Chapter 4

Quorum Sensing in Gram-Negative Plant Pathogenic Bacteria

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Abstract

Plant pathogenic bacteria regulate expression of specific genes through quorum sensing (QS). Some bacteria encode a single or more than one QS system while others encode a single LuxI and two or more LuxR homologs. Not all plant pathogenic bacteria encode the LuxI and in these situations the LuxR modulates cell behavior in a cell density manner by utilizing signal molecules that are produced by their plant hosts. The advantage of having more than one system is still not well understood. However, it has been speculated that it is essential for regulation of QS traits in different environmental conditions. Quorum sensing systems in plant pathogenic bacteria include those that use acyl homoserine lactones, 3-hydroxy palmitic acid methyl ester or methyl 3-hydroxypalmitate, virulence factor modulation genes and diffusible signal factors. This chapter discusses the various QS systems in Gram-negative plant pathogenic bacteria, notably those listed as the top 10 plant pathogenic bacteria that cause significant reduction in yields and inflict economic losses in agriculture. In addition, it explores the various biological processes influenced by QS and the extent of QS regulons in these bacteria.

Keywords: plant pathogenic bacteria, quorum sensing, signal molecules, QS regulon, inter kingdom signaling

1. Introduction

Bacteria are able to adapt to constantly changing environmental conditions by altering expression of genes that are crucial for fitness, adaptation and survival [1]. Some environmental changes encountered by bacteria include temperature, pH, osmolarity and nutrients availability [2]. Such environmental changes encountered by bacteria are best dealt with by

a group effort instead of by individual cells [3]. Most bacteria thus respond to fluctuations in both biotic and abiotic environments by altering gene expression in a process termed quorum sensing (QS). Quorum sensing refers to a process where bacteria accumulate, detect and respond to small diffusible communication signals called autoinducers [3]. The amount of signal molecules is directly proportional to the population cell density of the signal-producing bacteria [2]. Quorum sensing results in communication between cells in a population and leads to simultaneous coordinated behavior within a population [3].

The sequencing of genomes of plant pathogenic bacteria coupled with research on pathogenicity factors in different bacteria has revealed the involvement of QS in the regulation of virulence genes. The role of various QS systems is related to several phenotypes, and has been described (for examples see [4–24]) using methods such as site-directed mutagenesis or transposon mutagenesis. However, these methods fall short of clearly showing the biological pathways or genes that influence the observed QS phenotypes. One method used to circumvent this limitation is to determine the entire regulon controlled by QS using several techniques such as microarrays and RNA-Seq. These studies have unraveled the genes under the control of QS in several bacteria. This chapter focuses mainly on QS systems found in Gram-negative plant pathogenic bacteria, notably those listed as the top 10 most significant plant pathogenic bacteria [25]. In addition, it will explore the various biological processes in bacteria that are influenced by QS and highlight the difference in the size of the QS regulon for the different systems going from only a few genes to 26% of the transcriptome as exemplified by the *in planta* QS regulon of *Pectobacterium atrosepticum* (*Pa*) [26].

2. Overview of QS in the top 10 plant pathogenic bacteria

Plant pathogenic bacteria cause a reduction in yields and inflict economic losses in agriculture [25]. The key to a successful plant infection is regulation of pathogenicity traits. Plant pathogenic bacteria regulate expression of specific genes through QS. The major QS signals that have been characterized in plant pathogenic bacteria include acyl homoserine lactones (AHLs) and diffusible signal factor (DSF). Some plant pathogenic bacteria have a single QS system while others have more than one QS system. The advantage of having more than one QS system is still not well understood. However, it has been speculated that this could be beneficial for the regulation of QS traits in different environmental conditions [4]. Moreover, some plant pathogenic bacteria have been found to modulate their behavior in a cell density manner by utilizing some signal molecules that are produced by their plant hosts [5, 8, 27, 28].

The LuxI/R QS (depicted in **Figure 1**) has been extensively studied in a large number of Gram-negative plant pathogenic bacteria. This system regulates expression of various genes (i.e. for example see [9–11, 26, 29–34]). Bacteria encode one or more AHL synthases and one or more protein receptor molecules (discussed below). It was thought that in mixed populations, each bacterial species detects and responds to its specific AHL molecule [3]. However, there is evidence of inter-specific signaling that is the basis of the detection of AHL production by *Chromobacterium violaceum* 026 bio reporter [7]. Notably, the LuxI/R QS in plant pathogenic bacteria is species specific, for example, QS target genes differ in different *Pectobacterium* QS systems [12, 35] and the SolI/R QS plays no role in pathogenicity of *Ralstonia* [36, 37].

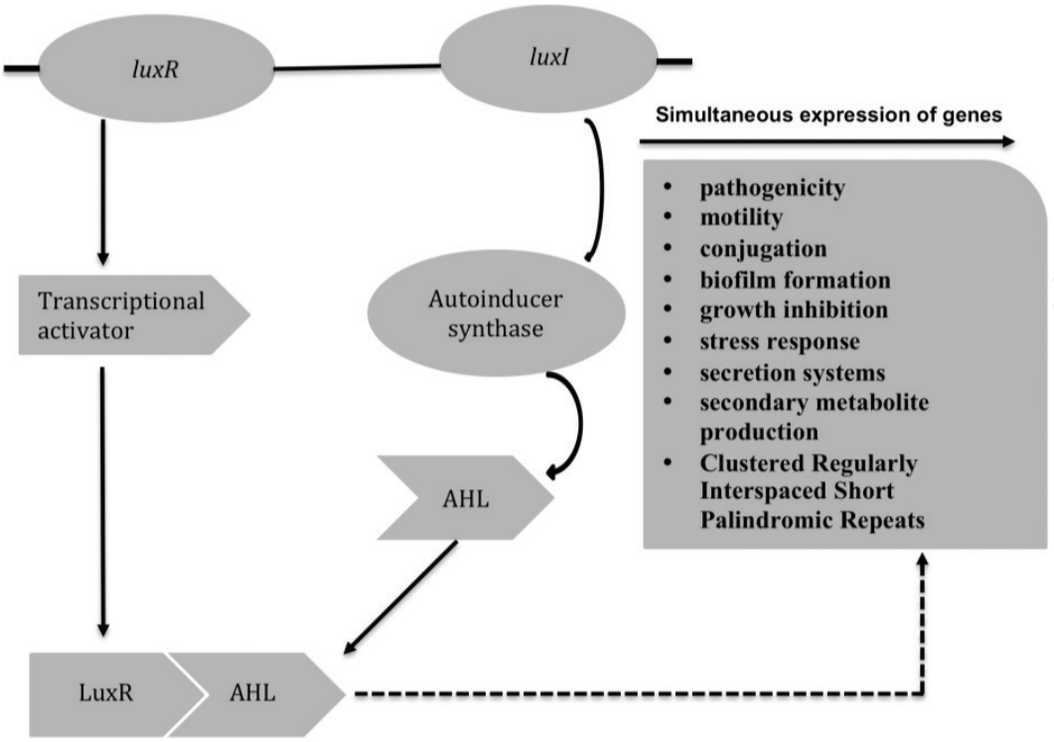

Figure 1. A schematic presentation of the LuxI/R quorum sensing system in Gram-negative bacteria. LuxI encodes an acyl homoserine lactone (AHL) synthase whereas LuxR encodes a protein receptor molecule. The AHL binds to the protein receptor molecule, the complex then binds to specific promoters and trigger multiple gene expression. The traits that are regulated by this system include pathogenicity, production of secondary metabolites, motility, secretion systems, stress response, conjugation, growth inhibition, biofilm formation and clustered regularly interspaced short Palindromic repeats (CRISPR-Cas).

2.1. QS systems in *Pectobacterium carotovorum* and *Pectobacterium atrosepticum*

Plant pathogenic bacteria belonging to the genus *Pectobacterium* cause soft rot and blackleg disease in economically important plants. The best studied *Pectobacterium* species include *carotovorum* subsp. *carotovorum (Pcc),* subsp. *brasiliense (Pcb)* and *Pa. Pectobacteria* are often called brute force pathogens due to their mode of host infection [26] i.e. the release of plant cell wall degrading enzymes (PCWDE) such as pectinases, polygalacturonases and cellulases that rupture the plant tissues during infection and cause rotting [38]. The precise timing for release of PCWDE is crucial for a successful infection [31]. Plant cell wall hydrolyzing enzymes help degrade the cell wall barrier in plants and thus facilitate entrance and spread of a pathogen in the host tissue.

Pectobacterium strains encode one LuxI homolog and two or more LuxR homologs. In *Pcc* there are three LuxR homologs, namely, CarR [39], ExpR [12] and VirR [35]. Each LuxR homolog in *Pectobacterium* plays an essential role. In contrast to CarR that regulates synthesis of antibiotics, the ExpR and VirR are involved in regulation of production of PCWDE [12, 35]. *Pectobacterium* spp. produces either one or two major AHL compounds and minute amounts of other AHL molecules depending on the species and strain [40]. The AHL synthases in *Pectobacterium* strains include the ExpI in *Pcc* SCC3193 [13, 14], *Pcc* SCR1193 [30], *Pcc* SCR11043 [15, 41], the AhlI in *Pcc* EC153 and *Pcc* 71 [15, 16, 35] and the CarI in *Pcc* ATCC390048 [35].

Secretion systems in bacteria are essential for transportation of effectors that are important for pathogenicity [42]. A transcriptomics study showed that AHL dependent QS regulate 26% of the entire transcriptome in *Pa* [26], representing the largest QS regulon in a plant pathogenic bacterium. In addition, it regulates Type 3 secretion system (T3SS) and a Type 6 secretion system (T6SS) in *Pa* [26]. The T6SS has been shown to transport proteins directly to target organism through direct cell–cell contact [43] and this secretion system has been implicated in bacterial competition [44]. The LuxI/R QS also regulates Type 1 (T1SS) and Type 2 (T2SS) secretion systems in *Pa* that are responsible for secretion of PCWDE [26]. In *Pcb*, QS is important for pathogenicity, production of PCWDE and cell aggregation in xylem tissues [17].

In *Pectobacterium* spp., QS regulates production of an antibiotic called carbapenem [39, 45]. Antibiotics give *Pcc* a competitive advantage over other bacteria coexisting during infection [46]. It is important to note that QS regulates motility in *Pcc* [11] and *Pcb* [17] and a cluster of genes for amino acids metabolism i.e. *ilvGMEDA*, *ilvIH*, *ilvBN* and *leuABCD*, signal transduction and lipid metabolism in *Pa* [18] Furthermore, the *xylAB* and *xylFGH* operons for xylose/xylulose metabolism as well as genes for anaerobic formate metabolism and operons for assimilation of hydrogen (*hyp* and *hyb*) are influenced by QS in *Pa* [18]. Notably, QS could help strike a balance in metabolism and nutrient acquisition by individual cells thus ensuring co-operative group activity (i.e. see [47]). Thus, QS regulation of metabolic processes is important for efficient utilization of resources by bacteria in a population.

2.2. QS in *Erwinia amylovora*

In some plant pathogenic bacteria, one LuxI/R QS system is encoded in the genome, for example the EamI/R in *E. amylovora* [34, 48]. *Erwinia amylovora* is a destructive plant pathogen that causes fire blight disease. The AHL-dependent QS system in *E. amylovora* regulates pathogenicity, exopolysaccharides production and tolerance to oxidative stress in this bacterium [34]. It is noteworthy that a unique QS system, namely LuxS was reported in this bacterium. Initial reports suggested that LuxS is restricted to metabolism and is not important for QS in *E. amylovora* [49, 50]. This bacterium is the only plant pathogenic bacterium in which the involvement of LuxS/autoinducer 2 QS signaling has been shown to regulate pathogenicity and pathogenicity traits [51]. However, contradictory reports on the role of the autoinducer 2 signaling in *E. amylovora* leaves gaps on the information available for QS in this plant pathogen. Determination of the entire QS regulon/s of this bacterium could help bring a better understanding of its QS systems.

2.3. QS in *Pantoea stewartii* subsp. *stewartii*

Another example of a plant pathogenic bacteria that encode more than one LuxR homolog, is *P. stewartii subsp. stewartii.* This bacterium encodes the *EsaR* [19, 52] and an additional LuxR homolog, the *sdiA* [53, 54]. Furthermore, one LuxI homolog that was designated as EsaI is encoded in this bacterium [19, 52]. The AHL QS regulates transcription of other transcriptional regulators for example the **r**egulation of **c**apsule **s**ynthesis A (RcsA) and **L**ys**R** **h**omolog **A** (LrhA), which influences exopolysaccharides (EPS) production and motility, respectively in *P. stewartii subsp. stewartii* [55]. The QS regulon in *P. stewartii subsp. stewartii* represents almost 8% of the entire genome [33]. A transcriptome study showed that QS regulates several stress

response genes in *P. stewartii subsp. stewartii* (see [33, 56]). The universal stress protein (Usp) is important for bacterial survival in adverse environmental conditions, for examples of such conditions, see [57]. Importantly, QS regulates EPS production in *P. stewartii* subsp. *stewartii* [52]. This EPS, also called sterwartan, plays a role in cell attachment and is an important constituent of biofilms in this bacterium [52]. In some plant pathogens, biofilm formation is a direct pathogenicity factor. In Stewart's wilt disease, biofilms clog the xylem vessels causing the wilt [52].

2.4. QS in *Dickeya dadantii* and *D. solani*

An AHL-dependent QS system, namely ExpI/R, is encoded in the genomes of *Dickeya solani* and *D. dadantii*. There are differences in the role played by the ExpI/R system in pathogenicity of different strains of *Dickeya.* For example, this system regulates production of protease and motility (swarming and swimming) in *D. solani* strains [58]. On the other hand, it plays no role in production of cell wall degrading enzymes, motility and pathogenicity of *D. dadantii* 3937 [59, 60]. Contrary, the ExpI/R was found to regulate pathogenicity in *D. dadantii* 3937 on potato tubers [58]. Furthermore, it was showed that the strength of AHL QS systems is strain specific in *Dickeya* spp., i.e. the effects of ExpI/R mutation were more pronounced in *D. solani* than in *D. dadantii* [20] indicating that this system regulates pathogenicity in *D. dadantii*. Together these findings may suggest that the regulation of pathogenicity by ExpI/R QS system in *D. dadantii* is host specific, strain specific and/or could be dependent on the experimental conditions used. Nonetheless, this leaves unanswered questions.

A QS system that differs from all QS systems described thus far in plant pathogenic bacteria was identified in *Dickeya* spp. This unique system (schematic presentation in **Figure 2**) makes use of **v**irulence **f**actor **m**odulating (*vfm*) [21]. This QS system directly regulates pathogenesis factors including production of PCWDEs in *Dickeya dadantii* and *Dickeya solani* [20, 21]. Mutation and characterization of *vfmA*, *vfmE*, *vfmH*, *vfmI* and *vfmK* suggested that all *vfm* gene transcripts are important for regulation of pathogenicity in *D. solani* [20]. Furthermore, there are variations in the degree of regulation of pathogenicity factors by VFM system in different *Dickeya* strains [20]. The VFM system is repressed by PecS, a global regulator of pathogenicity in *Dickeya* spp. [61] while ExpI/R and VFM QS systems do not work in synergy in modulating QS dependent traits [55]. Certainly, elucidation of the VFM QS regulon could help uncover many aspects of this QS system in *Dickeya* spp. that are not yet understood.

2.5. QS in *Pseudomonas syringae* subsp. *syringae* (Pss)

Pseudomonas syringae encodes a single LuxI homolog, designated AhlI [62] and four LuxR homologs, namely, AhlR [32], SalA, SyrF and SyrG [9, 29]. The AhlI/R QS system in *Pseudomonas syringae* subsp. *syringae* (*Pss*) is subject to modulation by other regulatory proteins. For example, **A**HL and **e**piphytic **f**itness **r**egulator (AefR), a novel regulatory protein and GacA influence the transcription of the AHL synthase gene, *ahlI* in *Pss* [63]. Most QS regulated processes in *Pss* are associated with epiphytic fitness and plant infection [32]. In addition, QS regulates motility in *P. syringae* [32]. Notably, in *Pss*, alginate production is regulated by the AhlI/R system that is in turn influenced by the GacS/GacA two component system [64].

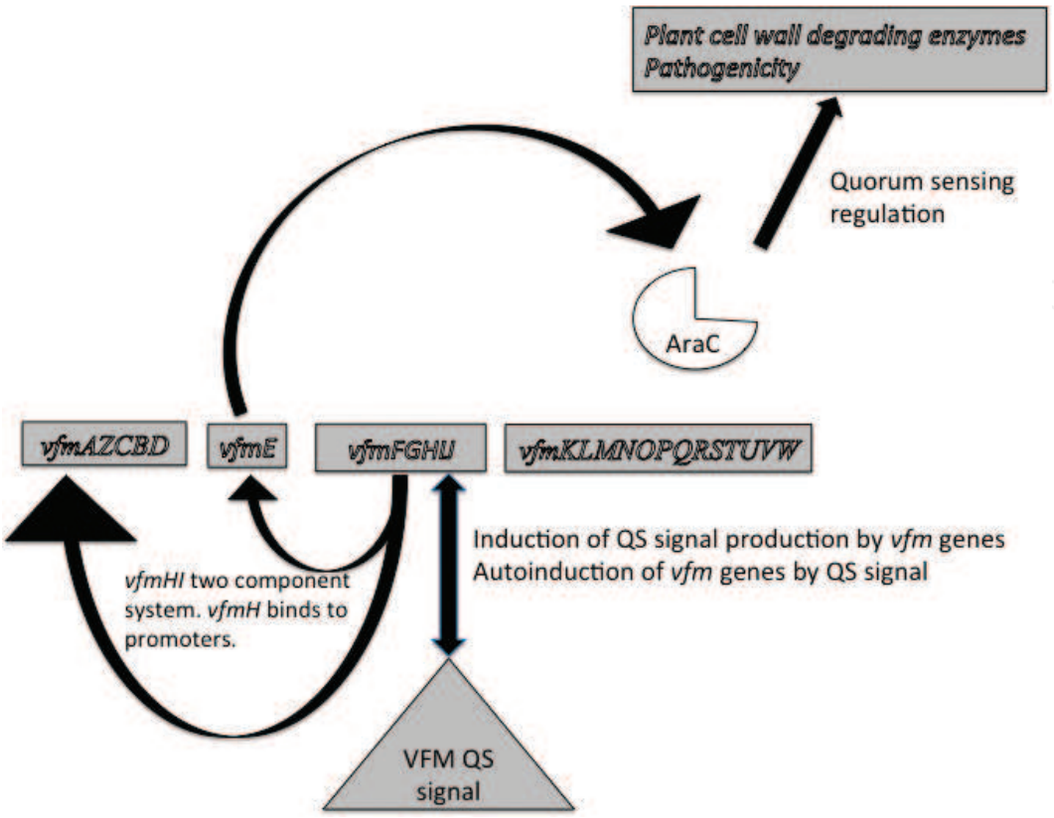

Figure 2. A schematic presentation of the VFM quorum sensing system in *Dickeya* spp. this QS system is made up of four gene transcripts, *vfmAZCBD*, *vfmE*, *vfmFGHIJ*, and *vfmKLMNOPQRSTUVW*. The *vfm* genes encode for the VFM QS signal, production of this QS signal results in auto induction of *vfm* genes. The *vfmHI* genes make up a two-component system where *vfmI* is a histidine kinase and VfmH binds to promoters of the *vfmAZCBD* and *vfmE* kinase. This results in activation of production of a transcriptional activator, AraC (encoded by *vfmE*) and regulation of specific phenotypes. Phenotypes regulated by the VFM QS include production of plant cell wall degrading enzymes and pathogenicity.

In *Pss*, the production of syringomycin and syringopeptin is regulated by LuxR homologs SalA and SyrF and SyrG, respectively [9, 29]. Phytotoxins produced by *P. syringae* cause chlorosis in plants and attenuated the pathogenicity of this bacterium [65–67]. Contrary to other plant pathogenic bacteria, the LuxI/R QS regulon of *Pss* was found to be very small, it is made up of about nine genes [68, 69] both in planta and *in vitro*. The AhlI/R QS regulon is composed of genes important for pyruvate metabolism and response to stress [68].

2.6. QS in *Agrobacterium tumefaciens*

Some plant pathogenic bacteria encode more than one LuxI homologs that are paired with their cognate LuxR. Typical examples include the TraI/TraR and TraI2/TraR2 in *A. tumefaciens*. Interestingly, the AHL QS system in *A. tumefaciens* differs from the model QS system based on *Vibrio* spp. This AHL dependent QS system is encoded on the Ti plasmid of *A. tumefaciens*. Quorum sensing regulates expression of type 4 secretion system (T4SS) [70] as well as conjugation [70, 71] and amplification of Ti plasmid in *A. tumefaciens* [72]. The TraI/R system depends on the expression of TraM whose transcription is indirectly regulated by QS. TraM binds to TraR forming an inactive complex, this helps prevent plasmid transfer before the optimal

cell densities for QS are reached [73]. A second QS system named TraI2/TraR2 was identified in *A. tumefaciens* [74]. This system also makes use of a TraR2 inactivator called TraM2. This second QS system in *A. tumefaciens* was postulated to play a redundant role in conjugation and replication of the Ti plasmid. The QS regulon was identified in *A. tumefaciens* strain P4, though this strain is non-pathogenic and outside the scope of this chapter, it is noteworthy that the QS regulon in this bacterium was found to constitute 32 genes [70]. Most genes in the QS regulon were those associated with conjugative transfer.

2.7. QS in *Ralstonia solanacearum*/*R. pseudosolanacearum*

Another plant pathogenic bacterium with two LuxI/R homologs is *R. solanacearum*/*R. pseudosolanacearum.* One of these LuxI/R homologs, the SolI/R system has been characterized. The SolI/R system is required for production of C6-HSL and C8-HSL in *R. solanacearum*/*R. pseudosolanacearum.* However, this QS system does not influence pathogenicity traits [36, 37]. To date, only three genes, *aidA, lecM* and *aidC,* have been reported to be influenced by *solI*/*R* [37]. The *aidA* and *aidC* genes encode proteins that have not yet been functionally characterized while *lecM* encode a mannose-fucose binding lectin. The physiological role of the LuxI/R QS systems in *R. solanacearum*/*R. pseudosolanacearum* still needs further investigation.

As the list of bacteria that employ QS for signaling increases, so does the list of new QS signaling systems. For example, *Ralstonia solanacearum*/*R. pseudosolanacearum* makes use of **ph**enotype **c**onversion (Phc) regulatory system [75] for signaling (simplified schematic diagram depicted in **Figure 3**). Phc is a LysR type transcriptional regular that makes use of 3-OH palmitic acid methyl ester (3-OH PAME) or methyl 3-hydroxypalmitate (3-OH MAME) (depending on the *R. solanacearum*/*R. pseudosolanacearum* strain) as a signal molecule [37, 76]. This system regulates pathogenicity traits such as exoenzyme production, exopolysaccharide synthesis [77], motility [78], siderophore production [79], production of phytotoxic ralstonins [80] and aryl furanones [81]. The aryl furanones are directly involved in QS signaling [81], biofilm formation [22] and pathogenicity [82]. The Phc in *R. solanacearum*/*R. pseudosolanacearum* regulates the expression of AHL dependent QS system, SolI/R mentioned above [75]. The Phc QS regulon in *R. solanacearum*/*R. pseudosolanacearum* constitutes a total of 620 (12% of the whole genome) genes [83]. Transcriptome profiling showed that this system influenced many genes associated with various metabolic pathways, transport systems, growth, several adhesins, attachment, dispersal and morphology of bacterial cells [83].

2.8. *Burkholderia glumae* quorum sensing

Bacteria belonging to the genus *Burkholderia* are not listed in the top 10 plant pathogenic bacteria. *Burkholderia glumae* was included in this chapter due to interesting findings in its QS regulon, an addition to the list of traits regulated by LuxI/R. *Burkholderia* spp. are characterized by multiple AHLs QS systems and additional LuxR homologs [84]. *Burkholderia glumae* causes grain rot in rice and inflicts serious yield losses internationally [85]. Within *Burkholderia* the LuxI/R QS system has been best studied in *B. glumae*, where this system has been named the TofI/R system [23]. The AHL QS regulon of three QS systems namely BGI1, BGI2 and BGI3 in *B. glumae* constituted 11.5% of the whole transcriptome [86]. Also of note, is the QS regulation of flagella biosynthesis and

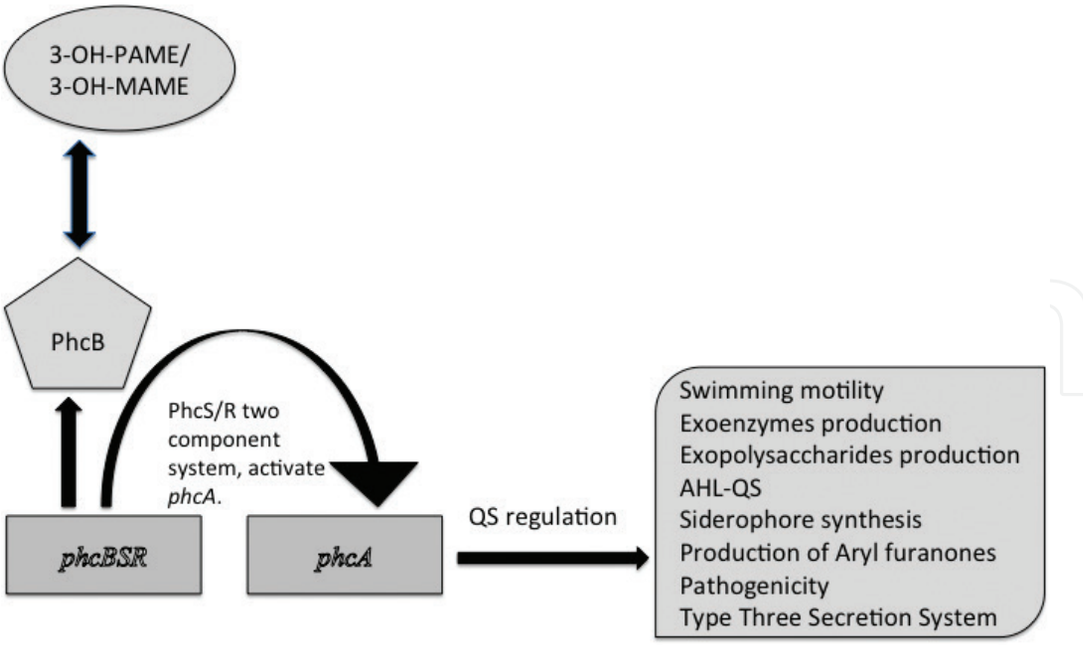

Figure 3. The phenotype conversion (Phc) quorum sensing system is encoded by the *phcA* and the *phcBSR* operon. The PhcB is a putative methyltransferase that catalysis the production of the QS signal molecule, 3-OH-PAME or 3-OH-MAME depending on strain. The PhcS/PhcR constitute a two-component system where PhcS, a histidine kinase phosphorylates PhcR. The phosphorylated PhcR responds to the presence of the QS signal and derepress PhcA resulting in elevated levels of functional PhcA at high cell densities. Phenotypes regulated by this system include swimming motility, exoenzymes production, exopolysaccharides production, acyl homoserine lactone dependent quorum sensing, siderophore synthesis, production of aryl furanones, pathogenicity and type three secretion system (T3SS).

swarming motility in *B. glumae* [87–89] and QS regulation of toxin biosynthesis, the phytotoxic toxoflavin [86, 90] an important pathogenicity factor in *B. glumae* [91]. Quorum sensing also regulates the Usp in *B. glumae* [92]. The Usp in *B. glumae* is important for surviving adverse temperatures [92]. Quorum sensing has also been reported to regulate metabolic pathways, for example, in *B. glumae* BG1. A transcriptome analysis *in vitro* showed that about 40% of the QS regulon in *B. glumae* BG1 is made up of genes for metabolic activities [86]. In addition, transcriptome analysis showed for the first time that QS influences the (CRISPR-Cas) associated proteins in *B. glumae* BG1 [86]. Given the biological role of the CRISPR-Cas system (see [93–99]), it is thus not surprising that this system has been found to be regulated by QS in a plant pathogenic bacterium.

2.9. QS in *Xanthomonas oryzae pv. oryzae*

Xanthomonas oryzae pv. *oryzae (Xoo)* causes bacterial leaf blight, one of the most destructive diseases, in rice. This bacterium does not produce AHLs. Its genome encodes a LuxR homolog called OryR [5]. The OryR protein has been found to impact pathogenicity of this pathogen [27]. Unlike LuxR proteins in other bacteria, the OryR does not bind to AHLs but binds to a yet to be identified diffusible plant molecule that acts as a QS signal [5]. The production of these plant signal molecules increases when a plant is infected. A schematic presentation of interkingdom QS signaling is shown in **Figure 4**. A transcriptomic study showed that OryR regulates 330 genes in *Xoo*, the majority of which influenced flagella and motility [100]. This is essential for movement, spread, colonization of host tissues and pathogenicity. Like in other LuxR that are without their LuxI (discussed below), the OryR regulates proline–imino-peptidase (*pip*) expression [100].

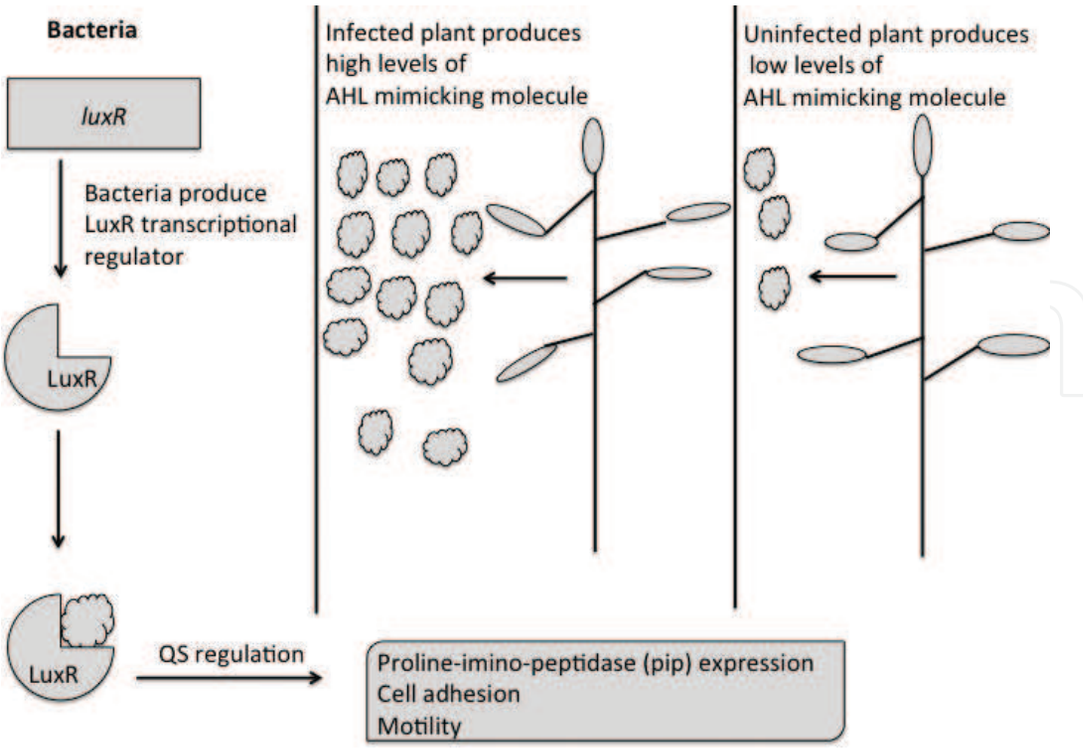

Figure 4. The LuxR in some plant pathogenic bacteria respond to acyl homoserine lactone (AHL) mimicking molecules produced by plants. The production of AHL mimicking molecules increases when a plant gets infected. These molecules bind to the LuxR in bacteria and trigger quorum sensing gene regulation of proline-imino-peptidase (pip) expression, cell adhesion and motility.

The second QS system in *Xoo* is the *DSF (*cis-11-methyl-2-dodecenoic acid) dependent QS [101]. The genes for biosynthesis and signaling of DSF are encoded on the **r**egulation of **p**athogenicity **f**actors (*rpfABCDEFG*) genes and the major catalyst in DSF production is RpfF [102]. The Rpf elements involved in DSF signaling are those that are part of the two- component system RpfCG. In this QS system, the DFS QS modulates the levels of second messenger cyclic di-GMP (see **Figure 5** for a schematic diagram of this QS system). At low cell density, the RpfG is inactive, the cyclic di-GMP levels are high while RpfC binds to RpfF and reduces its catalytic activity. Consequently, at low cell densities the cyclic di-GMP binds to the transcriptional activator, a cyclic di-GMP effector also called Clp and renders it inactive. At high cell densities, RpfC detaches from RpfF, the unbound RpfF then catalysis the production of more DFS signals, these signals then bind to RpfC. The RpfG is phosphorylated at high cell densities, it then binds and inhibits enzymes that synthesize cyclic di-GTP resulting in a decrease in cyclic di-GMP levels. The cyclic di-GMP detaches from Clp resulting in activation of the transcriptional activator, Clp [103]. Moreover, the DSF QS system in *Xoo* was found to be activated by the plant hormone, salicylic acid [104], indicating an involvement of interkingdom signaling in this QS system during plant infection.

In *Xoo*, the DSF QS system produces three distinct molecules i.e. DSF, BDSF (*cis*-2-dodecenoic acid) and *CDSF* (*cis*-11-methyldodeca-2,5-dienoic acid) [105]. The three DSF QS molecules are produced differentially during exponential growth, with BDSF production occurring ahead of the other two. The three DSF molecules influence production of EPS and exoenzymes in *Xoo*, however, CDSF is less active compared to the other two. In addition, the synthesis of the different DSF molecules varies depending on nutrients available, for example, DSF dominates

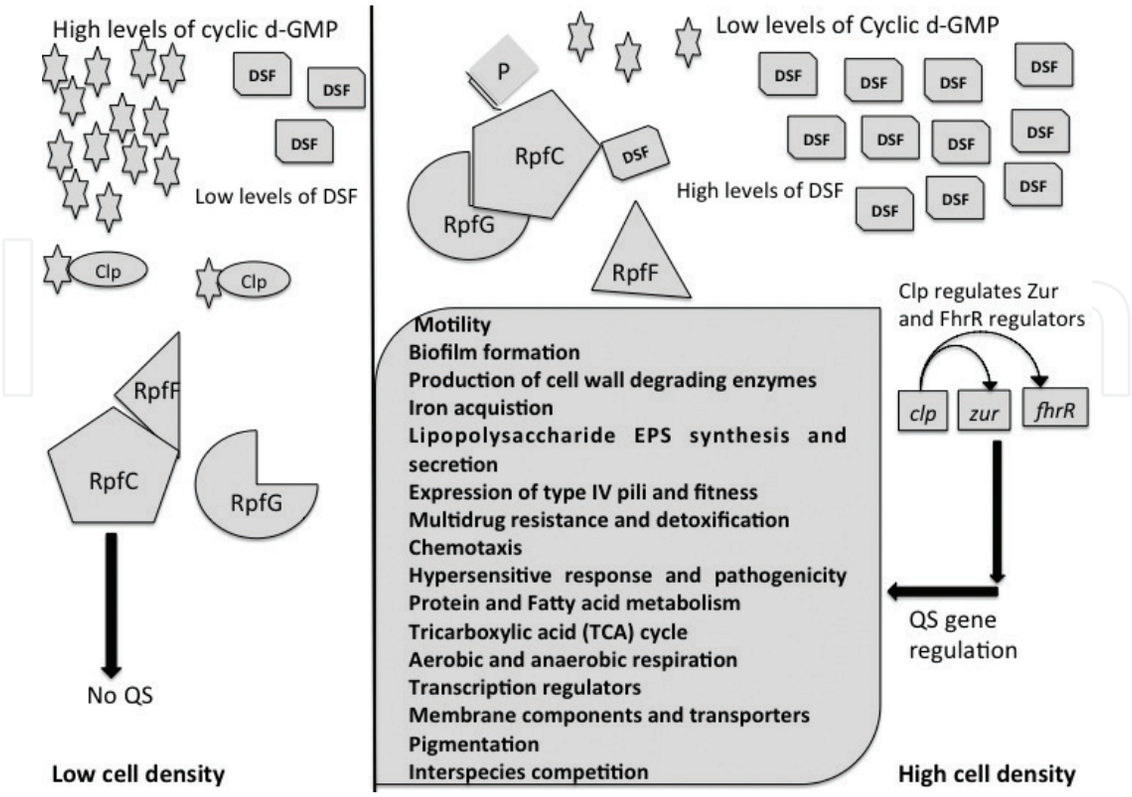

Figure 5. Schematic presentation of the DSF quorum sensing (QS) system showing the modulation of cyclic di-GMP. At low cell densities, the cyclic di-GMP levels are high, they bind to the transcription factor and prevent quorum sensing. The RpfF acts as an enzyme for synthesis of QS signal. At low densities, RpfF binds to RpfC and its catalytic activity is reduced. At high cell densities, RpfF is unbound, it is activated and produces the DSF which then binds to the phosphorylated RpfC. Phosphorylation of RpfC leads to a reduction in the levels of cyclic di-GMP which then detaches from the transcription factor leading to QS gene regulation. The phenotypes influenced by this QS system include motility, biofilm formation, production of plant cell wall degrading enzymes, iron acquisition, lipopolysaccharide/exopolysaccharides (EPS) synthesis and secretion, expression of type IV pili and fitness. Other traits regulated include chemotaxis, multidrug resistance and detoxification, pathogenicity, metabolism, transport, interspecies competition and pigmentation.

in nutrient rich medium whilst in poor nutrients BDSF dominates. One other trait regulated by DSF is iron acquisition in *Xoo* [6]. In addition to the mentioned QS systems, *Xoo* also harbors the Diffusible factor (DF) QS signaling, the autoinducer for this system was characterized as 3-hydroxybenzoic acid (3-HBA) [106]. The DF in *Xoo* regulates the synthesis of the yellow pigments, xanthomonadins that help protect the bacteria from photodamage. The production of both DSF and DF in *Xoo* are activated by the plant hormone, salicylic acid [104] implicating these QS systems in interkingdom signaling.

2.10. QS in *Xanthomonas campestris* pv. *campestris*

The QS systems in *Xanthomonas campestris* include the DSF and DF (3-hydroxybenzoic acid (3-HBA)) [105]. The enzyme involved in DF synthesis (XanB2) has not been identified [106]. The DSF and DF QS systems regulate the exopolysaccharide, xanthan, production. Other traits regulated by the DSF system in *X. campestris* include production of extra cellular enzymes, glucan production and biofilm formation [107, 108] and fitness advantage in interspecies competition [109].

Like the DSF system in *Xoo,* the DSF system in *X. campestris* was found to produce multiple DSF molecules i.e. DSF, BDSF, CDSF and the newly identified IDSF (*cis*-10-methyl-2-dodecenoic acid) [102, 109, 110]. However, the levels of IDSF reported in this bacterium [102] are not sufficiently high enough to have any regulatory effect. On the other hand, the DF system regulates EPS synthesis and production of a yellow pigment, xanthomonadin that acts as a shield against ultra violet (uv) light and thus contributes to epiphytic fitness and pathogenicity of *X. campestris* [111]. The DSF QS in *Xcc* regulates important pathogenicity factors in this bacterium, for example, xanthan and glucan have been shown to suppress the host's innate immune defense, possible through inhibition of callose deposition [24, 112] .

In *Xcc*, EPS production is co regulated by DSF QS and the RavS/RavR two component system [10]. In this pathogen, the DSF QS mutants were impaired in pathogenicity [108] and in fitness, for example, in the ability to cope in iron limiting environments [6, 10]. The regulation of different pathogenicity factors by different QS systems in different bacteria, coupled with differences in QS regulated processes, further emphasizes the specificity of QS systems in bacteria. The DSF QS regulon in *Xanthomonas campestris* pv. *campestris* has been identified and is made up of 165 genes of which 10 of them are hypothetical proteins [10]. The regulon represents 12 functional categories that include extracellular enzymes, lipopolysaccharide and EPS synthesis and secretion. In addition, multidrug resistance and detoxification, flagellum biosynthesis, motility and chemotaxis, hypersensitive response and pathogenicity (Hrp) system are regulated by DSF in this pathogen. Other factors regulated include iron uptake, protein metabolism, tricarboxylic acid (TCA) cycle, aerobic and anaerobic respiration, transcription regulators, membrane components and transporters, and fatty acid metabolism [10].

Another LuxR homolog that does not bind to AHLs is the XccR in *X. campestris*. The AHL synthase gene is absent in this bacterial species. The LuxR homolog found in *X. campestris* binds to yet to be identified molecules produced by the plant and regulates the proline–imino-peptidase (*pip)* gene, a pathogenicity factor in this bacterium [8]. In the absence of AHL mimicking molecules produced by plants, the XccR is repressed by a negative regulator, XerR [113]. The plant derived molecules interact with the repressor, XerR resulting in de repression of XccR. Such QS highlights an interesting inter-kingdom signaling between a plant and its pathogen.

2.11. QS in *Xanthomonas axonopodis*

In *X. axonopodis pv. glycines*, a bacterium that causes bacterial pustules on soybean, one LuxR homolog called XagR was found. Similarly to the other LuxR homologs that are without their cognate LuxI synthase in *Xanthomonas spp.,* XagR binds to signal molecules produced by the host resulting in QS regulation. The XagR regulates proline-imino-peptidase (*pip*) expression, cell adhesion, motility and pathogenicity [28]. XagR regulation of *pip* is not host specific, induction of *pip* expression was observed in soybean, rice and cabbage [28].

2.12. QS in *Xylella fastidiosa*

The complete genome sequence of *Xylella fastidiosa* revealed that this bacterium lacks an AHL synthase gene. This bacterium makes use of DSF for signaling [114], the QS regulated processes includes motility, biofilm formation, pathogenicity [115] and biosynthesis of DSF [116]. However,

the DSF QS system in *Xylella* is not the same as the DSF in *Xanthomonas* spp. The *Xylella* DSF signals have been characterized as cis-2-tetradecenoic acid (XfDSF1) and 2-cis-hexadecanoic acid (XfDSF2), [117, 118]. Whilst in *Xylella*, mutation of the DSF signaling results in up regulation of pathogenicity genes [114], production of cell wall degrading enzymes and expression of type IV pili in the mutants, the opposite happens in DSF QS mutants in *Xanthomonas* spp. [6].

3. Progress in understanding interkingdom QS

As noted in the discussion above, some plant pathogenic bacteria encode LuxR homologs that are capable of 'eavesdropping' by utilizing AHL mimicking low molecular weight compounds that are produced by plants. In place of the LuxI, the LuxR homologs in plant pathogenic bacteria are in most oftenly in close proximity to the *pip* gene [119]. The *pip* harbors an inverted repeat unit similar to *luxI* and is directly involved in pathogenicity, hence its biological role merits further investigation. Over the past decade, researchers have attempted to investigate these LuxR proteins especially on deciphering their role in QS signaling. The binding motifs of these LuxR homologs is unique and distinct from the conventional LuxR homolog, they lack one or two of the several conserved regions required for AHL binding [5, 8, 119]. The AHL binding domain of these proteins are substituted by methionine and tryptophan in the conserved region allowing specificity for binding to plant derived molecules [119]. The orthologs of these LuxR proteins are also encoded on the genomes of AHL producing bacteria including *Pseudomonas syringae* [8]. Consequently, questions arise, do these LuxR homologs bind to the AHL mimicking compounds and function in a similar way in the AHL producing and non AHL producing bacteria? In addition, the AHL mimicking molecules produced by plants still need to be characterized.

4. Conclusions

A variety of bacterial species are increasingly becoming resistant to the antimicrobial agents that are currently in use [120]. Resistance to streptomycin in plant pathogenic bacteria was reported within a decade of its use in controlling plant infections and diseases [121]. Research efforts are now focusing on alternative bacterial control strategies. The discovery of the involvement of QS in the regulation of bacterial virulence has led to escalated research efforts towards discovering possible biological control measures that target QS systems. The main advantage of control measures that target QS systems, though not yet scientifically proven, is that they are less prone to selective pressure [122].

For an effective application of QS inhibition as a biological antimicrobial measure, a better understanding of the genes influenced by QS is crucial. Latest technology including research tools such as RNA-Seq has made it possible for whole transcriptome investigations to be conducted. In addition, targeted mutation and characterization of mutants has helped in unveiling the biological significance of specific genes in bacteria, the complexity of bacterial transcriptomes and thus regulation of gene expression. Nonetheless, as additional experimental and analytical tools become available, the critical role of bacterial QS to plant pathogenesis will undoubtedly become much clearer.

The literature cited in this chapter reflects on QS and its role in influencing pathogenicity and pathogenicity-associated traits in Gram-negative plant pathogenic bacteria. The different QS systems, the extent of those QS regulons that have been elucidated as well as the different signaling molecules employed by plant pathogenic bacteria have been explored. This chapter highlights interesting similarities and differences of QS systems and the diversity of QS signal molecules utilized by plant pathogenic bacteria. Understanding QS regulation in plant pathogenic bacteria could provide useful tools for control and management of bacterial plant diseases.

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Conflict of interest

Authors declare no conflict of interest.

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