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REVIEW ARTICLE

QUORUM SENSING VS QUORUM QUENCHING: A COMMUNICATING MECHANISM IN PERIODONTAL PATHOGENS AND ITS INHIBITION - A REVIEW

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ABSTRACT

The human oral cavity is similar to an ecosystem and interactions among oral bacteria is important for the development of oral biofilm. For survival in the bio film, these microorganisms may express intra and/or inter species communication mechanisms by means of physical contact, signaling molecules, exchange of genetic material or metabolic products etc. This article deals with the process of quorum sensing which enables the bacteria for coordination of their behavior at a population level by the synthesis, release and subsequent detection of small diffusible molecules known as auto inducers and various approaches to inhibit this communication to control the diseases caused by bacteria. New approaches to treat periodontal disease using quorum sensing inhibition need to be explored as a future treatment strategy.

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INTRODUCTION

Major etiological factor of periodontal disease is dental plaque (oral biofilm) which is a complex microbial community comprising of several different bacterial species (Hanjuanshao and Donald r. Demuth, 2010). Bio film can be defined as aggregation of groups of different microorganisms, embedded in a self-produced matrix and adhering to a firm surface (Darije Plančak *et al.,* 2015).The oral biofilm is a dynamic community that forms on the tooth and tissue surfaces at high cell density (Socransky and Haffajee, 1992).Within the biofilm, they get a favorable environment for growth and are protected from antibacterial substances. For survival, oral biofilm bacteria must be capable of detecting and responding to the challenges in oral environment such as fluctuations in nutrient availability, PH, temperature and osmolarity (Hanjuanshao and Donald r. Demuth, 2010). As cell population density increases microorganisms can sense and respond to it by induction of genes by the process of quorum sensing. This includes the synthesis and release of low-molecular-weight signaling molecules known as auto inducers, which diffuse readily through the cell wall (Khmel *et al.,* 2008). Quorum sensing (QS) can be defined as a biological process by which bacteria are able to communicate, which modulates the expression of genes involved in processes related to survival, biofilm formation, virulence, and pathogenicityin response to cell density (Greenberg, 2007., March and Bentley, 2004 and Henke and Bassler, 2004). The bacterial communication within the biofilm plays a crucial role in initiation and progression of the periodontal disease. Therefore, for the formulation of a successful treatment regime for periodontal disease, understanding of these complex microbial communication mechanisms becomes essential (Fuqua *et al.,* 1994). The inhibition of quorum sensing by the use of enzymatic or non-enzymatic molecules is referred to as "quorum quenching". The process of quorum quenching may have a role in controlling periodontal infections. Newer methods and molecules that can inhibit the bacterialbio-film formation will be a future treatment strategy in fighting periodontal disease (Charu Gera and Srivastava, 2006).

Literature search and inclusion criteria: A survey of the literature was conducted using the databases MEDLINE/Pub Med. Cross-checking the bibliographies of relevant review articles have also been done.

Quorum Sensing, The term quorum-sensing was first used by Fuqua *et al*. (1994), which reflects the minimumthreshold level of individual cell mass required to initiate a population response (Lazazzera and Grossman, 1998). With the increase in number of cells in a bacterial colony the concentration of the auto inducers in extra cellular environment increases.

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As a threshold concentration is reached, binding of the auto inducer to cognate receptors of bacterial cells occurs, thus triggeringa signal transduction cascade and results in changes in gene expression (Shapiro, 1998).Hence quorum sensing can be defined as a regulation of gene expression in accordance with cell-population density (Darije Plančak *et al.,* 2015). Increased synthesis of the signal molecule causes a positive feedback loop, so quorum signals are calledautoinducers (Lazazzera and Grossman, 1998).

Historical Aspect of Quorum Sensing

The quorum-sensing system was first described in Vibrio fischeri which is a bioluminescent marine bacterium.In the light organ of the Hawaiian squid *Euprymnascolopes,* V.fischericolonizes and induce the expression of genes required for bioluminescence. The squid uses the light produced by the bacteria for counter illumination and the bacteria benefit from the rich nutrients available in the organ. When a *V. fischeri* cell is alone, the auto inducer acyl homoserine lactone (3 oxo C6 HSL, an AHL) is at a low concentration, and at high cell concentrations, the level of the auto inducer becomes sufficient to induce transcription of the genes that produce the enzyme luciferase, leading to bioluminescence (Charu Gera and Srivastava, 2006).

The sensory mechanism for production and response to the signal was found to consist of two proteins, which were designated LuxI and LuxR (Lazazzera and Grossman, 1998). LuxI and LuxR proteins control expression of the luciferase operon (*luxICDABE*) required for light production. LuxI is the auto inducer synthase, which produces the acyl-homoserine lactone (AHL/acyl-HSL) autoinducer and LuxR is the cytoplasmic auto inducer receptor/DNA binding transcriptional activator. AHL freely diffuses and increases in concentration with increasing cell density and when the signal reaches a critical, threshold concentration, LuxR-AHL complex is formed and this activates transcription of the operon encoding luciferase .This complex also induces expression of *luxI*because it is encoded in the luciferase operon. Thus the regulatory configuration creates a positive feedback loop that causes the population to switch into "quorum-sensing mode" and produce light (Shapiro, 1998).

Quorum Sensing Systems

QS system can be divided into three classes

- LuxI/Lux R type quorum sensing system utilizing fatty acid derivatives, called acyl homoserine lactones(AI1) in gram negative bacteria
- Oligopeptide/two component type quorum sensing system utilizingamino acids and short peptide derivatives(AI2) in gram positive bacteria
- Lux S encoded autoinducer-2 in both gram positive and gram negative bacteria (Dunny and Winans, 1999., Whitehead *et al.,* 2001., Costi and Sifri, 2008 and Christopher *et al.,* 2005).

Majority of gram-negative bacteria possess LuxIR-type proteins with AHL signals, used predominantly for intraspecies communication. Gram-positive bacteria use modified oligopeptides as signals and histidine kinases as receptors. Intraspecies quorum sensing is mostly facilitated through small peptides and interspecies communication has been linked to auto inducer 2 (AI 2), a furanosyl borate diester (Dunny and Winans, 1999., Whitehead *et al.,* 2001., Costi and Sifri, 2008 and Christopher *et al.,* 2005).

Quorum Sensing -Process: (FIG 1)

- Synthesis of small biochemical signal molecules by the bacterial cell.,
- release of the signal molecules into the surrounding medium.,
- Recognition of the signal molecules by specific receptors as they exceed a threshold concentration,
- Changes in gene regulation (Shapiro, 1998).

Quorum-Sensing Network Architecture: There are various signaling architectures and each particular network arrangement leads to distinct signaling features.

Parallel Quorum-Sensing Circuits: In Vibrioharveyi, quorum-sensing system consists of three auto inducers and three cognate receptors functioning in parallel to channel information into a shared regulatory pathway .This parallel arrangement may allow the network to function as a coincidence detector that significantly activates or represses gene expression only when all signals are simultaneously present or absent , may be critical for filtering out noise from the true signals and/or noise from signal mimics produced by other bacteria (Bassler *et al.,* 1993).

Quorum-Sensing Circuits Arranged in Series: In P. aeruginosa, regulatory systems are arranged in series rather than in parallel and is responsive to multiple auto inducers. This network architecture produces a temporally ordered sequence of gene expression that may be critical for the ordering of early and late events in a successful infection (Murray *et al.,* 2007).

Competitive Quorum-Sensing Circuits: These quorum-sensing networks are arranged such that the signals antagonize one another. Bacillus subtilis has two auto inducing peptides functioning in a network arrangement that allows B. subtilis to regulate two different developmental pathways: competence (the ability to take up exogenous DNA) and sporulation (Bassler *et al.,* 1993).

Quorum-Sensing Circuits with on-off Switches: These quorum-sensing circuits allow bacterial transition from a set of low cell density behaviors to a different set of high cell density behavior., promote transient expression of particular traits followed by reversion to the original set of behaviors. Such an on-off switch controls competence development in the Gram-positive bacterium Streptococcus pneumonia by autoinducer-competence stimulating peptide (CSP) to monitor cell density (Bassler *et al.,* 1993).

Quorum Sensing in Periodontal Pathogens: Culture medium from Fusobacteriumnucleatum, Porphyromonasgingivalis, and Prevotellainter media induced bioluminescence in the reporter strain, suggest that these organisms produce autoinducer2. Aggregatibacter actinomycetemcomitans, possesses an AI2 dependent quorum-sensing system, regulates expression of virulence factors, biofilm formation, iron uptake, influences the planktonic growth of the organism under conditions of iron limitation and upregulatesleukotoxic activity and production of leukotoxin polypeptide. AI 2 induced expression of AfuA, a periplasmic iron transport protein, fec BCDE, a putative ferric citrate transporter, and ftn AB, ferritin, suggest therole of LuxS

Table 1.

	ORIGIN	MOLECULES
1	Coffee extract	caffeine
2	Citrus flavonoids	flavoninenaringenin
3	Clove extract	eugenol,hexane and methanol[38]
4	Garlic	disulfides and trisulphides
5	Grapefruit extract	furocoumarins, carotenoids, limonoids, pectin, coumarin
6	Horseradish	Iberin
7	Nutmeg (Myristicacinnamomea)	nutmeg (Myristicacinnamomea) alabaricone C
8	Piper nigrum, Piperbetle and Gnetumgnemon	hexane, chloroform, and methanol[39]
9	Red marine alga (D. pulchra)	halogenated furanones
10	Sponge Agelasoroides	alkaloid oroidin
11	Sweet basil	osmarinic acid
12	Turmeric	Curcumin

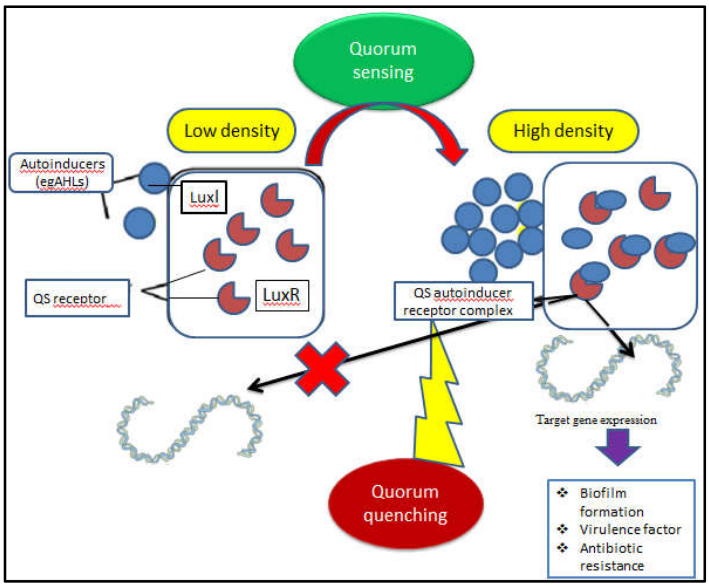

Fig. 1.

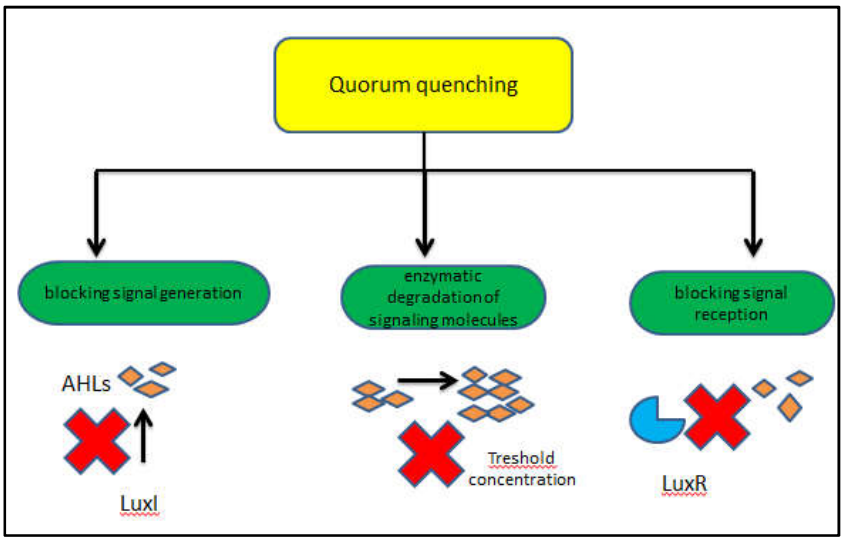

Fig. 2.

dependent signaling in the regulation of iron acquisition in A. actinomycetemcomitans. Iron acquisition is required for pathogens to survive within a host, so factors related to iron acquisition are considered as virulence factors. P. gingivalis obtains iron preferentially through the acquisition of hemin. LuxSmutant strain exhibited differential regulation of genes involved in various pathways of hemin uptake and acquisition (Shao *et al.,* 2007).

Quorum Sensing and Biofilm Formation: The intra and inter species bacterial communication plays role in the formation, growth, and maturation of the dental plaque and improves their chance of survival. Physical communication provides the site for adherence., metabolic communications favour the environmental changes for the growth of pathogens., signaling molecules help to regulate their response to changes in the environment., and genetic

communication helps to attain the microbial resistance against the antibiotics (Ajay Mahajan *et al.,* 2013). Quorum sensing play diverse roles such as modulating the expression of genes for antibiotic resistance, encouraging the growth of beneficial species in the biofilm, and discouraging the growth of competitors. Thus the bacterial communication has a major role in the etiopathology of the periodontal disease. Auto inducer 2 quorum sensing is closely linked to theability of A. actinomycetemcomitans to grow in a biofilm (Shao *et al.,* 2007). Cell to cell communication in S.mutans is induced by A.actinomycetemcomitans. S.mutans down regulated the expressionof genes encoding chaperones and genes involved in oxidative stress in co culture with A. acomitans suggesting protection from oxidative stress.

Two genes involved in immune response evasion, encoding catalase Kat A and the complement resistance protein ApiA were repressed suggesting A.acomitans more susceptible to the host immune defense in the presence of S.mutans. This explains negative relationship between caries and aggressive periodontitis (Shao *et al.,* 2007). S.mutans down-regulated the expression of genes involved inP. Gingival is which is known to adhere to some of the oral streptococci in a species specific manner (i.e., P. gingivalisadheres to species of viridans streptococci but not tomutans streptococci) and this may represent one mechanism by which P. gingivalis identifies a suitable niche for initial colonization of the dental biofilm. AI 2 cross talk occurs indual-species biofilms of Streptococcus gordonii and P. gingivalis. In this system, dual-species biofilms formed efficiently evenif one of the strains harbored a luxS mutation, but nobiofilms formed if both strains were LuxS deficient.AI2 mediated cross talkis possible between A. actinomycetemcomitans and P. gingivalisand that the AI 2 signal of A. actinomycetemcomitans is capableof modulating the expression of luxS regulated genesin P. gingivalis. The ability of Actinomycesnaeslundii and Streptococcus oralis to form dual species biofilms in saliva was dependent on AI 2 produced by S. oralis. The inability to detect or respond to AI 2 prevents the stimulation of theAI 2 response circuit and results in reduced biofilm growthand attenuated virulence, whereas the inability to produceAI 2 is likely overcome by the presence of exogenoussignals produced by other bacteria in the murine oral cavity.In P. aeruginosa, a lasI mutant was found to produce a thinner biofilm that was more susceptible to disruption by detergents. Hence strategies designed to block Quorum sensing may be an effective means of preventing biofilm formation (Persson *et al.,* 2005).

Measuring Quorum Sensing

Technique for measuring quorum sensing developed by Bassler et al. is based on the bioluminescent response of V. harveyi. A cell free conditioned medium from a culture of interest is incubated with a culture of V. harveyi and the bioluminescent response is recorded (Bassler *et al.,* 1993). Frommberger et al investigated a liquid chromatography based concentration and separation method with mass spectrometer determination of various AHLs in bacterial culture anda colorimetric method for determining salicylic acid carboxyl methyltransferase (SAMT) activity has been reported (Frommberger *et al.,* 2004). Hernández Getal used PCR probes and the random amplifiedpolymorphic DNA (RAPD) method for identifying V. harveyi pathogenic to shrimp, by building a consensusquorum gene cassette consisting of an autoinducing peptide,a receptor kinase, and a response regulator (Hernández and Olmos, 2004). Nakayama *et al*. distinguished PCR amplified quorum sensing regions from *Enterococcus*, *Clostridium*, and *Lactobacillus* species (Nakayama *et al.,* 2003) and Potvinetal screened *P. aeruginosa*mutants for infectivity ina rat model using signature tagged mutagenesis (STM) andhigh-throughput screening (Potvin *et al.,* 2003).

Quorum Sensing as a Therapeutic Target: Compounds that inhibit quorum sensing have been emerging as potentially novel class of antimicrobial agents (Vasil, 2003). Pharmacologic inhibition of quorum sensing is an attractive approach for the prevention or treatment of chronic infections like cystic fibrosis or chronic wound infections (2 Dong *et al.,* 2007).

Quorum Quenching: The biofilm formation can be controlled by inhibiting thequorum sensing mechanism of bacteria that form the plaque biofilm. The process of inhibitionof quorum sensing is commonly referred to asquorum quenching (Mounika Basavaraju *et al.,* 2016).(,Fig2) This can be accomplished by, (De Kievit and Iglewski, 2014)

- Enzymatic degradation of signaling molecules
- Blocking signal generation., and
- Blocking signal reception.

Enzymatic Degradation of Signaling Molecules

Enzymes such as - acylase, lactonase, oxireductases canselectively inactivate AHL in Gram-negative bacteria and dueto this AHL accumulation in the extracellular environmentdoes not occur and QS regulated genes are not expressed (Chen *et al.,* 2013).
Bacillus species produced anenzyme termed AiiA that catalyzed the hydrolysis of AHLmolecules. Many AHL lactonases similar to AiiA have beenrecognized (Givskov *et al.,* 1996).

Blockage of Ai Synthesis: AHL production can be blocked by developing structuralanalogs of S-adenosyl methionine and acyl carrier protein. For E.g. Molecules like - L/D-S-adenosylhomocysteine, S-adenosylcysteine, and sinefungin suppress production of AHL. Some macrolide antibiotics like erythromycin are capable of repressing AHL synthesis when applied at lower concentrations (Chen *et al.,* 2013).

Inhibition of AHL Signal Reception: Quorum sensing can be inhibited by preventing the AHL molecule from binding to its receptor. It can be competitiveinhibition by molecules that bind to the receptor in preferenceto the AHL molecule. Slight changes in AHL acyl side chainor in the lactone ring or changes in both acyl side chain andlactone ring produce molecules that can bind with LuxR typereceptor protein, but will not cause the signal generation (Chen *et al.,* 2013).

Quorum Sensing Inhibitors., According to the structure and functions, quorum sensing inhibitors are of two groups (Chen *et al.,* 2013).

Group I

Consists of molecules that structurally mimic quorumsensing signals. For example halogenated furanones and synthetic AI peptides (AIPs) which are similar to AHL and AIP signals, respectively. These interfere with the binding of the corresponding signal to the receptor (Givskov *et al.,* 1996) or decrease the receptor concentration (Lyon *et al.,* 2000). Furan ones (produced by Australian red alga Deliseapulchra) have

structural similarity to AHLs (Manefield *et al.,* 2002). Binding of furan ones to LuxR (in E.Coli) renders it highly unstable and accelerates its turnover rate. These molecules completely inhibits swarming motility and biofilm formation in E. coli and bioluminescence in AI-1 and AI-2 indicator strains of V. harveyi (Ren *et al.,* 2001). Studies in E.Coli showed that human hormones like epinephrine/ norepinephrine signals cross communicate with its quorum sensing system via LuxS dependent AI3, which in turn might influence the infectious process (Ren *et al.,* 2001).

Group II

Includes enzyme inhibitors such as triclosan,closanteletc(29). Triclosan reduces AHL production by inhibitingenoyl-acyl carrierprotein (ACP) reductase, which is an essential intermediate in AHL biosynthesis. Closantel is apotent inhibitor of histidine kinase sensor of the twocomponentsystem (Chen *et al.,* 2013). AHL-lactonases is a member of the metallohydrolasesuper-family, hydrolyze the lactone ring inthe homoserine moiety of AHLs (Sperandio *et al.,* 2003). AHL-acylase degrades AHL signals by hydrolysing theamide bond of AHLs and producing corresponding fatty acids and homoserine lactone (Teplitski *et al.,* 2000). Paraoxonase (PON) enzymes, exhibit a wide range of physiologically important hydrolytic activities, includingdrug metabolism and organophosphate detoxification (Esterela and Abraham, 2013).

Quorum Quenching Molecules: Source of quorum quenching compounds are plants (Koh *et al.,* 2013), bacteria, fungi, algae, protozoa and sponges. (Table1) Marine cyanobacteria is the best source for obtaining biologically active and structurally unique quorum quenching natural products (Koh *et al.,* 2013).

Quorum Quenching in Periodontal Disease

Periodontal pathogens like Porphyromonasgingivalis, ActinobacterActinomycetumcommitans communicate and coordinate their pathogenic behavior through quorum sensing. Hence means of inhibiting quorum sensing may have arole in controlling periodontal infections. The AI-2 and CSP system can be used as target for weakening bacterial virulence by interfering with cell-to-cell communication. A new class of specifically targeted antimicrobial peptides (STAMPs) has been reported for use which have two-sided structure. The first is a shorthoming sequence of CSP, as unique to a bacterium as afingerprint and will find their target. The second is a non-specific antibacterial peptide that is linked chemically to the homing sequence and kills the targeted bacteriumon delivery. It has been suggested that STAMPs, which weredesigned based on the CSP of *S. mutans*, are potentially capable of eliminating *S. mutans* from multispecies biofilms without affecting the closely related oral streptococci such as *S. gordonii*and *S. sanguinis* (Eckert *et al.,* 2006).Hence along with mechanical plaque removal and dailyoral hygiene measures quorum sensing inhibitors may help to reduce periodontal disease initiation and progression.ie use of quorum quenching molecules as therapeutic agents mayhave some benefit in controlling periodontal disease (Sudheer *et al.,* 2015., Dong *et al.,* 2007 and Biradar and Devi, 2011).

Conclusion

In a biofilm the microorganisms work in a well-coordinated manner and intra and interspecies communication plays an important role in the formation and maturation of the biofilm. For assessing the pathogenic ability of oral bacteria, it is essential to consider the community as a whole rather than of individual components. We can control the structure of biofilm by promoting or inhibiting the bacterial communication. This will open a new era of periodontal therapy .ie oral health could be achieved by promoting the interactions between the commensal bacteria, and by blocking the interaction among the periodontal pathogens. Development of therapeutic agents which can control bacterial communication may offer an alternative to antibiotics and reduce the risk for development of antibiotic resistance. Quorum quenching compounds are being innovated as alternative of antibiotics to treat pathogenic-infections. Future research is necessary for attaining this promising and fascinating therapeutic regime.

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