Quorum Quenching in *Agrobacterium tumefaciens*: Chance or Necessity?\(^V\)

Catharine E. White and Turlough M. Finan*

*Center for Environmental Genomics, Department of Biology, McMaster University, Hamilton, Ontario L8S 4K1, Canada*

Cell-cell communication or “quorum sensing” (QS) between members of a population is an established phenomenon that has been described for many different bacterial species. A number of different types of QS systems have been discovered; however, a unifying theme is the synthesis of a small signal molecule, often called an autoinducer or pheromone, which activates a specific response when it accumulates to a threshold concentration within a population. A relatively new and exciting aspect of the field of QS that has received much recent attention is “quorum quenching” (QQ), or interference of a QS signaling system. This occurs through either the inhibition of a QS component or the depletion of the signal itself, resulting in an attenuation of the response. In the plant pathogen *Agrobacterium tumefaciens*, an enzyme (BlcC) that destroys the bacterium’s QS signal has been recently described, prompting much speculation that this enzyme is specifically involved in the quenching of the QS system. A variety of explanations for the adaptive significance of QQ in the QS system of *A. tumefaciens* and implications for the bacterium’s role as a plant pathogen have been suggested in the literature (for example, see references 4 and 27). However, the role of BlcC in QQ was never directly addressed. In *A. tumefaciens*, the QS system regulates Ti (tumor-inducing) plasmid conjugation. In this issue, Khan and Farrand (12) directly address the biological significance of BlcC by examining its effect on Ti plasmid conjugation both in culture and in planta. Their study has implications for our understanding of the possible roles in *Agrobacterium* and other bacteria of BlcC-like enzymes, which are generally thought to function as quorum quenchers of proteobacteria.

**QUORUM SENSING AND VIRULENCE IN AGROBACTERIUM TUMEFACIENS**

The most widespread and best-studied type of QS system in proteobacteria is the LuxR-LuxI-type system. The LuxI-type protein synthesizes a small diffusible signal molecule called an N-acylhomoserine lactone (AHL), while LuxR is the cytoplasmic receptor for that signal, regulating target genes in response to inducing concentrations of the cognate AHL (26). In *A. tumefaciens*, the LuxI-type protein, called TraI, synthesizes the AHL N-3-oxooctanoyl-3-homoserine lactone (OOHL), which is recognized with high specificity by the receptor protein TraR.

TraI, TraR, and all known QS-regulated genes in *A. tumefaciens* occur on the Ti plasmid, which is required for the formation of tumors, called crown galls, on a wide range of host plants (25). During the infection process, a segment of the Ti plasmid is transferred to the nucleus of host plant cells, where it directs the overproduction of phytohormones (hence, the formation of a tumor) and the production of novel compounds called opines. The infecting strain of *A. tumefaciens* carries the complement of genes, again on the Ti plasmid, that are required for the utilization of the opines as sources of carbon and nitrogen. By thus harnessing the metabolism of the host plant to produce a novel food source, the bacteria provide a specialized niche for themselves and, presumably, a competitive advantage over other plant-colonizing bacteria.

The virulence system and the TraR-TraI system of the Ti plasmid are intimately linked (9, 14, 21). The expression of traR requires the presence of opines, which are found only at the site of a tumor. Therefore, the QS system functions only in host plants and only after infection has occurred. As active TraR-OOHL complexes are required for Ti plasmid conjugation, this means that Ti plasmid transfer is restricted to members of an infecting population on a transformed host plant. In addition, TraR-OOHL also upregulates the expression of the Ti plasmid replication genes, resulting in an increase in copy number per cell in response to QS (14, 21). This leads to the intriguing question of the QS system’s role in pathogenesis. One possibility is that the increase in Ti plasmid copy number may benefit a plant-associated population through increasing the gene dose of virulence and opine utilization genes.

**IS QUORUM QUENCHING IN A. TUMEFACIENS REAL?**

The speculation that QQ may be involved in the regulation of TraR-TraI activity was prompted by the discovery of a family of lactonases that possess activity against homoserine lactones (HSLs). The first member of this family to be described, AiiA (autoinducer inactivation gene A) from *Bacillus cereus*, was shown to have a high level of activity against AHLs, hydrolyzing the lactone ring and thus inactivating signal activity (7). The expression of aiiA in the plant pathogen *Erwinia carotovora* (in which a LuxR-LuxI system regulates virulence factors) attenuates disease, and the same effect can be achieved by aiiA expression in the plant host (7). These discoveries led to the concept of QQ, and many other examples and additional mechanisms have since been reported.

The blcC (formerly *attM*) gene of *A. tumefaciens* is in the

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\(^*\) Corresponding author. Mailing address: Center for Environmental Genomics, Department of Biology, McMaster University, 1280 Main St. W, Hamilton, Ontario L8S 4K1, Canada. Phone: (905) 525-9140. Fax: (905) 522-6066. E-mail: finan@mcmaster.ca.
agrobacteria would be exposed to. During infection at a wound site, one could predict that the pathogenic bacterium
Staphylococcus aureus
uses short oligopeptides as a QS signal, in this case, to induce the expression of virulence genes. In
S. aureus,
these signals (called AIPs) vary slightly in sequence between different strains, and it has been shown that the signal of one strain can block the signal receptor of another, perhaps conferring a competitive advantage during host colonization (16, 19).

A number of reports also suggested that eukaryotes employ
QQ
to control colonizing or pathogenic bacteria (reviewed in reference 11). Vascular plants are thought to secrete compounds that disrupt
QS, although active components have not yet been identified (11). Halogenated furanones produced by red algae appear to block
QS
and inhibit biofilm formation on
their surfaces, although the mechanism of inhibition is not entirely clear (6, 17, 18, 22).

Much effort is being invested in the synthesis of synthetic signal antagonists or mimics that can be applied in medicine to attenuate pathogenesis and in industry to minimize biofouling. A number of preliminary successes in this endeavor have been reported, usually where families of compounds have been designed based on known natural quorum quenchers, such as LuxR-inhibiting furanones, or peptide mimics of AIPs (10, 16, 20).

No doubt, many more potential QQ systems and mechanisms will come to light in future research, and it will be most interesting to follow these developments. In defined systems in the laboratory, many interactions may be proven to involve signal quenching. The real question will be whether or not, in the context of complex interspecies communication in nature, these systems are chance or necessity.

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