Journal of Multidisciplinary Dental Research

Review Article

Nanobiomaterials in the Management of Oral Biofilms

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ARTICLE INFO

Article history:
Received 24.05.2023
Accepted 24.08.2023
Published 28.12.2023

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https://doi.org/10.38138/JMDR/v9i2.23.20

ABSTRACT

The oral cavity inhabits diverse microorganisms with members of all age groups including children being associated with oral infections. Bacteria being the principle component of this resident microflora along with the diverse group of other species reflect the wide range of viscerously derived nutrients, the heterogenous habitats for colonization contributing to the survival of the biofilm. Biofilms constitute surface- adherent communities of microorganisms like *Streptococcus mutans* along with other bacterial species embedded in an extracellular matrix material. The commensal relationship between the host and the microflora can be disrupted in numerous ways, resulting in compromised oral health causing conditions like dental caries and endodontic infections, gingival and periodontal conditions, oral candidiasis and peri-implantitis. Biofilm-related infections prove to be a major threat from both an economical and health perspective. Innovative treatment options remain limited despite of advancements in understanding the mechanisms of biofilm formation. The concept of nanotechnology is based on controlling atoms on an individual basis and creating structures less than 100 nm (10^{-7} m) in size thereby greatly influencing the properties. Incorporation of metals and other nanoparticles with polymers and coating of surfaces provide antimicrobial and anti-adhesive benefits within the oral cavity. Therefore, this paper seeks to throw light into the current advancements in nanoparticle mediated treatment approaches of oral biofilms and its future implications in pediatric dentistry.

Keywords: Biofilm; Oral Cavity; Metal Oxides; Nanoparticles; Reactive Oxygen Species; Antibiofilm Efficacy

1 INTRODUCTION

The past decade has shown nanotechnology to be one of the rapidly emerging platforms in the field of medicine and science. Nano biomaterials refer to those materials that exhibit unique properties at the nanoscale (10^{-9}–10^{-7} m) and possess numerous biological and biomedical uses, including those for artificial implants, medication delivery, and medical imaging[(1)].According to definitions, biofilms are collections of microbes that are frequently immersed in a viscous matrix of extracellular polymeric substances (EPS) that either bind to one another or provide a surface with a multilayered scaffold enabling contact between the cells favoring an environment that affects pH, redox potential and nutrient availability[(2)].Many nanoparticle-based approaches, through specific adjustments of composition, size and drug release have focused to inhibit biofilms within the oral cavity, either being directly bactericidal or escalate drug aqueous solubility. Nanoparticle drug delivery systems can render stimuli-responsive drug release thereby safeguarding the conventional medications from

pH or enzymatic degradation in the hostile biofilm environments[3].This article aims to provide a comprehensive review of nanoparticle-based approaches in the treatment of biofilms and for clinical translation of these therapeutic approaches.

2 SIGNIFICANCE OF BIOFILMS

Dental caries is mediated by multiplex interactions between acidogenic bacteria and host factors. The principal bacterial species of streptococci and lactobacilli contribute to carious damage in the presence of fermentable sugars, producing acidic metabolic by products, thereby initiating subsurface demineralization of the tooth surface[4]. The oral cavity proves to be a classic habitat to investigate novel strategies for biofilm treatments due to the convenience of approach and extensive species diversity which can then be extended to the biofilm associated health conditions or for industrial applications. The greatest advantage offered is the topical therapy thereby eliminating the hurdles of systemic delivery associated with biofilms[3].

3 MECHANISM OF BIOFILM FORMATION

Acquired enamel pellicle, a proteinaceous film that coats the tooth surface, is derived from sources pertaining to the host (salivary proteins) and microbial community (exoenzymes). The chief pathogen involved in causation of dental caries, *Streptococcus mutans*, coexist with numerous other bacterial communities within the biofilm[5].Minor group of bacteria like Streptococci and Actinomyces species within the microbial niche, adhere to the surfaces coated with the pellicle by means of highly specific receptor interactions supplemented by hydrophobic or electrostatic forces that facilitate coadhesion and initiation of biofilm formation on tooth surfaces. The glucosyltransferases (Gtfs) produced by *S. mutans* splits sucrose to produce extracellular glucans and free fructose which are the primary constituents of cariogenic biofilms, promoting colonization and accumulation of microbes along with a matrix that limits diffusion thus, disrupting the potent balance between the commensal microbes and pathogenic species[6].The fermentation of dietary sugars by the bacteria produces a highly acidic condition (pH 4.5–5.5) which will further induce biofilm accumulation and enamel demineralization acting as an onset for carious activity[3].The biology of exopolysaccharide matrix has revealed a multifunctional scaffold that continues to expand as the biofilm matures, increasing its adhesiveness and cohesiveness which is in par with the ecological plaque hypothesis[6].

4 CONVENTIONAL TREATMENT OPTIONS

The challenges of treating oral biofilm are largely based on chlorhexidine, which is a broad spectrum antimicrobial drug having adverse effects of tooth staining and calculus formation hence rendering it unsuitable for long term usage. Other alternatives include terpenoids, essential oils, and flavinoids that derange the biofilm assembly and reduce the synthesis of exo polysccharides causing an impact on the viability and acidogenicity of *S. mutans*[7].The drawbacks offered by topically applied drugs include swift salivary clearance, meager exopolysaccharide matrix penetration and minimal retention on to the tooth surfaces. With the microenvironment of the exopolysaccharide being altered, the drug access and bacterial tolerance is reduced making it difficult to treat without causing harm to the commensals. The acidic pH can contribute to the limited efficacy of numerous antibiotics[3].

5 NANOPARTICLE BASED ORAL BIOFILM TREATMENT

The development of the numerous preparations for biofilm treatment was possible due to the relative ease and flexible nature of the nanoparticles which are either directly bactericidal or enhance the aqueous solubility facilitating transport into the bacterial cells through modifications in the chemical compositions. The substantivity and antibiofilm efficacy is enabled by the potent drug to drug combination and high surface-area-to-volume ratios that help in overcoming the usual resistant mechanisms of the bacteria and prevent the degradation of the conventional drugs in the harsh environments[3]. Bacteria being hydrophobic consume positively charged nanoparticles, while hydrophilic particles adhere to the exopolysaccharide matrix.The particle size favours the rapid diffusion upto diameters of 130nm and the core properties enabling drug loading and sensitization of agents for drug delivery[7].Studies exploiting the biofilm of *S. mutans* to simulate the antibiofilm efficacy have shown to enable multiple surface binding facilitated by pH responsive functional groups like amides and amines. A uniform distribution of nanoparticles throughout the biofilm is facilitated by the tertiary cationic residues enabling drug retention until the pH turns to the acidic range[3].

Studies conducted by Gao et al have shown that when nanoparticles are combined with hydrogen peroxide, reactive oxygen species (ROS) are produced and the oxidative stress that results causes severe cellular damage. Naha et al used the matrix's acidic pH to develop activated iron oxide nanoparticles known as CAT-NP, which mediated antibiofilm activity and has the benefit of lowering the chance of drug resistance as it is a drug-free method. However, these particles exhibit poor colloidal stability and tissue binding hence limiting its application clinically. In order to limit the potent chronic effects due to repeated treatments, the efficacy of the nanoparticle based strategies have been ensured by introducing target groups that increase the selectivity towards virulent bacteria. An evidence of this is the conjugation of immunoliposomes with anti-Streptococcus oralis, which exhibit lower affinity for other

oral bacterial biofilms but efficient adsorption to *S. oralis* biofilms[3].

6 SAFETY OF NANOPARTICLE BASED BIOFILM TREATMENT

It is typical for topical applications to be cleared through food, which could lead to systemic circulation and tissue distribution, which makes it even more important to assess the impact of biodistribution. Weight loss may occur as a result of the gastrointestinal tract's absorption of metal oxide-based nanoparticles and oxidative stress in the vital organs like liver, spleen, brain additionally causing damage to the DNA and tissue fibrosis despite of a low bioavailabilty[7]. Approaches that minimize the systemic exposure by dissociating into nontoxic and degradable biomaterials is to be brought into consideration. The bactericidal activity of vancomycin has been found to be enhanced by the high degradability of poly(lactide-co-glycolide)-based nanoparticles. Polymers with similar proton catalyzed antibiofilm effects that release nitric oxide (NO) have been developed. They can be coupled with polyphosphazenes or degradable polyesters to reduce the longterm exposure to nanoparticles[8].

7 AN OUTLOOK INTO THE FUTURE PERSPECTIVES

Since the microbial interactions prove to play a pivotal role, newer nucleotidebased bacterial detection techniques have been developed for the detection of cariogenic bacteria. O^{16}/O^{18} reverse proteolytic labelling can be used to detect the presence of Porphyromonas gingivalis which is a causative organism for periodontitis[5]. The combination of quartenary ammonium compounds and silver nanoparticles have found to effectively cause bacterial damage by penetrating the dentinal tubules attributing to its small size. Amorphous calcium phosphate based nanoparticles promotes remineralization of the carious lesions[2]. Newer studies have shown the efficacy of Quarternary Ammonium compounds and nano ACPs that exhibited antibacterial and remineralizing capacities without compromising the bond strength[9]. Semiconductor based nanocrystals were utilized by Chalmers et al and concluded that the photostability of these semiconductor-based quantum dots enables microbial manipulation of the communities[5].

Antimicrobial Photodynamic Therapy (APDT) that has found its application in restorative, endodontic and periodontal conditions involves the generation of reactive oxygen species as a result of the interaction of a photosensitizer with low-energy laser light in the presence of oxygen, which damages DNA and bacterial cells through oxidative stress[2].

As a non-antibiotic treatment option, cold atmospheric plasma (CAP) uses a highly reactive mixture of ions and electrons in the ground or excited state along with tiny amounts of electromagnetic radiation (UV photons and visible light), all of which are operated under atmospheric conditions without injuring the tissues in the vicinity. The accumulation of charges on the membrane surface of the bacteria will result in damage to the cells[9].

Alternative biomimetic approaches utilizing mucin MUC5B in saliva that plays a crucial role in preventing surface attachment of *S. mutans* may help to maintain the balance within the oral biofilm. The complex nature of these mucin molecules pose a challenge to developing the engineered mucin based biomimetics[5].

8 CONCLUSION

The development of the colonizing microbiota depends on the interactions with the host factors from the time of birth. The synergistic interaction of the bacterial species and exopolysaccahride matrix can compromise the balance between the commensal oral microbiome resulting in biofilm accumulation proceeding to caries. In the past decade numerous innovative techniques have been developed to control these biofilms mediated infections. Although nanoparticle-based therapeutic approaches show promise for oral antibiofilm treatments, they still need to surmount a few hurdles before they can be successfully used in clinical settings. Since the literature pertaining to these novel methods are largely based on *in vitro* studies and of short durations, more evidences need to be obtained by extending researches under *in vivo* conditions in order to establish the longevity and antibiofilm efficacy.

8.1 SUMMARY

A vast diversity of microorganisms exist in a commensal relation with the human host. Any imbalance in this mutually benefitting relation will result in numerous oral infections initiated by the formation of oral biofilm. Biofilms constitute surface- adherent communities of microorganisms like *Streptococcus mutans* along with other bacterial species embedded in an extracellular matrix material. Limitations to the treatment of these biofilm mediated diseases still remain limited. Incorporation of metals and other nanoparticles with polymers and coating of surfaces provide antimicrobial and anti-adhesive benefits within the oral cavity. Nanoparticle drug delivery systems can render stimuli-responsive drug release thereby safeguarding the conventional medications from pH or enzymatic degradation in the hostile biofilm environments. Numerous studies have shown that the combination of nanoparticles with oxidative compounds produce reactive oxygen species causing severe cellular damage. Combinations of quarternary ammonium compounds with silver nanoparticles exhibited enhanced antimicrobial efficacy without compromising the bond strength. Applications like Antimicrobial photodynamic therapy (APDT), cold atmospheric plasma (CAP)

and biomimetic approaches using mucin help to prevent adhesion of the colonizing microbes and maintain a healthy intra oral state. Although nanoparticle-based therapeutic approaches show promise for oral antibiofilm treatments, more evidences need to be obtained by extending researches under *in vivo* conditions in order to establish the longevity and antibiofilm efficacy.

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