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Review Article

Quorum Sensing Versus Quorum Quenching: An Endless Battle

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ABSTRACT:
Biofilm can be defined as an aggregation of one or more groups of different microorganisms, embedded in a self-produced matrix and adhering to a firm surface. Many studies are being done on the benefits of a quorum sensing inhibition and its use in medicine. Hence; in the present review, we have attempted to summarize some of the significant aspects of Quorum sensing and Quorum quenching.
Key words: Plaque, Quorum sensing, Quorum quenching.

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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. 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.[1]

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]

Quorum sensing (QS) is a communication mechanism used by bacteria to recognize population density fluctuations and control gene expression, which play a critical role both in intraspecies and interspecies communications and regulates microbe-host interactions. Low-molecular-weight signal compounds, such as acyl-homoserine lactone and autoinducing peptide, are used by QS to control the expression of different pathogenic factors. Thus QS--and QS signal molecules in particular--is an attractive target for developing novel antimicrobial methods. Quorum-quenching enzymes, which hydrolyze or modify signal molecules in QS circuit systems to inhibit the expression of bacteria virulence factors, have been identified both in prokaryotes and eukaryotes. Understanding the mechanism of action of quorum-quenching enzymes also provides a promising means to control bacterial infection.[3, 4]

QUORUM SENSING

Quorum sensing (QS) is a signaling system that occurs in the pathogenic kingdom to sense its own population density and synchronize the expression of the virulence gene via the secretion of small, diffusible signal molecules, such as N-acyl-homoserine lactone (AHL), termed autoinducers. Autoinducers play a critical role in triggering virulence gene expression in QS-dependent pathogens, such as in the production of rotting enzyme. Interfering with the microbial QS system by quorum quenching (QQ) has been suggested as a potential strategy for disease control because QQ aims to shut down the virulence expression in pathogenic bacteria rather than restrict cell growth and has shown potential to overcome drug toxicities, complicated super-infection

and antibiotic resistance. The interest in enzymatic function for protecting against microbial infection has intensified in recent years. QQ enzymes have been identified in a number of bacteria that have shown considerable promise as quorum quenchers since AHL-lactonaseAiiA was first identified from Bacillus species to attenuate virulence in Erwinia carotovora.[4- 6]

QQ can be developed as a technique for disrupting the ability of a pathogen to sense its cell density and disable or diminish the capability of triggering the virulent expression. This capability ensures that the host has time to eradicate the pathogens naturally through normal immune system function, resulting in overcoming the pathogenic infection. Because it is different from conventional antibiotic therapy, which kills bacteria by interfering with DNA, RNA or protein synthesis, leading to the emergence of antibiotic-resistant superbugs, QQ is a promising approach that may lead to the development of very effective next generation antibacterial drugs based on interfering with bacterial communication to block QS-mediated pathogenic infection.[6, 7]

QUORUM SENSING OF PERIODONTAL PATHOGENS

The term 'quorum sensing' describes intercellular bacterial communication which regulates bacterial gene expression according to population cell density. Bacteria produce and secrete small molecules, named autoinducers, into the intercellular space. The concentration of these molecules increases as a function of population cell density. Once the concentration of the stimulatory threshold is reached, alteration in gene expression occurs. Gram-positive and Gram-negative bacteria possess different types of quorum sensing systems. Canonical LuxI/R-type/acyl homoserine lactone mediated quorum sensing system is the best studied quorum sensing circuit and is described in Gram-negative bacteria which employ it for inter-species communication mostly. Gram-positive bacteria possess a peptide-mediated quorum sensing system. Bacteria can communicate within their own species (intra-species) but also between species (inter-species), for which they employ an autoinducer-2 quorum sensing system which is called the universal language of the bacteria. Periodontal pathogenic bacteria possess AI-2 quorum sensing systems. It is known that they use it for regulation of biofilm formation, iron uptake, stress response and virulence factor expression.[8, 9]

QUORUM SENSING AND BIOFILM FORMATION

Biofilms are now considered ubiquitous in the natural world. In nature, bacteria are frequently found encased in polysaccharide matrix attached to a solid surface. This mode of growth, referred to as a biofilm, offers protection from environmental agents that would otherwise threaten their planktonic counterparts. Bacterial biofilms have been observed to be extremelyheterogeneous, both structurally and with regard to the physiologyof the bacterial cells within them. The prevailing conceptualmodel depicts bacterial biofilms as being made up of microcolonies,which serve as the basic unit of the greater biofilm structure. Microcolonies are hydrated structures consisting of bacterialcells enmeshed in a matrix of exopolymeric substances (EPSs).Bacteria may proliferate on the attachment surface, leadingto microcolony expansion. Eventually, community growth becomeslimited by substrate availability due to increased diffusiondistances, and the biofilm reaches a steady state. Such maturebiofilms often consist of "towers"and "mushrooms" of cells in anEPS matrix. Interstitial voids and channels separatethe biofilm structures and facilitate a convective flow in orderto transport nutrients to interior parts of the biofilm andremove waste products. Biofilmshave become evident in many, if not most, environmental, industrial,and medical bacteria related problems. A recent public announcementfrom the NIH stated that more than 60% of all microbial infectionsinvolve biofilms.[8- 10]

Gram-negative bacteria use N-acyl homoserine lactone (AHL)auto inducer signal molecules for quorum sensing. Three core components of all AHL based quorum sensing systems are:

i. The LuxI-type synthase molecule
ii. The AHL signaling molecule
iii. The LuxR type receptor protein.[11]

Gram-positive bacteria use peptides processed from precursors as autoinducers. These are auto inducing peptides; Gram-positive bacteria use two processes in quorum sensing. They are:

1. A two component signal transduction system
2. Internalization.

Dental plaque is the etiologic factor for periodontitis. Dental plaque is in the form of a bio-film and is difficult to completely eliminate. At present, the treatment of periodontitis is based on mechanical removal of the bio-film by scaling and root planning along with adjunctive use of antibiotics. The problem with this approach is that the bio-film formation restarts immediately after the mechanical cleaning has finished, and antibiotics cannot be used continuously. A lot depends on the oral hygiene maintained by the patient. What we need is a treatment approach, which either delays or disrupts the bio-film formation along with patient's oral hygiene measures.[11, 12]

USING BACTERIAL COMPONENTS TO MANIPULATE QUORUM SENSING

Quorum Quenchers

Dong et al initially identified AiiA from Bacillus species and showed that this enzyme inactivates the AHL signal and attenuates virulence when expressed in Erwiniacarotovora. Another study on quorum quenching isolated more than 20 bacteria belonging to the Bacillus cereus group which were capable of enzymatic inactivation of AHLs. Further genetic analyses revealed that the enzymes responsible for AHL inactivation were homologs of AiiA from Bacillus species strain 240B1. This enzyme is an AHL lactonase, known to act by hydrolyzing the lactone bond in the AHL. A second class of quorum-quenching enzymes was identified in Ralstonia strain XJ12B. The acylaseAiiD isolated from

this strain is capable of hydrolyzing the AHL amide. Expression of AiiD in P. aeruginosa PAO1 decreased its ability to swarm, produce elastase and pyocyanin and paralyze nematodes, all of which are quorum-sensing regulated phenotypes in this bacterium.[13]

Quorum quenching enzymes

Bacteria use cell-to-cell communication systems based on chemical signal molecules to coordinate their behavior within the population. These quorum sensing systems are potential targets for antivirulence therapies, because many bacterial pathogens control the expression of virulence factors via quorum sensing networks. Since biofilm maturation is also usually influenced by quorum sensing, quenching these systems may contribute to combat biofouling. One possibility to interfere with quorum sensing is signal inactivation by enzymatic degradation or modification. Such quorum quenching enzymes are wide-spread in the bacterial world and have also been found in eukaryotes. Lactonases and acylases that hydrolyze N-acyl homoserine lactone (AHL) signaling molecules have been investigated most intensively, however, different oxidoreductases active toward AHLs or 2-alkyl-4(1H)-quinolone signals as well as other signal-converting enzymes have been described. Several approaches have been assessed which aim at alleviating virulence, or biofilm formation, by reducing the signal concentration in the bacterial environment. These involve the application or stimulation of signal-degrading bacteria as biocontrol agents in the protection of crop plants against soft-rot disease, the use of signal-degrading bacteria as probiotics in aquaculture, and the immobilization or entrapment of quorum quenching enzymes or bacteria to control biofouling in membrane bioreactors. While most approaches to use quorum quenching as antivirulence strategy are still in the research phase, the growing number of organisms and enzymes known to interfere with quorum sensing opens up new perspectives for the development of innovative antibacterial strategies.[14, 15]

Applications of enzyme-based quorum quenching

Different biocontrol strategies have been assessed which aim at reducing the QS signal concentration in the bacterial environment, in order to control infections by plant or animal pathogens, or to mitigate biofouling. However, since bacteria use QS to control many functions that are essential for their competitiveness or for the establishment of beneficial interactions, possible negative effects of QQ cannot be excluded. For example, AHL signalling contributes to the symbiotic relationship between N2-fixing rhizobacteria and leguminous plants. Expression of an aiiAlactonase in Sinorhizobiummeliloti indeed was observed to reduce its efficiency in initiating root nodule formation on Medicagotruncatula host plants.[16]

The biocontrol strain Pseudomonas chlororaphis relies on phenazine production for protection of plants against Fusariumoxysporum. Recombinant Pseudomonas fluorescence producing an AiiAlactonase, when coinoculated together with P. chlororaph is into tomato plants, severely impaired the protective activity of the biocontrol strain. These examples illustrate that QQ approaches directed toward “general” signals such as AHLs that are used by many bacteria must be assessed with great care, especially when addressing complex communities in their natural environment.[17]

Strategies aiming at inhibiting a limited group of bacteria, or even individual pathogens, should be less prone to affecting beneficial organismic interactions and should be promising tools for selective disease control. Therefore, QS systems that are less wide-spread, such as the AQ-based systems of P. aeruginosa or Burkholderia pseudomallei, are attractive targets for interference.[18]

The discovery of antibiotics to eliminate infectious diseases has been one of the most remarkable medical achievements at the beginning of twentieth century. However, within the past few decades, bacteria have rapidly co-evolved to become resistant against antibiotics through horizontal gene transfer or by mutation in target genes. These issues must be addressed, and that need is growing. Currently, the uncontrolled use of antibiotics has led us to the nascent era of antibiotic-resistant microorganisms, commonly known as multidrug-resistant (MDR) and extensive drug resistant (XDR) microorganisms. The WHO (World Health Organization) has reported a serious shortfall in the new antibiotics pipeline to defeat the growing threat of antimicrobial resistance, mainly because most of the drugs currently in clinical trials are modifications of existing antibiotics and are only short-term solutions. The WHO has also published a list of “antibiotic-resistant priority pathogens"—a catalog of 12 families of bacteria divided into three categories. These are sorted upon the urgency of the need for new antibiotics as critical, high, and medium, to guide and encourage research and development of new antibiotics.[17- 19]

An alternative approach: quorum sensing (QS), has been discovered that bacteria are able to communicate through signalling pheromones or auto-inducers by a system called QS, a specialized mechanism used to sense population density. Bacteria are able to sense their own population density and use it as a trigger to switch to virulent and pathogenic behaviors that can facilitate their survival. It has been essential to find better strategies to tackle this serious issue, which led to the discovery of QS quenchers or QS inhibitors (QSIs). QSIs inhibit QS of bacteria (e.g., through the inactivation of virulence factors) rather than killing them, which helps to decrease damage to commensal microbiota.[19]

CONCLUSION

Quorum sensing restriction in periodontal treatment is still in the research stage, and more research needs to be done on natural products that can inhibit quorum sensing in periodontal pathogens.From a wider perspective, question still exists in relation to the ecological role of quorum sensing and quorum quenching in the oral microbiota.

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