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RESEARCH HIGHLIGHT

Quieting cross talk – the quorum sensing regulator LsrR as a possible target for fighting bacterial infections

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Antibiotic-resistant bacteria continue to emerge at alarming rates and all aspects of the infection process are being re-examined so that new procedures for prevention, diagnosis, and treatment of bacterial infections can be developed that reduce their occurrence and severity as well as the economic impact on health care systems. One of the most problematic pathogens is methicillin-resistant *Staphylococcus aureus* (MRSA). First reported among intravenous drug users in Detroit, MI (USA) in 1981 and later associated with the deaths of four children in Minnesota in 1997, MRSA was reported to be the cause of a staggering 85% of health care-associated infections in 2007 as well as the most common origin of skin and tissue infections presented to hospital emergency rooms in the United States [1]. These statistics illustrate the scale and impact that bacteria can have on a population and its health care system.

Contrary to common perception that bacteria operate as autonomous unicellular entities, recent work has demonstrated that they actually employ highly selective and refined intercellular communication networks. These networks are comprised of many components, which when targeted by drugs, become disabled so the bacteria can survive but in a less lethal mode. Fuqua *et al*. first used the term 'quorum sensing' to describe a population density based transduction mechanism of intraspecies communication which uses chemical signal molecules called autoinducers to trigger unique and varied changes in bacterial gene expression [2]. The extremely selective and often staggeringly complex nature of these response cascades has resulted in many incompletely understood intracellular mechanisms; even if each individual component of a transduction cascade is nominally identified, its exact function and significance has often remained unknown.

In quorum sensing systems, an autoinducing signal molecule is both produced and taken up by cells, varying the intracellular and extracellular concentrations. As cell density increases in a confined space, the extracellular concentration of the signal molecule reaches a threshold, triggering the transduction cascade and resulting in a population-dependent shift in gene expression [3]. Autoinducer-2 (AI-2) signaling is regarded as a 'universal' bacterial communication system due to its capability to prompt population-based changes in multiple species of both Gram-positive and Gram-negative bacteria. This effect was first noted after mid-exponential phase cell supernatant from *Salmonella typhimurium* was shown to trigger a quorum sensing response (in the form of bioluminescence) in *Vibrio harveyi*, and in 1999 AI-2 gained recognition as a sort of 'bacterial Esperanto', synthesized by LuxS and its homologues in multiple bacterial strains and evoking considerable changes in gene expression [3, 4].

Taga *et al*. [5] linked LuxS and AI-2 in *Salmonella typhimurium* to the expression of the *lsr* (LuxS responding) operon, encoding an ATP binding cassette (ABC)-type transporter determined to be responsible for the uptake of AI-2 into the cells. The divergent gene set was also shown to encode its cognate repressor, LsrR which was, in turn, ineffective in the presence of AI-2. However, low levels of native AI-2 detected in cell lysates led to the speculation that the signal molecule was somehow modified after uptake and that native AI-2 did not affect LsrR repression. It was later demonstrated in *Escherichia coli* that the kinase LsrK is directly responsible for the post uptake modification of AI-2, and the resulting intracellular phospho-AI-2 provoked de-repression of the *lsr* operon via LsrR [6, 7].

In deciphering expression of the *lsr* operon and its subsequent impact throughout the bacterial genome, focus

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has shifted to a systems level approach that includes the interplay between signaling, uptake, and a variety of other physical processes. Li *et al*. [8] showed the importance of LsrR as not only a determinant of *lsr* expression, but as a regulator of hundreds of genes, many of which would likely be involved in virulence processes such as motility and biofilm formation.

With the significance of LsrR emerging, Xue *et al*. [9] evaluated the exact binding site for the repressor via DNA footprinting and protein binding assays. LsrR was shown to directly bind two separate sites within the intergenic region of the *lsr* operon, repressing expression in opposite directions. Also, LsrR binding was apparently unaffected by the presence of native AI-2; increasing levels of phospho-AI-2, however, resulted in proportionate decreases in LsrR binding. These results confirm that the AI-2 must be modified by LsrK prior to antagonizing the cognate repressor. The direct regulation of the *lsr* operon by LsrR reaffirms the suspicion from Li *et al*. [8] that LsrR serves as an important 'global' regulator of AI-2 quorum sensing in bacteria.

Cued as a single signal regulator but with wide genetic impact, LsrR represents a promising new avenue for deciphering the complex nature of quorum sensing. Moreover, it represents another target for drug therapies which fight bacterial infection by preventing intercellular communication. Further progress will depend on a full understanding of LsrR and its effects on gene expression as well as the subsequent physiological changes spurred by its regulation, and Xue *et al*. have provided a significant step towards a comprehensive understanding of LsrR functions.

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