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Review Article

Quorum Sensing Inhibition, Relevance to Periodontics

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Abstract:

Quorum sensing helps bacteria to communicate with each other and in coordinating their behavior. Many diseases of human beings, plants, and animals are mediated by quorum sensing. Various approaches are being tried 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 explored.

Key Words: Acyl homoserine lactone, bio-film, periodontitis, quorum sensing, quorum sensing inhibition, quorum quenching

Introduction

Microorganisms communicate with each other through chemical molecules secreted by them. These chemical molecules are useful in both intra and inter-species communication and help the bacteria in coordinating their behavior. The process by which microorganisms monitor and regulate their population density through chemical signaling is termed quorum sensing (Federle and Bassler, 2003).[1]

Quorum Sensing

Quorum sensing enables the bacteria to coordinate their behavior along with other bacteria. Various characteristic features such as motility, toxin production, bio-film formation, etc. are modulated by quorum sensing. When bacteria are in individual state, they are susceptible to host immune response and the action of antibiotics. When they are in the form of a bio-film the host immune cells and antibacterial agents find it difficult to destroy them. We need large doses of antibiotics to fight the bacteria in the bio-film form. The creation of these bio-films is regulated by quorum sensing signaling. In general, when bacteria are in less numbers, the quorum sensing signal concentration is less, as the number of bacteria increases, signal concentration increases, and at a certain level quorum needed to activate the genes is reached, then gene expression occurs leading to the production of various products which increase bacterial pathogenicity. Ex., bio-film formation. Some bacteria like cholera bacteria use quorum sensing to dissolve the bio-film leading to dispersal of bacteria causing a highly infectious condition.

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.

Gram-positive bacteria use peptides processed from precursors as autoinducers. These are auto inducing peptides (Sifri, 2008), 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 planing 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.

Quorum quenching-quorum sensing inhibition

The bio-film formation can be disrupted by disturbing the quorum sensing mechanism utilized by the various species of bacteria that together form the plaque bio-film. The inhibition of quorum sensing is commonly referred to as "quorum quenching." It initially meant stopping quorum sensing by enzymatic hydrolysis of AHL autoinducers, there have been changes and presently the phrase quorum quenching is

now commonly used in a more general sense to refer to any inhibition of quorum sensing due to the use of enzymatic or non-enzymatic molecules.[2]

Quorum sensing can be blocked by stopping the signal molecule production, destroying the signal molecule, and by preventing the signal molecule from binding to its receptor.

Blockage of AI synthesis

AHL production can be blocked by developing structural analogs of S-adenosyi methionine and acyl carrier protein. E.g. Molecules like - L/D-S-adenosyl homocysteine, *S*-adenosylcysteine, and sinefungin suppress production of AHL. Some macrolide antibiotics like erythromycin are capable of repressing AHL synthesis when applied at lower concentrations. It is not known clearly how these antibiotics interfere with bacterial quorum sensing.

Inactivation of AI in Gram-negative bacteria

Enzymes such as - acylase, lactonase, oxireductases can selectively inactivate AHL in Gram-negative bacteria and due to this AHL accumulation in the extracellular environment does not occur and QS regulated genes are not expressed.[3]

Dong *et al*. found a *Bacillus* species that produced an enzyme termed AiiA that catalyzed the hydrolysis of AHL molecules. Many AHL lactonases similar to AiiA have been recognized. E.g. AttM in *Agrobacterium tumefaciens*, AiiB in *A. tumefaciens* C58, AiiS in *A. tumefaciens* K84, AhlK in *Klebseilla pneumoniae*.

Inhibition of AHL signal reception

Quorum sensing can be inhibited by preventing the AHL molecule from binding to its receptor. It can be competitive inhibition by molecules that bind to the receptor in preference to the AHL molecule. Slight changes in AHL acyl side chain or in the lactone ring or changes in both acyl side chain and lactone ring produce molecules that can bind with LuxR type receptor protein, but will not cause the signal generation.

Quorum sensing blockage by molecules produced by various plants, algae, and other organisms.

Various plants, algae, fungi, etc. produce molecules which might play a role in inhibiting quorum sensing in bacteria. Some of them are:

- Horseradish-Iberin[4]
- Garlic-ajoene[4]
- Turmeric-curcumin[4]
- Citrus flavinoids-flavonine naringenin[4]
- Sponge *Agelas oroides*-alkaloid oroidin[4]
- Red marine alga known as *Dalea pulchra*-halogenated furanones[5]
- Grape fruit extract-furocoumarins, carotenoids, limonoids, pectin, and coumarin[5]
- Nutmeg (*Myristica cinnamomea*)-Malabaricone C[5]
- Nutmeg (*M. cinnamomea*)-Alabaricone C[5]
- Sweet basil-osmarinic acid[5]
- Garlic-disulfides and trisulphides[5]
- Clove extract-eugenol[6]
- Clove extract-hexane and methanol[7]
- *Piper nigrum*, *Piper betle* and *Gnetum gnemon*-hexane, chloroform, and methanol[8]
- Coffe extract-caffeine[9]

Quorum quenching in periodontal bacteria

Many oral bacteria like *Porphyromonas gingivalis, Actinobacillus, Actinomycetum commitans*, *Streptococcus* species, etc. are known to communicate and coordinate their pathogenic behavior through quorum sensing. Various means of inhibiting quorum sensing that we have discussed above may have a role to play in controlling periodontal infections. These methods along with mechanical plaque removal, daily oral hygiene may help us reduce periodontal disease severity. We have seen that many plant products have quorum quenching potential, use of such plant based molecules may cause some benefit in oral cavity.

Discussion

Many studies are being done on the benefits of a quorum sensing inhibition and its use in medicine. Much research has been done on *Pseudomonas aeruginosa*. Quorum sensing plays a major role in pathogenicity of *P. aeruginosa*. Many of the above-mentioned molecules play a role in inhibiting quorum sensing in *P. aeruginosa*. Research is being done on benefits of a quorum sensing inhibition in addition to antibiotics. Effect of quorum quenching in controlling periodontal disease needs more research. Newer molecules that can inhibit the bacterial bio-film formation will be a welcome addition to our arsenal in fighting periodontal disease. All these new treatment modalities are useful additions, but good oral hygiene is and will be a gold standard for periodontal health.

Conclusion

Quorum sensing inhibition in periodontal treatment is still in the research stage, more research needs to be done on natural products that can inhibit quorum sensing in periodontal pathogens.

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