Plant responses to bacterial quorum sensing signals

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Bacterial infection of plants often depends on the exchange of quorum sensing signals between nearby bacterial cells. It is now evident that plants, in turn, 'listen' to these bacterial signals and respond in sophisticated ways to the information. Plants also secrete compounds that mimic the bacterial signals and thereby confuse quorum sensing regulation in bacteria.

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Abbreviations
AHL *N*-acyl homoserine lactone
QS quorum sensing

Introduction

Bacterial pathogens and symbionts depend substantially on quorum sensing (QS) to colonize and infect their hosts. Thus, it seems reasonable that eukaryotic hosts, in turn, might have devised ways to take advantage of such dependency. This review examines evidence that plants have evolved at least two potentially potent ways in which to take advantage of the bacterial dependence on quorum sensing.

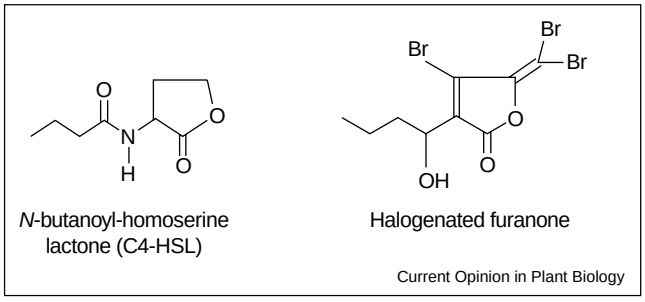
QS is the population-density-dependent regulation of gene expression in bacteria [1–3]. It enables the individual bacterial cells in a local population to coordinate the expression of certain genes, helping them to act somewhat like a multicellular organism. QS works via the exchange of small signal molecules between nearby bacterial cells. As the local population increases, so does the signal concentration. Operationally, a 'quorum' of bacteria is present when the signal concentration reaches levels that are capable of triggering changes in gene expression. Many different behaviors are subject to QS regulation in bacteria. Recent global studies with the opportunistic pathogen and environmental bacterium *Pseudomonas aeruginosa* indicate that 5–20% of its genes and proteins are directly or indirectly subject to QS regulation [4•,5•,6,7]. This suggests that the coordination of gene expression in local populations is valuable to bacteria in many ways. QS is particularly important for the ability of pathogenic bacteria to infect plant and animal hosts successfully [3,8,9]. Mutants that have defective QS are usually avirulent or have significantly reduced virulence. QS is also important to the regulation of gene expression and behaviors in bacterial symbionts of plants [10•,11].

QS mimics

Recent studies demonstrate that both plants and algae are able to confuse QS in bacteria by secreting compounds that mimic the bacterium's own QS signals. The most widely studied QS 'mimic' compounds are halogenated furanones, which are produced by the marine red alga *Delisea pulchra*. Kjelleberg and co-workers [12] recognized that the *Delisea* furanones are similar in structure (Figure 1) to *N*-acyl homoserine lactones (AHLs), the most common QS signals among Gram-negative bacteria. They showed that the furanones specifically inhibit AHL-regulated behaviors in several bacteria. The furanone QS mimics of *Delisea* appear to act by binding to AHL receptor proteins in bacteria and by promoting the proteolytic degradation of these receptors [13,14•]. Furanone AHL mimics have been shown to affect *P. aeruginosa* biofilm structure *in vitro* [15] and to block the induction of normal virulence functions [5•]. Their secretion by *Delisea* also substantially alters the structure of natural bacterial communities that develop on the algal surface in marine environments [16,17].

As indicated in Figure 2, higher plants, including pea, tomato, *Medicago truncatula* and rice, also secrete compounds that affect AHL QS regulation in bacteria [18,19••,20]. By contrast to the furanone AHL mimics from *Delisea*, which are all inhibitory, most of the AHL mimics that have been detected in plants and the unicellular green alga *Chlamydomonas reinhardtii* stimulate gene expression in specific AHL receptors [19••,21•]. The chemical identities of the AHL mimic compounds that are produced by plants are still unknown, but most of them partition into organic solvents in a different manner to that of bacterial AHLs, and most of them appear to be specific in their interaction with particular AHL receptor proteins. These characteristics suggest that they are likely to be novel plant compounds that interfere with normal

Figure 1



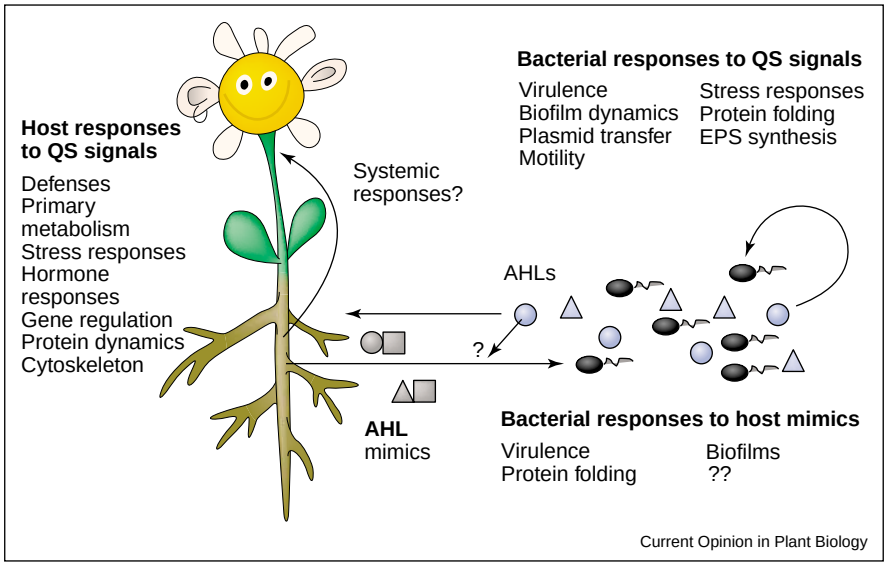
Structural similarities between a typical bacterial AHL and a halogenated furanone AHL mimic from *Delisea pulchra*.

QS in bacteria in biochemically specific ways. Interestingly, a highly purified AHL mimic from *Chlamydomonas*, which specifically stimulated the LasR receptor from *P. aeruginosa*, was found to have both stimulatory and inhibitory effects on the accumulation of various QS-regulated proteins in *Sinorhizobium meliloti*, the nitrogen-fixing bacterial symbiont of legumes [21•]. It may be that the interaction of a mimic compound with some AHL receptors leads to transcriptional activation, whereas interactions with other receptors lead to the cancellation of AHL stimulation or inhibition via proteolytic degradation of the receptor protein.

In addition to AHLs, there are around half a dozen other kinds of QS signals that have been chemically identified in various bacteria [2,3]. It is not yet clear whether plants synthesize compounds that correspond to or mimic these other classes of QS signals. Recent studies have shown that *M. truncatula*, *C. reinhardtii* and *Chlorella* spp. do secrete unidentified substances that stimulate or inhibit an AI-2-specific reporter [19••,21•,22••]. AI-2 is a furanosyl borate diester QS signal [23] that is used by *Vibrio harveyi*, *Vibrio cholerae*, and perhaps other enteric bacteria [1,2,24] to regulate host-related behaviors. Thus, it seems likely that plants produce AI-2 mimics in addition to AHL mimics. Wang *et al.* [25] recently identified an α-β unsaturated fatty acid QS signal from *Xanthomonas campesteris*. This signal is structurally and functionally related to farnesoic acid [25], a signal that regulates the morphology and virulence of the fungal pathogen *Candida albicans*. It is not clear whether *Candida* produces mimic compounds that effectively disrupt QS in *Xanthomonas*. There is also an intriguing report that the mammalian hormone epinephrine stimulates the expression of virulence genes in *Escherichia coli* via the AI-3 QS receptor [26•]. It might be that bacteria use the hormonal signals of a eukaryotic host as cues to trigger the QS-regulated machinery for infection of that host.

When considering natural encounters between plants and bacteria, the disruption of QS regulation by other bacteria may be as important as disruption by QS mimics from the host plant. Various bacterial species that produce AHL QS signals have been found to activate gene expression in a *Pseudomonas* reporter strain in a native wheat rhizosphere [27], indicating that there is significant QS

Figure 2



Schematic model of QS-related interactions between plants and bacteria. AHL QS signals (triangles and circles) from bacteria (ovals) affect QS-regulated behaviors in the bacteria and also elicit a diversity of responses in the plant. The plant produces and secretes AHL mimic compounds (circle/square, triangle/square) that disrupt or manipulate QS-regulated behaviors in the bacteria. Plant responses to bacterial AHLs might affect the secretion of AHL mimic compounds. AHL mimics from the plant may also affect synthesis of AHLs in the bacteria.

crosstalk between bacteria on a plant root. It appears that AHL-responding bacteria do not need to be particularly close to the AHL-producing cells on the host root surface [28]. Thus, the rhizosphere might be thought of as a region of overlapping, cross-talking populations of bacteria, each defined by mutual recognition of specific QS signals, and each affected in different ways by the secretion of QS mimics by the host plant. The same may be true for epiphytic or endophytic bacterial communities. Some bacteria actively disrupt QS regulation in other bacteria [10•,29]. One important mechanism for such disruption in a diversity of soil bacteria is the enzymatic inactivation of AHLs, known as 'quorum quenching' [30,31]. Transgenic plants that expressed a bacterial enzyme for AHL inactivation were highly resistant to soft-rot infection [31,32]; thus, the destruction of bacterial QS signals could be a potentially potent weapon for plants. There is no evidence to date, however, to suggest that plants make or use AHL-degrading enzymes, and such enzymes might hinder beneficial bacteria. As indicated in the following sections, it is possible that plants find it more useful to 'listen' to bacterial QS signals and to mimic them than to destroy them.

Eukaryotic responses to AHL QS signals

Various studies have provided evidence that bacterial AHLs stimulate interesting responses in animals, including immunomodulatory effects [33–36], the inhibition of smooth muscle contraction [37], enhanced bradycardia [38], the promotion of apoptosis [39], and the stimulation of inflammatory and immunogenic responses [40•]. We recently found that the accumulation of more than 4% of the resolved proteins from the model nematode, *Caenorhabditis elegans*, was significantly affected by exposure to bacterial AHL QS signals (U Mathesius, FIA Pellerone, A Eberhard, M Nizamidin, CA Behm, WD Bauer, unpublished). In addition to these diverse protein-level effects, the nematode was found to use AHLs as potent chemoattractants, an appropriate response because this species normally feeds on bacteria. Motile zoospores of the sea weed *Enteromorpha* were also found to use AHLs as chemoattractants in their search for bacterial biofilms that are suitable for attachment [41].

These observations raise the question of whether plants can also perceive and respond to bacterial AHL QS signals. In a recent proteomic study, Mathesius and colleagues [22••] found that nanomolar concentrations of AHLs significantly affected the accumulation of more than 7% of the 2000 proteins recovered from roots of *M. truncatula*. AHLs induced large (more than four-fold) changes in the accumulation of most of these proteins, making it likely that the corresponding molecular functions are significantly affected. Of the 100 root proteins that were identified by peptide mass fingerprinting, approximately 25% had functions that were consistent with a role in host defense responses. Others had putative roles in primary metabolism, plant hormone responses, transcriptional regulation, protein processing or cytoskeletal activity (Figure 2). Different AHLs elicited several different responses in the host, indicating that the plant can distinguish between AHLs of different structure. AHLs also induced the tissue-specific transcriptional activation of an auxin-inducible gene and three chalcone synthase genes in white clover [22••]. Taken together, these results indicate that plants possess the ability to detect various AHLs at or below the threshold concentrations used by bacteria, and are able to use this information to mount a truly global and sophisticated set of responses.

In related work, recent microarray studies indicate that a range of defense responses is elicited in the shoots of tomato plants after treating the roots with AHLs [42]. The ability of plants to detect AHLs in one tissue and elicit systemic responses could be of considerable importance in potentiating host defenses. Other evidence for a systemic response was obtained by Joseph and Phillips [43], who found that exposing the roots of bean plants to 10 nM of homoserine lactone led to 20–30% increases in stomatal conductance and transpiration in the shoot of the plant. Homoserine lactone is one of the products of enzymatic degradation of AHLs by soil bacteria [44]. Increased transpiration, induced by homoserine lactone, should result in an increased flow of water and nutrients from the bulk soil to the rhizosphere, potentially benefiting both the plant and the bacteria.

The responses of plants to bacterial AHLs and the production of AHL mimics by plants might be interconnected behaviors. The amounts or types of AHL mimics that are secreted by *M. truncatula* were found to shift after exposure of the roots to AHLs [22••]. This opens up the possibility that plants may be sophisticated enough to recognize an AHL and to enhance the secretion of mimics of the inducing AHL (Figure 2). Reciprocally, the secretion of particular mimics by the plant might actively alter the synthesis of AHLs by bacteria. The genes encoding AHL synthases are often positively regulated by the receptor for the AHL, leading to self-amplification of AHL synthesis by bacteria [1–3]. Thus, the interaction of a plant mimic compound with an AHL receptor that regulates AHL synthesis could substantially affect rates of AHL synthesis, positively or negatively, and thereby affect host responses to the AHL.

Conclusions and perspectives

Our understanding of how plants respond to bacterial QS signals is at an infant stage. Studies to date have established that plants can detect physiological levels of one class of bacterial QS signal (i.e. AHLs), and have clearly demonstrated that plants respond extensively to AHLs. But we know nothing, as yet, about the 'AHL signal transduction pathway' that connects these responses, nor

anything about the putative AHL receptors and their specificity. Genome-level transcriptional studies are needed to gain a better perspective of the full range of functions that are altered in plants responding to AHLs. Studies with AHL receptor mutants or AHL pre-treated plants are needed to establish just how important AHL perception and responses are to the actual colonization and infection of host plants by particular bacteria. Recent studies have also demonstrated that plants can produce and secrete various compounds that mimic the QS signals of bacteria and thus have the potential to actively disrupt QS regulation in bacteria; however, we do not know the chemical structures of any of these compounds. Chemical identification and synthesis are central to analyzing the biochemical mode of action of mimics, determining their effects on relevant bacteria, identifying the enzymatic pathways of mimic synthesis, and exploring the potential for the use of plant QS mimics to improve the health of plants and animals.

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