Cost of cell-cell signaling in *Pseudomonas aeruginosa*: why it can pay to be signal-blind

In a recent, largely theoretical review, Laurent Keller and Mike Surette provide a cost-benefit analysis of cell-cell communication in bacteria[1]. The authors argue that it is costly for bacteria to produce signal molecules as signal production represents a metabolic burden. Furthermore, the response to a signal might also incur a cost to individual cells. The question then arises as to whether it is advantageous for bacterial populations to consist purely of signaling-proficient cells or whether there might be situations in which "cheaters" would be favored. Cheaters are defective for signaling and they benefit from the metabolic activities of signaling-proficient strains, e.g. from the expression of extracellular enzymes that degrade macromolecules.

There is a solid body of experimental evidence demonstrating that cheaters of the species *Pseudomonas aeruginosa* have a place in natural environments. *P. aeruginosa* naturally uses *N*-acyl-homoserine lactones (AHLs) for cell-cell communication (termed quorum sensing). Yet roughly 20% of all environmental and clinical isolates are quorum sensing-deficient – in the above terminology they could be called cheaters. Interestingly, it turns out from about 10 recently published papers (reviewed in ref. 2) that cheaters of *P. aeruginosa* are not defective in signal production, they are signal-blind. That is, a vast majority of quorum sensing-negative isolates of *P. aeruginosa* that have been analyzed by molecular tools are defective in the master regulator of quorum sensing, the transcription factor LasR. Without LasR function, cells cannot respond to AHL signaling. By contrast, defects in the signal-producing enzymes LasI and RhlI are rare in natural isolates, and when such defects do occur they appear to be associated with a primary *lasR* mutation[2]. It is easy to see the reason behind this. Only ≤ 0.01% of the total cellular amount of ATP is needed to make the AHL signal molecules *N*-(3-oxo-dodecanoyl)-homoserine lactone and *N*-butanoyl-homoserine lactone at biologically active (sub-micromolar) concentrations. This estimate is based on the ATP content that *Escherichia coli* uses to drive biosynthetic pathways and macromolecular syntheses[3]. By contrast, when the AHL signals activate the quorum sensing response in *P. aeruginosa*, this activity consumes at least 5% of the total energy supply, as at least 5% of all *P. aeruginosa* genes are induced during the quorum sensing response[4]. So, for cheaters, it does not pay to abandon signal synthesis, it is much more rewarding not to react to the signals.

In vitro, quorum sensing-proficient cells of *P. aeruginosa* have a selective metabolic

advantage over quorum sensing-deficient cells, e.g. when casein or adenosine is the carbon source because the degradation of these substrates is ensured by quorum sensing-controlled enzymes[5,6]. However, opposite selective forces can also be demonstrated: in a nutrient-rich, alkaline environment, *lasR*-negative mutants have a better chance to survive in stationary phase by comparison with the quorum sensing-proficient parental cells, which are more vulnerable to cell lysis. Again, these conditions do not select for signal-deficient cells but for signal-blind cells[6].

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References

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