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Research Paper

Current strategies in prevention of streptococcus mutans and candida albicans biofilms in caries progression. A literature Review

Dr Ambikathanaya U.K[1], Dr Sunil Tejaswi K.L[2]
[1-] *Lecturer Dept of Conservative Dentistry and Endodontics,JSSDCH ,JSSAHER,Mysore*
[2-] *Reader Dept of Conservative Dentistry and Endodontics,JSSDCH ,JSSAHER,Mysore*
Corresponding Author
Dr Ambikathanaya U.K, Lecturer Dept of Conservative Dentistry and Endodontics,JSS Dental College and Hospital ,JSSAHER, Mysore
ambikathanayauk@gmail.com

Abstract
Dental caries is the microbial dental disease that commonly found in all the age group of the population which effects oral health of an individuals. The predominant factor is the biofilm formation later which matures into plaque, progress into demineralization of the teeth at a particular pH. Therefore biofilm formation plays an important role in demineralization process. Recent studies has revealed that biofilm formation with polymicrobial species had predominant effect when compare to single microbial species. C albicans along with S mutans had a major role in demineralization process. New innovative approaches helps in inactivating microorganisms and removal of biofims.

Key Words: *Dental Caries, S mutans, C albicans, Biofilms, Innovative approaches*

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I. Introduction

Dental caries is one of the most common oral disease that cause socioeconomic burden to the humans. It is one of the highest oral disease that ranked one in incidence and two in prevalence.[1] Root caries is a subtype of dental caries that affects majority of age old individuals.[2] It occurs when there is a gingival recession or when root portion is exposed to oral environment. It is a polymicrobial infectious disease which is associated with acidogenic/aciduric species.(ex Streptococcus mutans and Streptococcus sanguinis).[3] There is a positive correlation exist between these two microorganisms, apart from that studies has revealed that role of microbial ecology plays a vital role in the development of root caries.[4,5]

Dental plaque is a biofilm consisting of multiple bacterial and fungal species. Bacteria in the mature biofilm ferment sugars into acids, most notably lactic acid which results in demineralization of the teeth. Studies concentrate on polymicrobial cause of dental caries rather than single bacterial species. S mutans produce dextransucrase which is an essential component of the mature biofilm matrix. C albicans is a opportunistic pathogen which causes mucosal and systematic infections.[6,7]

S mutans is highly prevalent bacteria in biofilm inhabited with C albicans. It uses the lactic acid produced by the S mutans for its own metabolism which reduces the oxygen tension to preferred levels for S mutans and finally C albicans provide growth stimulatory factor for S mutans. [8] Lactic acid is the most preferred carbon source in hypoxic condition for C albicans. Saccharolytic bacteria quickly metabolize all available sucrose into lactic acid forcing C albicans to rely on it for carbon source. It provides new adhesion sites for S mutans cells via dextran on the hyphal body, which might not have been able to attach to the substrate otherwise.[9]

Candida albicans is a common fungal species which is found among 18 to 40% healthy individuals. It is higher among immune comprised patients. Hyphal formation and pH levels are essential for C albicans pathogenecity.It has significant impact on virulence of polymicrobial biofilm.[10,11,12] There is a positive correlation between C albicans and early childhood caries. [13,14,15] C albicans is significantly found in root

caries lesions. It cause significant microbial dysbiosis with distinct microbial composition and structure as compared to biofilm without C albicans. These results revealed that candida species impact on bacterial biofilm specially among denture patients leading to more cariogenic biofilm.[16] Studies states that deletion of gene among C albicans responsible for hyphae formation results in inhibition of cariogenicity of C alibicans/S mutans mixed biofilms.[17] Apart from that robust production of extracellular α glucans by S mutans via glycosyltransferases (GTFs) under sugar rich condition plays an important role among coaggregation and biofilm formation of C albicans which in turn promotes the growth and GTFs expression of S mutans by secreting polysaccharides,quorum sensing molecules as well as metabolic cross feedings.PHR2 the gene in C albicans responsible for environment adaptation under differed pH condition.[18,19] Therefore deletion of PHR2 gene inhibits the cariogenic promoting effect of C albicans on the biofilms

Biofilms are highly organized communities of microorganisms attached to biotic and abiotic surfaces and surrounded by extracellular matrix. Composition, activities and interactions among these microbial communities maintain normal levels of fluctuations. Dysbiosis state occurs which results in pathogenic state of microorganisms which trigger infectious diseases such as caries, periodontitis and peri implantitis.[20,21] These factors includes excessive carbohydrates consumption ,reduced salivary flow,alcohol or tobacco overuse, poor oral hygiene and so on.[22,23] Recent years candida species infection is well recognized and role in etiology of caries has gained more attention. It forms dense biofilms that comprise yeast cells, pseudo hyphae.[24] It co adhere with pioneer bacteria to achieve tight adhesion to tooth surface , it does not decompose sucrose due to lack of α glucosidase, but metabolize fructose, glucose or lactose to produce short chain carboxylic acids to lower the pH. It shows acid tolerance which is related to the proton pump and H^+ ATPases on the cell membrane surface. Its main advantage is its interspecies relationship which alters the ecological niche.[25]

Physical Interaction

Co adhesion between C albicans and S mutans is not just dependent on cell physical direct binding but is also mediated by Gtf enzymes secreted by S mutans. Glucosyltransferase B produced by S mutans binds tightly to surface of C albicans yeast cells and contributes to the in situ production of glucan by C albicans cells. C albicans mutants with defects in genes encoding mannoprotein biosynthesis, including och1 and pmt4, showed reduced abilities in binding with GtfB and robust biofilm formation. Atomic force microscopy (AFM) is an advanced tool for imaging and unveiling biophysical properties of the binding interactions between microorganisms. By using this technology it helps to measure binding force and dynamics of GtfB- C albicans. Data showed that the bond between GtfB – C albicans is highly stable with low dissolution. [26]

Metabolic interaction

C albicans stimulates S mutans adherence and biofilms. It shows that S mutans and C albicans share metabolities and cooperatively metabolize complex molecules to complement the metabolic requirements for biosynthetic pathways. Ellepola et al showed that S mutans enhanced C albicans gene expression related to carbohydrates metabolism, including sugar transport system, glycolysis,pyurate degradation to ethanol and acetate production, the tricarboxylic acid cycle and the electron transport chain. Transcriptome changes also somewhat influence the protein level , some proteins associated with carbohydrates metabolism of C albicans were also significantly increased in mixed species biofilms. Carbohydrate metabolism is a crucial part of dental caries development.

Accelerated metabolism of lactose make C albicans transform from yeast to virulent hyphae. Other small chemical molecules including farnesol are also involved in the mediation of the growth kinetics between C albicans and S mutans. Low level of farnesol [25-50 M] could boost S mutans growth and stimulate gtfB expression, which is associated with the microcolony development of S mutans.

Exact mechanism underlying how these molecules modulate competition and cooperation in cross kingdom biofilms remains unclear, but their potential significance is high. [27]

Impact on Virulence traits

Biofilm continues to grow by the formation of EPS. EPS matrix is one of the biofilm virulence factors contributes to intercellular interactions and biofilm stability. Mixed C albicans –S mutans biofilms display an abundance in EPS matrix compared to monospecies biofilm format. Research studies had showed that increase in EPS matrix to the upregulated gtfB expression in the S mutans – C albicans cross kingdom biofilm. gftB is responsible for the synthesis of water insoluble glucose which is linked by α- 1,3 glucosidic linkages to from glucan, an essential fraction of the EPS matrix. Along with gftB S mutans also enhance the expression of C albicans hwp1,als1 and als3 in cross kingdom biofilms. Unregulated genes are critical for the adherence, filamentous growth and biofilm formation of C albicans. S mutans and C albicans cross kingdom biofilms are potent in acidogenicity owing to their metabolic mutualism relationship that facilitates the exchange of carbohydrates between the partners. It shows maximum reduction in pH concentration which facilitates ease

growth of microorganisms. This acidogenicity results in damage to mineralized tooth which results in growth of caries. Thus biofilm consists of C albicans and S mutans showed high prevalence in acidic environment.[28]

Therapeutic strategies

Clinical and experimental studies states that C albicans and S mutans contributes to progression of early childhood caries and root caries. Earlier it was done with mechanical removal following minimal invasive technique. But C albicans and S mutans which left behind cause recurrence of caries. Therefore natural products developing new nanomaterials or by applying laser therapy reduce the caries occurrence.

Natural Compounds

Natural compounds such as curcumin, polyphenol usage reduce the biofilm biomass and inhibit EPS matrix formation of C albicans and S mutans cross kingdom biofilm. Mechanism of action includes inhibition of cell division, block of efflux pump activities, disruption of cell membrane and quench of quorum sensing. Antibacterial mechanism against C albicans or S mutans is through inhibition of several physiological activites, including yeast- hyphal transformation, filamentation, acidogenecity & acidurity. The efficacy of caffeic acid phenethyl ester is suppressing the growth, biofilm formation and EPS synthesis of C albicans and S mutans. Eugenol also inhibits C albicans and S mutans. The unique characteristics of these drugs is multiple taget sites, high biocompatibility, low resistance rate and cost of manufacturing is less. Its efficacy depends on the use of nanotechnology in increasing bioavailability, targeting and controlled release. Further studies has to be carried out to test the actual effectiveness of these natural compounds.[29]

Nanomaterials

Dimensions varies from 1-100nm range, are versatile and bioactive and have received much attention in biomedical applications. Advantage over conventional drugs such as large surface area to volume ratio, ultra small sizes and excellent chemical and physical properties. Due to intrinsic antimicrobial potential, organic and inorganic nonmaterial's could acts as biofilm targeting agents and drug carriers. Antimicrobial mechanisms of nanomateirals on various microorganisms are not clearly mentioned. It could penetrate microbial cell membrane easily and inhibit cell respiration and other essential biologic processes. Additionally nanomateirals could induce the burst of oxidative stress in microorganisms leading to death.[30]

Probiotics

It influence the microbial community and confer health benefits on the host in adequate amounts. Alternative component to treat oral infectious diseases owing to their reported beneficial effects in modulating the chronic inflammatory conditions of the gut. Etiology of oral infections originates from the dysbiosis of microbial communities and administration of probiotics may contribute to clearance of pathogens, favor the growth of beneficial species and reduce the biofilm virulence. Consumption of probiotics in adequate amounts is effective in reducing cariogenic pathogen amounts through competing colonization sites in the mouth and secreting some harmful substance.[31]

Antimicrobial peptide

Alternative drug to antibiotics due to several attractive properties such as inhibit broad spectrum pathogens, down regulate the virulence genes and low possibility to induce antimicrobial resistance. It can be divided into natural and synthetic antimicrobial peptides. Recognized antimicrobial mode of AMP is they insert into membrane bilayers and form transmembrane pores which could be described by some models. It acculumulates on cell surfaces of microbes and inhibit cell wall formation and induce cell membrane depolarization leading to cell death. It also interferes with the normal metabolic activities of pathogen.AMP introduction increased the availability of treatment of C albicans and S mutans cross kingdom biofilm, however some challenges still exist in their therapeutic utility.[32]

Antimicrobial photodynamic therapy

It is a process in which a non toxic substance called photosensitizer interacts with the light source in the presence of oxygen. After receiving the appropriate wavelength of light illumination, the photosensitizer would undergo intersystem crossing to transform into a much longer lived triplet photosensitizer. Triplet photosensitizer can interact with molecular oxygen via electron or energy transfer to produce reactive oxygen species. ROS are highly reactive and could target various cellular components leading to microbial death. Its mechanism of action is that it penetrate the biofilm matrix and then bind to microbial cell surface or enter into the cellular cytoplasm. Once the photosensitizer is located, the generated ROS could induce a series of attacks on adjacent molecules, including biofilms matrix components, cell wall or cell membrane and inside the cells. Due to this multi target action of a PDT, it is reasonable to assume that a PDT can inactivate bacteria regardless of the level or mechanisms of bacterial resistance. Apart from this , aPDT has less opportunity to induce

antimicrobial resistance when compared to antibiotics. Antiplanktonic and anti biofilm effects of a PDT on gram positive and gram negative bacteria and fungus. Therefore it is considered to be promising alternative in the treatment of oral infectious diseases.[33]

II. Conclusion

New innovative therapeutic approaches such as natural extracts, nanomateirals have shown significant potential in inactivating microorganisms and eliminating biofilms. Therefore along with antibiotic therapy other adjunct innovative methods helps in enhancing selectivity, effectively enhancing the action of the drug by reducing its concentration and the possibility of resistance**.**

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