Quorum sensing: A nobel target for antibacterial agents

INTRODUCTION

Traditionally, it was believed that cell-to-cell communication and social cooperation only present in the eukaryotes. Recently, it has been revealed that this signaling process also present in Prokaryotes.[1] Communication between bacterial cells termed as quorum sensing (QS).[2] QS has not only been described between cells of the same species, but also between different species and between bacteria and higher organisms. The term QS was first used in a review by Fuqua *et al.,* which essentially reflected the minimum threshold level of individual cell mass required initiating a concerted population response. The first incidence of such a biological phenomenon came to light with the discovery of luminescence produced by certain marine bacteria such as *Vibrio fischeri* and *Vibrio harveyi*.[3] It is now appreciated that bacteria are highly interactive and exhibit a number of social behaviors, such as swarming motility, conjugal plasmid transfer, antibiotic resistance, biofilm maturation, and virulence.[4-6] Many of these behaviors are regulated by diverse QS systems, which are found in both Gram-negative and Gram-positive bacteria. Bacteria are sensitive to an increase in population density and respond quickly and coordinately by inducting certain sets of genes. This mode of regulation, known as QS, is based on the interaction of low-molecular-weight signal molecules called auto-inducers (AIs) or pheromones with a sensor kinase and response regulator to activate or repress gene expression. QS systems are considered to be global regulators and play a key role in controlling many metabolic processes in the cell, including, bacterial virulence. These systems offer attractive targets for a novel class of antibacterial drugs, capable of inducing chemical attenuation of pathogenicity.[7] The subsequent discovery of compounds that inhibit cell-to-cell communication, dubbed anti-QS agents could provide a novel method of combating infection.[4,8]

QUORUM SENSING

QS is a population-dependent phenomenon first characterized in the 1970s in luminescent marine species of *Vibrio*.[9] The ability to sense the size of a bacterial population is mediated through small signaling molecules or AIs.[10,11] These molecules are constantly produced and received at a basal level by bacterial cells. With high population density, there is a surplus of signaling molecules in the environment. These signals diffuse back in to the cell where they facilitate the regulation of gene expression.[10] QS systems are ubiquitous among bacteria, and have since been found to regulate diverse functions such as luminescence, biofilm formation, antibiotic and virulence factor generation, pigment production, plant-microbe interactions, and motility.[4-6] Although, there are a number of different QS systems,[12] the most widely studied paradigm is based on the Lux system of *Vibrio fisheri* and *V. harvey*i.[13,14] This QS phenomenon involves a three component-system: a freely diffusible signal, a synthase to make this signal, and a regulator that interacts in conjunction with the signal to regulate gene expression. The main signaling molecules produced by Gram-negative bacteria are acyl-homoserine lactones (AHLs).[15] They differ in the length of their side chains and substitution at the C3 carbon, based on the organism that produces them.[16,17]

AHL-mediated QS systems based on the LuxI/LuxR (LuxI/LuxR, is the counterpart in marine bacteria of the luciferase system. They mediate bioluminescence, and are products of genes regulated by the *lux* operon. Light production in *V. fischeri* is controlled by two regulatory proteins named LuxI and LuxR. LuxI is the autoinducer synthase that is responsible for the synthesis of the acyl-HSL autoinducer. LuxR is a transcriptional activator protein that, when bound to autoinducer, promotes transcription of the luciferase structural operon *luxCDABE)* paradigm have been characterized in human pathogens such as *Pseudomonas aeruginosa*,[18] *Yersinia* pseudotuberculosis,[19] and *Escherichia coli*,[20] as well as plant associated bacteria such as *Rhizobium leguminosarum*,[21] *Ralstonia solanacearum*, and *Erwinia* carotovora.[22] In all cases, these systems can regulate virulence. Thus, the discovery of QS has given us a new target-a new way to attack and attenuate bacterial pathogenicity.

ANTI-QS

The subsequent discovery of compounds that inhibit cell-to-cell communication, dubbed anti-QS agents could provide a novel method of combating infection.[4,8]

Anti-QS agents were first characterized in the red marine alga, *Delisea* pulchura.[23] This alga was investigated for its anti-fouling properties, and was found to contain halogenated furanones, compounds, which block AHLs via competitive inhibition and destabilization of LuxR.[24]

QS inhibitions

There are a number of ways to inhibit cell-cell communication including competitive inhibition, signal binding, degradation of the signaling molecule, and inhibition of upstream precursors or genetic regulation systems. Success has been seen with competitive inhibition in the case of the furanones, however, many other QS antagonists have since been discovered.[8] These antagonists are based on the C12-AHL structure and cause a reduction in LasR activity. AHL-antibodies have also been developed to suppress QS through signal binding.[25,26] A C12-AHL–protein conjugate was able to successfully inhibit lasB expression, and a similar molecule with extremely high binding affinity for C12-AHL was recently crystallized and characterized.[25] Blocking S-adenosyl methionine or the fatty acid precursors necessary to synthesize AHLs leads to decreased production of C12-AHL by LasI.[27] Of course, genetic modification of up-stream global regulators such as Vfr and GacA has also been shown to greatly reduce QS activity and the subsequent production of virulence factors.[28,29] Numerous bacteria including *Bacillus* sp., *Variovorax paradoxus*, *Arthrobacter* sp., and *Agrobacterium tumefaciens* produce lactonases-enzymes that cleave and deactivate the lactone ring of various AHLs.[30,31] Lactonase expression in *P. aeruginosa*, results in a significant decrease in AHL production and virulence factor expression.[4,32]

CONCLUSION

Interest is growing in practical applications of anti-QS especially, when faced with increased incidence of drug failure due to the large number of pathogenic bacteria developing resistance to available antibiotics. It has been suggested that targeting pathogenesis instead of killing the organism may provide less selective pressure and therefore, decreased emergence of resistant strains.

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