Quorum sensing: A cell-cell signalling mechanism used to coordinate behavioural changes in bacterial populations

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The Quorum Sensing concept

One of the most important mechanisms for bacterial cell-to-cell communication and behaviour coordination under changing environments is often referred to as "quorum sensing" (QS). QS relies on the activation of a sensor kinase or response regulator protein by, in many cases, a diffusible, low molecular weight signal molecule (a "pheromone" or "autoinducer") (Camara *et al.*, 2002). Consequently, in QS, the concentration of the signal molecule reflects the number of bacterial cells in a particular niche and perception of a threshold concentration of that signal molecule indicates that the population is "quorated" i.e. ready to make a behavioural decision. Bacteria cell-to-cell communication is perhaps the most important tool in the battle for survival; they employ communication to trigger transcriptional regulation resulting in sexual exchange and niche protection in some cases, to battle host' defences and coordinate population migration. Ultimately, bacteria cell-to-cell communication is used to effect phenotypic change. The importance of coordinated gene-expression (and hence phenotypic change) in bacterial can be understood if one realizes that only by pooling together the activity of a quorum of cells can a bacterium be successful. It is increasingly apparent that, in nature, bacteria function less as individuals and more as coherent groups that are able to inhabit multiple ecological niches (Lazdunski *et al.*, 2004). Within quorum sensing process several key elements must be considered: (i) the gene(s) involved in signal synthesis, (ii) the gene(s) involved in signal transduction and (iii) the QS signal molecule(s).

In Gram-negative bacteria, some of the most studied signal molecules are the N-acylhomoserine lactones (AHLs) (Fig. 1A). During the growth of a bacterial population, signal molecules either diffuse or are exported out of the cell into the surrounding environment; their concentration increases and they then act on neighbouring bacterial cells. Achievement of a critical threshold concentration results in: (i) activation of a sensor/response regulator, responsible for signal transduction (T), which in turn triggers the expression of multiple genes and (ii) activation of a positive autoinductive feedback loop to amplify QS signal molecule generation (Figure 1B)

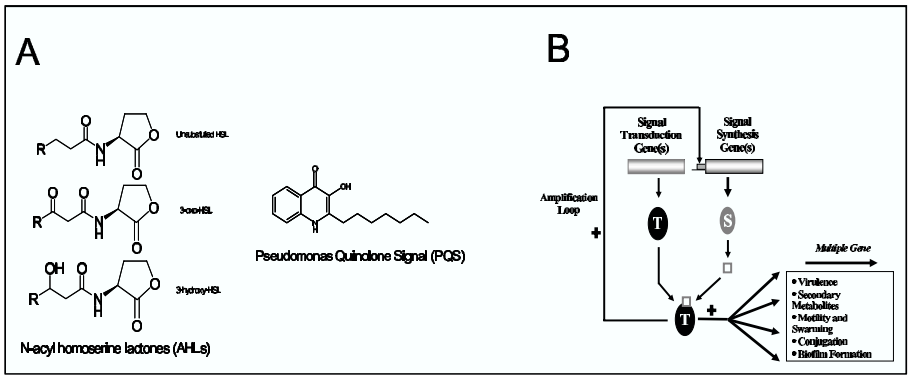

Fig. 1. A. Chemical structures of N-acylhomoserine lactones and PQS B. Generic quorum sensing signal generation and transduction circuit

Hence the term "autoinducer" is sometimes used to describe the QS signal molecule. Important in governing the size of the "quorum" is 'compartment sensing' (Winzer *et al.*, 2002). The concentration of a given QS signal molecule may be a reflection of bacterial cell number, or at least the minimal number of cells (quorum) in a particular physiological state. To achieve the accumulation of a QS signal there is a need for a diffusion barrier, which ensures that more molecules are produced than lost from a given microhabitat. This 'compartment sensing' enables the QS signal molecule to be both a measure of the degree of compartmentalization and the means to distribute this information through the entire population. Likewise, the diffusion of QS signal molecules between detached subpopulations may convey information about their numbers, physiological state and the specific environmental conditions encountered.

Quorum sensing in *P. aeruginosa*: a complex regulatory network resulting in fine signal tuning

Pseudomonas aeruginosa is a very versatile organism that can adapt to many different environments and can cause diseases in plants, animals and humans (Rahme *et al.*, 1995). It possesses a large 6.3MB genome encoding 5,570 predicted genes including 521 putative regulatory genes suggesting the existence of a highly complex gene regulation which enables it to adapt quickly to environmental changes (Stover *et al.*, 2000). This organism produces a broad range of exoproducts, which are regulated in a population density-dependent manner via cell-to-cell communication or "quorum sensing" (Camara *et al.*, 2002). Two intertwined QS systems (the *las* and the *rhl* systems) have been shown to be involved in virulence, biofilm development, and many other processes in *P. aeruginosa* (Gambello and Iglewski, 1991; Latifi *et al.*, 1995; Ochsner and Reiser, 1995; Passador *et al.*, 1993). These QS systems each produce and respond to specific AHL

signal molecules (Pearson *et al.*, 1994; Winson *et al.*, 1995). In addition, each system modulates a regulon comprising an overlapping set of genes. However, the *las* and the *rhl* systems are not independent of each other, but form a regulatory hierarchy where LasR-C12-HSL activates the transcription of *rhlR* (Latifi *et al.*, 1996; Pesci *et al.*, 1997)(Figure 2). Transcriptome analysis of *P. aeruginosa* has revealed that N-acylhomoserine lactone (AHL)-dependent QS regulates up to 10% of the genes in the genome of this organism (Schuster *et al.*, 2003; Whiteley *et al.*, 1999).

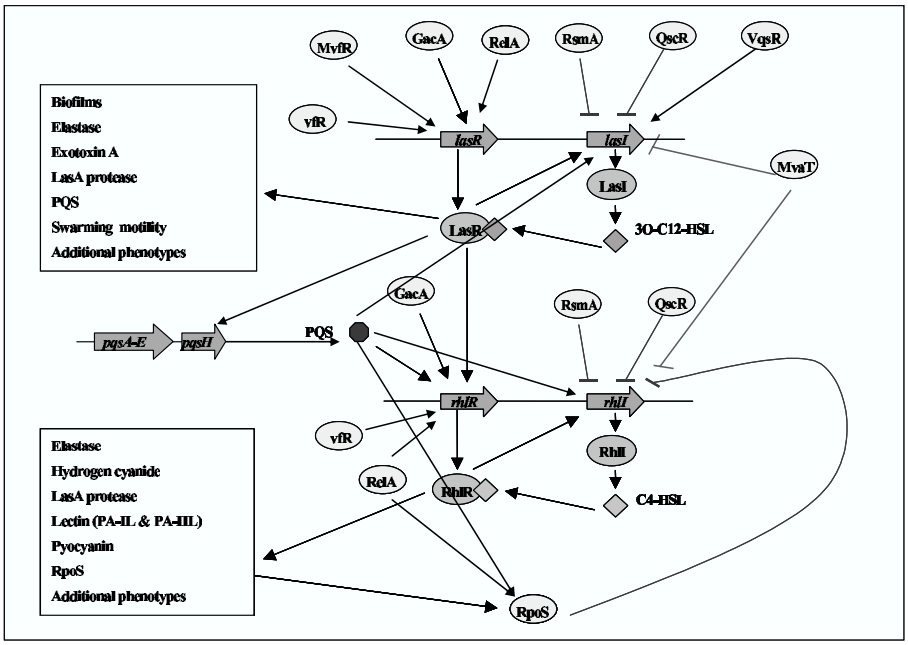

Fig. 2. Interactions between the different regulators of QS in P. aeruginosa. (–?) indicate positive regulation and (?—) negative regulation.

In addition to AHLs, *P. aeruginosa* releases a 4-quinolone signal molecule into the extra-cellular milieu, the synthesis and bioactivity of which has been reported to be mediated via the las*las* and *rhl* systems respectively. This molecule has been chemically identified as 2-heptyl-3-hydroxy-4(1H)-quinolone and termed the Pseudomonas Quinolone Signal (PQS) (Fig. 1) (Pesci *et al.*, 1999). LasR has been shown to regulate PQS production and the provision of exogenous PQS induces expression of *lasB* (coding for elastase), *rhlI* and *rhlR* (McKnight *et al.*, 2000; Pesci *et al.*, 1999) suggesting that PQS activity constitutes a regulatory link between the *las* and *rhl* QS systems. The QS-dependent production of exo-products in *P. aeruginosa* is tightly regulated with respect to growth phase and growth environment. In contrast to the AHL-dependent induction of biolumi-

nescence in *Vibrio fischeri* (Eberhard *et al.*, 1981) and carbapenem antibiotic production in *Erwinia carotovora* (Williams *et al.*, 1992), the provision of exogenous AHLs does not advance the expression of several QS dependent genes in wild type *P. aeruginosa* PAO1 such as *lecA, lasB* or *rhlR* expression (Diggle *et al.*, 2002; Pearson, 2002). This is due to the contribution of additional regulatory factors in addition to LasR and RhlR. Figure 2 shows a simplified diagram of how the different regulators have so far been shown to interact with the QS regulatory cascade at both the transcriptional and posttranscriptional level. This shows an example of the intricate control of QS-mediated responses by a network of regulators which results in a fine tuning of adaptative responses to environmental changes.

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