encoding degradative enzymes and enterotoxin. Microbiology 1999;145:3129–38.
[87] Pomerantsev A, Pomerantseva O, Camp A, Mukkamala R, Goldman S, Leppla S. PapR peptide maturation: role of the NprB protease in *Bacillus cereus* 569 PlcR/PapR global gene regulation. FEMS Immunol Med Microbiol 2009;55:361–77.
[88] Gominet M, Slamti L, Gilois N, Rose M, Lereclus D. Oligopeptide permease is required for expression of the *Bacillus thuringiensis* plcR regulon and for virulence. Mol Microbiol 2001;40:963–75.
[89] Bouillaut L, Ramarao N, Buisson C, Gilois N, Gohar M, Lereclus D, et al. FlhA influences *Bacillus thuringiensis* PlcR-regulated gene transcription, protein production, and virulence. Appl Env Microbiol 2005;71:8903–10.
[90] Declerck N, Bouillaut L, Chaix D, Rugani N, Slamti L, Hoh F, et al. Structure of PlcR: insights into virulence regulation and evolution of quorum sensing in Gram-positive bacteria. Proc Natl Acad Sci 2007;104:18490–5.
[91] Magnuson R, Solomon J, Grossman A. Biochemical and genetic characterization of a competence pheromone from *B. subtilis*. Cell 1994;77:207–16.
[92] Schneider KB, Palmer TM, Grossman AD. Characterization of comQ and comX, two genes required for production of ComX pheromone in *Bacillus subtilis*. J Bacteriol 2002;184:410–9. https://doi.org/10.1128/JB.184.2.410.
[93] Solomon J, Magnuson R, Srivastava A, Grossman A. Convergent sensing pathways mediate response to two extracellular competence factors in *Bacillus subtilis*. Genes Dev 1995;9:547–58.
[94] Nakano M, Xia L, Zuber P. Transcription initiation region of the srfA operon, which is controlled by the comP-comA signal transduction system in *Bacillus subtilis*. J Bacteriol 1991;173:5487–93.
[95] Nakano M, Zuber P. The primary role of comA in establishment of the competent state in *Bacillus subtilis* is to activate expression of srfA. J Bacteriol 1991;173:7269–74.
[96] Solomon J, Lazazzera B, Grossman A. Purification and characterization of an extracellular peptide factor that affects two different developmental pathways in *Bacillus subtilis*. Genes Dev 1996;10:2014–24.
[97] Core L, Perego M. TPR-mediated interaction of RapC with ComA inhibits response regulator-DNA binding for competence development in *Bacillus subtilis*. Mol Microbiol 2003;49:1509–22.
[98] Grossman A. Genetic networks controlling the initiation of sporulation and the development of genetic competence in *Bacillus subtilis*. Annu Rev Genet 1995;29:477–508.
[99] Perego M. A peptide export-import control circuit modulating bacterial development regulates protein phosphatases of the phosphorelay. Proc Natl Acad Sci USA 1997;94:8612–7.
[100] Clatworthy A, Pierson E, Hung DT. Targeting virulence: a new paradigm for antimicrobial therapy. Nat Chem Biol 2007;2:541–8.
[101] Bouayed N, Dietrich N, Lafforgue C, Lee C, Guigui C. Process-oriented review of bacterial quorum quenching for membrane biofouling mitigation in membrane bioreactors (MBRs). Membranes (Basel) 2016;6. https://doi.org/10.3390/membranes6040052.
[102] Hentzer M, Givskov M. Pharmacological inhibition of quorum sensing for the treatment of chronic bacterial infections. J Clin Invest 2003;112:1300–7. https://doi.org/10.1172/JCI200320074.One.
[103] Murray EJ, Crowley RC, Truman A, Clarke SR, Cottam JA, Jadhav GP, et al. Targeting *Staphylococcus aureus* quorum sensing with nonpeptidic small molecule inhibitors. J Med Chem 2014;57:2813–9. https://doi.org/10.1021/jm500215s.
[104] O'Loughlin CT, Miller LC, Siryaporn A, Drescher K, Semmelhack MF, Bassler BL. A quorum-sensing inhibitor blocks *Pseudomonas aeruginosa* virulence and biofilm formation. Proc Natl Acad Sci 2013;110:17981–6. https://doi.org/10.1073/pnas.1316981110.
[105] Ng WL, Perez L, Cong J, Semmelhack MF, Bassler BL. Broad spectrum pro-quorum-sensing molecules as inhibitors of virulence in vibrios. PLoS Pathog 2012;8.. https://doi.org/10.1371/journal.ppat.1002767.
[106] Hibbing M, Fuqua C, Parsek M, Peterson S. Bacterial competition: surviving and thriving in the microbial jungle. Nat Rev Microbiol 2010;8:15–25.
[107] Torres M, Uroz S, Salto R, Fauchery L, Quesada E, Llamas I. HqiA, a novel quorum-quenching enzyme which expands the AHL lactonase family. Sci Rep 2017;7:943. https://doi.org/10.1038/s41598-017-01176-7.
[108] Chen F, Gao Y, Chen X, Yu Z, Li X. Quorum quenching enzymes and their application in degrading signal molecules to block quorum sensing-dependent infection. Int J Mol Sci 2013;14:17477–500. https://doi.org/10.3390/ijms140917477.
[109] D'Angelo-Picard C, Faure D, Penot I, Dessaux Y. Diversity of N-acylhomoserine lactone-producing and -degrading bacteria in soil and tobacco rhizosphere. Environ Microbiol 2005;7:1796–808.
[110] Dong Y, Zhang L. Quorum sensing and quorum-quenching enzymes. J Microbiol 2005;43:101–9.
[111] Dong Y, Wang L, Xu J, Zhang H, Zhang X, Zhang L. Quenching quorum-sensing-dependent bacterial infection by an N-acyl homoserine lactonase. Nature 2001;411:813–7.
[112] Leadbetter J. Plant microbiology. Quieting the raucous crowd. Nature 2001;411:748–9.
[113] Wang LH, Weng LX, Dong YH, Zhang LH. Specificity and enzyme kinetics of the quorum-quenching N-acyl homoserine lactone lactonase (AHL-lactonase). J Biol Chem 2004;279:13645–51. https://doi.org/10.1074/jbc.M311194200.
[114] Tang K, Zhang XH. Quorum quenching agents: resources for antivirulence therapy. Mar Drugs 2014;12:3245–82. https://doi.org/10.3390/md12063245.
[115] Dong Y, Xu J, Li X, Zhang L. AiiA, an enzyme that inactivates the acylhomoserine lactone quorum-sensing signal and attenuates the virulence of Erwinia carotovora. Proc Natl Acad Sci USA 2000;97:3526–31.
[116] Dong Y, Gusti A, Zhang Q, Xu J, Zhang L. Identification of quorum-quenching N-acyl homoserine lactonases from Bacillus species. Appl Environ Microbiol 2002;68(1754):1759.
[117] Afriat L, Roodveldt C, Manco G, Tawfik D. The latent promiscuity of newly identified microbial lactonases is linked to a recently diverged phosphotriesterase. Biochemistry 2006;45:13677–86.
[118] Hawwa R, Aikens J, Turner R, Santarsiero B, Mesecar A. Structural basis for thermostability revealed through the identification and characterization of a highly thermostable phosphotriesterase-like lactonase from Geobacillus stearothermophilus. Arch Biochem Biophys 2009;488:109–20.
[119] Chow J, Xue B, Lee K, Tung A, Wu L, Robinson R, et al. Directed evolution of a thermostable quorum-quenching lactonase from the amidohydrolase superfamily. J Biol Chem 2010;285:40911–20.
[120] Seo M, Lee B, Pyun Y, Park H. Isolation and characterization of N-acylhomoserine lactonase from the thermophilic bacterium, Geobacillus caldoxylosilyticus YS-8. Biosci Biotechnol Biochem 2011;75:1789–95.

[121] Zhang H, Wang L, Zhang L. Genetic control of quorum-sensing signal turnover in *Agrobacterium tumefaciens*. Proc Natl Acad Sci USA 2002;99:4638–43.
[122] Park S, Lee S, Oh T, Oh J, Koo B, Yum D, et al. AhlD, an N-acylhomoserine lactonase in *Arthrobacter* sp., and predicted homologues in other bacteria. Microbiology 2003;149:1541–50.
[123] Mei G, Yan X, Turak A, Luo Z, Zhang L. AidH, an alpha/beta-hydrolase fold family member from an *Ochrobactrum* sp. strain, is a novel N-acylhomoserine lactonase. Appl Environ Microbiol 2010;76:4933–42.
[124] Wang W, Morohoshi T, Ikenoya M, Someya N, Ikeda T. AiiM, a novel class of N-acylhomoserine lactonase from the leaf-associated bacterium Microbacterium testaceum. Appl Environ Microbiol 2010;76:2524–30.
[125] Park S, Hwang B, Shin M, Kim J, Kim H, Lee J. N-acylhomoserine lactonase producing *Rhodococcus* spp. with different AHL-degrading activities. FEMS Microbiol Lett 2006;261:102–8.
[126] Momb J, Wang C, Liu D, Thomas P, Petsko G, Guo H, et al. Mechanism of the quorum-quenching lactonase (AiiA) from *Bacillus thuringiensis*. 2. Substrate modeling and active site mutations. Biochemistry 2008;47:7715–25.
[127] Kim M, Choi W, Kang H, Lee J, Kang B, Kim K, et al. The molecular structure and catalytic mechanism of a quorum-quenching N-acyl-L-homoserine lactone hydrolase. Proc Natl Acad Sci USA 2005;102:17606–11.
[128] Liu D, Lepore B, Petsko G, Thomas P, Stone E, Fast W, et al. Three-dimensional structure of the quorum-quenching N-acyl homoserine lactone hydrolase from *Bacillus thuringiensis*. Proc Natl Acad Sci USA 2005;102:11882–7.
[129] Leadbetter J, Greenberg E. Metabolism of acyl-homoserine lactone quorum-sensing signals by *Variovorax paradoxus*. J Bacteriol 2000;182:6921–6.
[130] Czajkowski R, Krzyżanowska D, Karczewska J, Atkinson S, Przysowa J, Lojkowska E, et al. Inactivation of AHLs by *Ochrobactrum* sp. A44 depends on the activity of a novel class of AHL acylase. Environ Microbiol Rep 2011;3:59–68.
[131] Czajkowski R, Jafra S. Quenching of acyl-homoserine lactone-dependent quorum sensing by enzymatic disruption of signal molecules. Acta Biochim Pol 2009;56:1–16.
[132] Park S, Kang H, Jang H, Lee J, Koo B, Yum D. Identification of extracellular N-acylhomoserine lactone acylase from a Streptomyces sp. and its application to quorum quenching. Appl Environ Microbiol 2005;71:2632–41.
[133] Lin Y, Xu J, Hu J, Wang L, Ong S, Leadbetter J, et al. Acyl-homoserine lactone acylase from Ralstonia strain XJ12B represents a novel and potent class of quorum-quenching enzymes. Mol Microbiol 2003;47:849–60.
[134] Shepherd R, Lindow S. Two dissimilar N-acyl-homoserine lactone acylases of *Pseudomonas syringae* influence colony and biofilm morphology. Appl Environ Microbiol 2009;75:45–53.
[135] Morohoshi T, Nakazawa S, Ebata A, Kato N, Ikeda T. Identification and characterization of N-acylhomoserine lactone-acylase from the fish intestinal *Shewanella* sp. strain MIB015. Biosci Biotechnol Biochem 2008;72:1887–93.
[136] Romero M, Avendaño-Herrera R, Magariños B, Cámara M, Otero A. Acylhomoserine lactone production and degradation by the fish pathogen Tenacibaculum maritimum, a member of the Cytophaga-Flavobacterium-Bacteroides (CFB) group. FEMS Microbiol Lett 2010;304:131–9.
[137] Uroz S, D'Angelo-Picard C, Carlier A, Elasri M, Sicot C, Petit A, et al. Novel bacteria degrading N-acylhomoserine lactones and their use as quenchers of quorum-sensing-regulated functions of plant-pathogenic bacteria. Microbiology 2003;149:1981–9.
[138] Kim Y, Yoon K, Khang Y, Turley S, Hol W. The 2.0 Å crystal structure of cephalosporin acylase. Structure 2000;8:1059–68.
[139] Uroz S, Chhabra S, Cámara M, Williams P, Oger P, Dessaux Y. N-acylhomoserine lactone quorum-sensing molecules are modified and degraded by *Rhodococcus erythropolis* W2 by both amidolytic and novel oxidoreductase activities. Microbiology 2005;151:3313–22.
[140] Chowdhary P, Keshavan N, Nguyen H, Peterson J, González J, Haines D. *Bacillus megaterium* CYP102A1 oxidation of acyl homoserine lactones and acyl homoserines. Biochemistry 2007;46:14429–37.
[141] Bijtenhoorn P, Mayerhofer H, Muller-Dieckmann J, Utpatel C, Schipper C, Hornung C, et al. A novel metagenomic short-chain dehydrogenase/reductase attenuates *Pseudomonas aeruginosa* biofilm formation and virulence on *Caenorhabditis elegans*. PLoS One 2011;6:e26278.
[142] Chang C. Inhibiting N-acyl-homoserine lactone synthesis and quenching Pseudomonas quinolone quorum sensing to attenuate virulence. Front Microbiol 2015;6:1–7. https://doi.org/10.3389/fmicb.2015.01173.
[143] Teasdale M, Liu J, Wallace J, Akhlaghi F, Rowley D. Secondary metabolites produced by the marine bacterium *Halobacillus salinus* that inhibit quorum sensing-controlled phenotypes in Gram-negative bacteria. Appl Environ Microbiol 2009;75:567–72.
[144] Teasdale M, Donovan K, Forschner-Dancause S, Rowley D. Gram-positive marine bacteria as a potential resource for the discovery of quorum sensing inhibitors. Biotechnol 2011;13:722–32.
[145] Li J, Wang W, Xu S, Magarvey N, McCormick J. *Lactobacillus reuteri*-produced cyclic dipeptides quench agr-mediated expression of toxic shock syndrome toxin-1 in staphylococci. Proc Natl Acad Sci USA 2011;108:3360–5.
[146] Chu Y, Nega M, Wolfle M, Plener L, Grond S, Jung K, et al. A new class of quorum quenching molecules from Staphylococcus species affects communication and growth of Gram-negative bacteria. PLoS Pathog 2013;9:e1003654.
[147] Singh V, Kavita K, Prabhakaran R, Jha B. Cis-9-octadecenoic acid from the rhizospheric bacterium *Stenotrophomonas maltophilia* BJ01 shows quorum quenching and anti-biofilm activities. Biofouling 2013;29:855–67.
[148] Clark B, Engene N, Teasdale M, Rowley D, Matainaho T, Valeriote F, et al. Natural products chemistry and taxonomy of the marine cyanobacterium *Blennothrix cantharidosmum*. J Nat Prod 2008;71:1530–7.
[149] Dobretsov S, Teplitski M, Alagely A, Gunasekera S, Paul V. Malyngolide from the cyanobacterium *Lyngbya majuscula* interferes with quorum sensing circuitry. Environ Microbiol Rep 2010;2:739–44.
[150] Kwan J, Teplitski M, Gunasekera S, Paul V, Luesch H. Isolation and biological evaluation of 8-epi-malyngamide C from the Floridian marine cyanobacterium *Lyngbya majuscula*. J Nat Prod 2010;73:463–6.
[151] Kwan J, Meickle T, Ladwa D, Teplitski M, Paul V, Luesch H. Lyngbyoic acid, a "tagged" fatty acid from a marine cyanobacterium, disrupts quorum sensing in *Pseudomonas aeruginosa*. Mol Biosyst 2011;7:1205–16.
[152] Choi H, Mascuch S, Villa F, Byrum T, Teasdale M, Smith J, et al. Honaucins A-C, potent inhibitors of inflammation and bacterial quorum sensing: synthetic derivatives and structure-activity relationships. Chem Biol 2012;19:589–98.
[153] Rasmussen TB, Skindersoe ME, Bjarnsholt T, Phipps RK, Christensen KB, Jensen PO, et al. Identity and effects of quorum-sensing inhibitors produced by Penicillium species. Microbiology 2005;151:1325–40. https://doi.org/10.1099/mic.0.27715-0.
[154] Cugini C, Calfee MW, Farrow JM, Morales DK, Pesci EC, Hogan DA. Farnesol, a common sesquiterpene, inhibits PQS production in *Pseudomonas aeruginosa*. Mol Microbiol 2007;65:896–906. https://doi.org/10.1111/j.1365-2958.2007.05840.x.
[155] Nakayama J, Uemura Y, Nishiguchi K, Yoshimura N, Igarashi Y, Sonomoto K. Ambuic acid inhibits the biosynthesis of cyclic peptide quormones in gram-positive bacteria. Antimicrob Agents Chemother 2009;53:580–6. https://doi.org/10.1128/AAC.00995-08.
[156] Dobretsov S, Teplitski M, Bayer M, Gunasekera S, Proksch P, Paul VJ. Inhibition of marine biofouling by bacterial quorum sensing inhibitors. Biofouling 2011;27:893–905. https://doi.org/10.1080/08927014.2011.609616. Inhibition.
[157] Figueroa M, Jarmusch AK, Raja HA, El-Elimat T, Kavanaugh JS, Horswill AR, et al. Polyhydroxyanthraquinones as quorum sensing inhibitors from the guttates of *Penicillium restrictum* and their analysis by desorption electrospray ionization mass spectrometry. J Nat Prod 2014;77:1351–8. https://doi.org/10.1021/np5000704.
[158] Martín-Rodríguez AJ, Reyes F, Martín J, Pérez-Yépez J, León-Barrios M, Couttolenc A, et al. Inhibition of bacterial quorum sensing by extracts from aquatic fungi: first report from marine endophytes. Mar Drugs 2014;12:5503–26. https://doi.org/10.3390/md12115503.
[159] Truchado P, Lopez-Galvez F, Gil M, Tomas-Barberan F, Allende A. Quorum sensing inhibitory and antimicrobial activities of honeys and the relationship with individual phenolics. Food Chem 2009;115:1337–44.
[160] Bulman Z, Le P, Hudson A, Savka M. A novel property of propolis (bee glue): anti-pathogenic activity by inhibition of N-acyl-homoserine lactone mediated signaling in bacteria. J Ethnopharmacol 2011;138:788–97.
[161] Park J, Kaufmann G, Bowen J, Arbiser J, Janda K, Solenopsin A. a venom alkaloid from the fire ant *Solenopsis invicta*, inhibits quorum-sensing signaling in *Pseudomonas aeruginosa*. J Infect Dis 2008;198:1198–201.
[162] Tello E, Castellanos L, Arevalo-Ferro C, Duque C. Disruption in quorum-sensing systems and bacterial biofilm inhibition by cembranoid diterpenes isolated from the octocoral *Eunicea knighti*. J Nat Prod 2012;75:1637–42.
[163] Kaplan F, Badri D, Zachariah C, Ajredini R, Sandoval F, Roje S, et al. Bacterial attraction and quorum sensing inhibition in *Caenorhabditis elegans* exudates. J Chem Ecol 2009;35:878–92.
[164] Skindersoe M, Ettinger-Epstein P, Rasmussen T, Bjarnsholt T, de Nys R, Givskov M. Quorum sensing antagonism from marine organisms. Biotechnol (NY) 2008;10:56–63.
[165] Keshavan N, Chowdhary P, Haines D, Gonzalez J. L-canavanine made by *Medicago sativa* interferes with quorum sensing in *Sinorhizobium meliloti*. J Bacteriol 2005;187:8427–36.
[166] Kiran M, Adikesavan N, Cirioni O, Giacometti A, Silvestri C, Scalise G, et al. Discovery of a quorum-sensing inhibitor of drug-resistant staphylococcal infections by structure-based virtual screening. Mol Pharmacol 2008;73:1578–86.
[167] Vandeputte O, Kiendrebeogo M, Rajaonson S, Diallo B. Identification of catechin as one of the flavonoids from *Combretum albiflorum* bark extract that reduces the production of quorum-sensing-controlled virulence factors in *Pseudomonas aeruginosa* PAO1. Environ Microbiol 2010:243–53.
[168] Chong Y, Yin W, Ho C, Mustafa M, Hadi A, Awang K, et al. Malabaricone C from *Myristica cinnamomea* exhibits anti-quorum sensing activity. J Nat Prod 2011;74:2261–4.
[169] Packiavathy I, Priya S, Pandian S, Ravi A. Inhibition of biofilm development of uropathogens by curcumin-an anti-quorum sensing agent from *Curcuma longa*. Food Chem 2014;148:453–60.
[170] Akyuz L, Kaya M, Ilk S, Cakmak YS, Salaberria AM, Labidi J, et al. Effect of different animal fat and plant oil additives on physicochemical, mechanical, antimicrobial and antioxidant properties of chitosan films. Int J Biol Macromol 2018;111:475–84. https://doi.org/10.1016/j.ijbiomac.2018.01.045.
[171] Kaya M, Ravikumar P, Ilk S, Mujtaba M, Akyuz L, Labidi J, et al. Production and characterization of chitosan based edible films from Berberis crataegina's fruit extract and seed oil. Innov Food Sci Emerg Technol 2018;45:287–97. https://doi.org/10.1016/j.ifset.2017.11.013.

[172] Fray RG. Altering plant-microbe interaction through artificially manipulating bacterial quorum sensing. Ann Bot 2002;89:245–53. https://doi.org/10.1093/aob/mcf039.
[173] Fray R, Throup J, Daykin M, Wallace A, Williams P, Stewart G, et al. Plants genetically modified to produce N-acylhomoserine lactones communicate with bacteria. Nat Biotechnol 1999;17:1017–20. https://doi.org/10.1038/13717.
[174] Toth I, Newton J, Hyman L, Lees A, Daykin M, Ortori C, et al. Potato plants genetically modified to produce N-acylhomoserine lactones increase susceptibility to soft rot erwiniae. Mol Plant Microbe Interact 2004;17:880–7.
[175] Jafra S, Przysowa J, Czajkowski R, Michta A, Garbeva P, van der Wolf J. Detection and characterization of bacteria from the potato rhizosphere degrading N-acyl-homoserine lactone. Can J Microbiol 2006;52:1006–15.
[176] Grandclément C, Tannières M, Moréra S, Dessaux Y, Faure D. Quorum quenching: role in nature and applied developments. FEMS Microbiol Rev 2015;40:86–116. https://doi.org/10.1093/femsre/fuv038.
[177] Yeon K, Cheong W, Oh H, Lee W, Hwang B, Lee C, et al. Quorum sensing: a new biofouling control paradigm in a membrane bioreactor for advanced wastewater treatment. Environ Sci Technol 2009;43:380–5.
[178] Bassler BL. Small talk: cell-to-cell communication in bacteria. Cell 2002;109:421–4. https://doi.org/10.1016/S0092-8674(02)00749-3.
[179] LaSarre B, Federle MJ. Exploiting quorum sensing to confuse bacterial pathogens. Microbiol Mol Biol Rev 2013;77:73–111. https://doi.org/10.1128/MMBR.00046-12.
[180] Wynendaele E, Bronselaer A, Nielandt J, Hondt MD, Stalmans S, Bracke N, et al. Quorumpeps database: chemical space, microbial origin and functionality of quorum sensing peptides. Nucleic Acids Res 2018;41:655–9. https://doi.org/10.1093/nar/gks1137.
[181] Rajput A, Kaur K, Kumar M. SigMol: repertoire of quorum sensing signaling molecules in prokaryotes. Nucleic Acids Res 2016;44:634–9. https://doi.org/10.1093/nar/gkv1076.