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REVIEW ARTICLE

Quorum quenching: Signal jamming in dental plaque biofilms

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Abstract Quorum sensing helps bacteria to communicate with each other and in coordinating their behavior. Many diseases of humans, plants, and animals are mediated by communication called quorum sensing. Various approaches are being investigated to inhibit this communication to control the diseases caused by bacteria. Periodontal pathogens also communicate through quorum sensing and new approaches to treat periodontal disease using quorum sensing inhibition need to be explored.
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Introduction

Dental plaque is an example of microbial biofilm with a complex microbial composition containing as many as 500 different species of bacteria that have been identified from the oral cavity. These exhibit coordinated group behavior that causes periodontal diseases and dental caries.[1] The dental biofilm is a dynamic microbial community that forms high cell density on the tooth and tissue surfaces in the oral cavity. The community adheres tightly to the acquired salivary pellicle and is thought to develop by the coordinated and successive colonization of different microbial species.

These characteristics of biofilm growth and development suggest that oral organisms may express complicated intraspecies and/or interspecies communication mechanisms that facilitate a coordinated response by members of the microbial community in environmental flux.[2]

The process by which microorganisms monitor and regulate their population density through chemical signaling is termed quorum sensing.[3] The mechanism by which quorum sensing can be inhibited is called quorum quenching. Work over the past few years has confirmed that quorum-quenching mechanisms are widely preserved in many prokaryotic and eukaryotic organisms. These naturally occurring quorum-quenching mechanisms appear to play important roles in microbe–microbe and

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pathogen–host interactions. The discovery of quorum sensing signal-degradation enzymes in mammalian species represents a new milestone in quorum sensing and quorum quenching research.[4]

Quorum sensing

Quorum sensing is a process of chemical communication among bacteria, and is defined as gene regulation in response to cell density, which influences various functions, such as virulence, acid tolerance, and biofilm formation. The first indication that bacteria communicate through small chemical signals arose from studies of the marine organism *Vibrio fischeri*.[2,5] *V. fischeri* is bioluminescent, but produces light primarily at high bacterial cell density. Quorum sensing relies upon the interaction of a small diffusible signal molecule with a sensor or the transcriptional activator to initiate gene expression for coordinated activities.

Quorum sensing systems in bacteria have been generally divided into at least three classes[6]: (1) LuxI/LuxR-type quorum sensing in Gram-negative bacteria, which use acyl-homoserine lactones (AHL) as signal molecules; (2) oligopeptide-two-component-type quorum sensing in Gram-positive bacteria, which use small peptides as signal molecules; and (3) LuxS-encoded autoinducer (AI)-2 quorum sensing in both Gram-negative and Gram-positive bacteria.

A study was conducted by Frias et al[5] to examine the production of quorum sensing signaling molecules in bacteria isolated from dental plaque, especially in major putative periodontal pathogens such as *Porphyromonas gingivalis* or *Aggregatibacter actinomycetemcomitans*. This study revealed that at least three genera of periodontal isolates, *Fusobacterium*, *Prevotella*, and *Porphyromonas gingivalis*, were able to stimulate the production of light in *Vibrio harveyi* BB 170, which responds to autoinducer AI-2.[5]

Quorum sensing in Gram-positive bacteria

A number of Gram-positive bacteria are known to use quorum sensing systems. The nature of the signaling molecules used in these systems differs from those of Gram-negative organisms, and to date, no Gram-positive bacteria have been shown to produce AHLs. Gram-positive quorum sensing systems typically make use of small post-translationally processed peptide signaling molecules. These peptide signals interact with the sensor element of a histidine kinase two-component signal transduction system.[7,8]

Quorum sensing in Gram-negative bacteria

Most Gram-negative quorum sensing systems that have been studied thus far utilize AHL as a signaling molecule. When in high concentration, these molecules can bind to and activate a transcriptional activator, or R protein, which in turn induces expression of target genes.[7,9]

Table 1 Various mechanisms involved in quorum sensing and quorum sensing inhibition. AHL = acyl homoserine lactone; AI = autoinducer.

Quorum sensing inducers	Quorum sensing inhibitors
AIs	AHL-lactonase
• acyl homoserine lactone	AHL-acylase
• AI-2	Paraoxonase
• cyclic dipeptides	L-Canavanine
• bradyoxetin	Furanones
AI synthases	Human hormones
• AHL synthases	Other compounds
• AI-2 synthase	

Quorum quenching

The biofilm formation can be disrupted by alarming the quorum sensing mechanism utilized by the various species of bacteria that together form the plaque biofilm. The inhibition of quorum sensing is commonly referred to as quorum quenching.

Inhibition of quorum sensing can be accomplished in several ways, including[7]: enzymatic degradation of signaling molecules; blocking signal generation; and blocking signal reception. The inhibitors of quorum sensing can be roughly grouped into two categories according to their structures and functions.[10] One group consists of molecules that structurally mimic quorum sensing signals, such as halogenated furanones and synthetic AI peptides (AIPs) that are similar to AHL and AIP signals, respectively. These inhibitors interfere with the binding of the corresponding signal to the receptor or decrease the receptor concentration. The other groups of small chemicals include enzyme inhibitors. For example, triclosan, a potent inhibitor of the enoyl-acyl carrier protein (ACP) reductase that is involved in the synthesis of acyl-ACP, one of the essential intermediates in AHL biosynthesis, reduces AHL production, and closantel is a potent inhibitor of histidine kinase sensor of the two-component system.

Various mechanisms involved in quorum sensing and quorum sensing inhibition are listed in Table 1.[7,9,11]

Mechanisms of small quorum-sensing inhibitors

The known small chemicals that inhibit quorum sensing can be roughly grouped into two categories according to their structures and functions. One group is the structural mimics of quorum-sensing signals, such as the halogenated furanones and the synthetic AIPs that are similar to the AHL and AIP signals, respectively. Evidence shows that these inhibitors act by interfering with the corresponding signal binding to the receptor,[12] or by decreasing the receptor concentration.[13] The other group of small chemicals is the enzyme inhibitors. For example, triclosan inhibits enoyl-ACP reductase whose product is the essential intermediate in AHL biosynthesis, and closantel is a potent inhibitor of histidine kinase sensor of the two-component system.

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