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NANOSOLDIERS FOR PERIODONTAL RESCUE!!!

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ABSTRACT

The era of nanotechnology is fast approaching. Virtually unheard of two decades, all disciplines will be impacted by advances in nanotechnology in near future. Growing interest in the future medical applications of nanotechnology is leading to the emergence of a new field called nanomedicine - the science and technology of diagnosing, treating, and preventing disease and traumatic injury, of relieving pain, and of preserving and improving human health, using nanoscale-structured materials, biotechnology and genetic engineering, and eventually complex molecular machine systems and nanorobots. Similarly, development of “nanodentistry” will make possible the maintenance of near-perfect oral health through the use of nanomaterials. The present article is a review, which describes about the potential use of nanotechhnology in the field of periodontics therapy.

KEYWORDS

Nanotechhnology, Nanorobots, Nanodentistry and Nanomaterials.

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INTRODUCTION

Periodontal disease is a multifactorial chronic inflammatory disease causing destruction of periodontal assembly i.e. alveolar bone, periodontal ligament and cementum. The ultimate goal of periodontal therapy is thus to restore the lost tissues either by repair or regeneration. Many therapeutic modalities have been tried to overcome this purpose.

‘Nanotechnology’ the term described by Kevie Eric Drexler in 1986, was the vision laid by renowned physicist Richard Feynman in 1959 in his lecture

There's is plenty of room at the bottom delivered at California Institute of Technology. Nanotechnology has its application in dentistry for creating nanomaterials which can improve the traditional methodologies.

The present paper reviews some of the potential application of nanotechnology in the periodontal therapy.

Dentin Hypersensitivity

Dentin hypersensitivity is the one amongst the frequently occuring complaints experienced by the patients suffering from periodontal disease owing to the denudation of the root surface. Hence it's management should be dealt during supportive periodontal therapy.

Few In vivo Studies[1,2,3,4] used nano-HAP containing agents on hypersensitivity and suggested that The HAP containing toothpaste was effective in reducing dentin hypersensitivity .The mechanism suggested was-

1. An enhanced occlusion of dentinal tubules caused due to rapid integration of nano size HA in the dentinal tubules compared to micro sized HA
2. Sealing of the tubules, prevents exposure of the nerves to the external stimuli.
3. Enhanced binding to the dentin apatite and tooth enamel because of a higher surface area, biological activity and chemical reactivity, which facilitate its binding. This creates a new apatite layer that remineralizes the enamel and protects the surface of the tooth.

Liu CHC et al[5] found that Gold nano particles (GNP's) s were easily adsorbed on the inner dentinal tubule walls and the application of silver staining was then used to help to occlude the open tubules and reduce the dentin sensitivity. After brushing the opened tubules with highly concentrated GNPs, laser irradiation promoted the aggregation of nanoparticles to occlude the exposed tubules.

Some Commercially available Nano particles containing tooth paste for dentin hypersensitivity are Nano XIM• Care Paste, Nano-P (FGM, Joinville, Brazil), Aclaim Toothpaste (Group Pharmaceuticals limited)

Tissue Engineering

Nanotechnology in tissue engineering has allowed significant improvement of these scaffolding materials to present unique 3D matrix conditions for cells and tissues[6].

Nanoengineered scaffolds possess intrinsic mechanical properties of materials that cannot be readily achieved by conventional technologies. The nanotopological surfaces provide more definitive physicochemical cues to cells that can recognize the nanoscale structures in their adhesion and differentiation. Furthermore, many biological proteins and active molecules can be integrated with the scaffolding materials at the nanoscale level to exert therapeutic efficacy and to spatially control the cellular behavior. Therefore, the nanotechnology-driven tissue engineering can achieve native tissue mimicking architectures and/or evoke the phenomena that occur in nature, ultimately to create constructs that are equivalent to tissues in dentistry, including dentin, pulp, PDL, cementum, and alveolar bone.

A key aspect of the nanofibrous structures is their morphological trait largely mimicking the native tissue architecture because most of tissue proteins such as collagen and elastin are nanofibrous. Owing to their large surface area relative to volume, the surface-related properties are dominant, and these include surface reactivity, protein adsorption, and surface degradation, which ultimately control the cellular behaviors[7,8].

Electrospinning is a more common method to generate nanofibers. Some recent studies have developed nanocomposite and nanofibrous scaffolds made of biopolymers with bioactive glass, where the bioactive glass role was to provide high bioactivity. The dental pulp stem cells showed improved proliferation, differentiation, and mineralization on the nanofibers containing bioactive glass when compared to the pure polymer nanofibers[9,10].

The electrospunnanofibers of poly (lactic-co-glycolic acid) (PLGA) or gelatin were used to

culture human PDL cells, showing the ability to adhere, proliferate, and osteogenically differentiate[11-13]. It was seen that the incorporation of silica or HA nanoparticles on the surface of these nanofibers has been shown to enhance protein adsorption, which resulted in improved adhesion of PDL fibroblast cells[14]. Also, when the scaffolds containing nanosized HA, protein adsorption, cell adhesion, and in vivo bone formation were found to be significantly higher than scaffolds containing conventional HA, as it was seen that when PDL stem cells were seeded on the engineered nanosurface, cell viability and differentiation were enhanced[15].

The scaffolds constructed with PDL stem cells and tailored scaffolds with silk scaffolds and nanohydroxyapatite to have mineralized surface demonstrated substantial level of periodontal regeneration in an in vivo implantation in dogs, suggesting a potential scaffolding matrix for periodontal tissue engineering[16].

In a similar way, the nanosized bioactive glass particles when incorporated into alginate scaffolds, showed enhanced proliferation and differentiation of human PDL fibroblasts when compared to the alginate-only scaffolds[17].

Other than the electrospunnanofibers, the self-assembling peptides containing the RGD-binding sequences (PRG) and laminin cell adhesion motif (PDS) were also designed, which demonstrated significant promotion of PDL fibroblast adhesion, proliferation, and protein production[18].

Alveolar bone defects have also been regenerated with nanometric-engineered scaffolds. In an animal study[19.20], the nanohydroxyapatite/polyamide nanocomposite scaffolds were produced by a phase-separation method and were combined with bone marrow stromal cells and then implanted into rabbit jaw bone. The results showed the enhancement of osteogenic markers in the implanted samples with cells, showing the ability of these scaffolds to stimulate osteogenesis, although the amount of new bone formed was not enhanced in the presence of the cells. Similar results were obtained using nanosized β-tricalcium phosphate within a collagen matrix, which showed enhanced bone regeneration when implanted with MSCs[21].

Drug delivery

The delivery of therapeutically relevant molecules is a promising approach to improve the regeneration ability of damaged tissues and to treat diseases effectively. These molecules are usually loaded in carriers, such as scaffolds or nanoparticles, to allow controlled and sustained release, ultimately influencing a series of biological processes, such as cell homing, attachment, proliferation, and differentiation. The therapeutic molecules should be safely loaded in large quantities and then delivered in a controlled and targeted manner. Therefore, the design of delivery carriers is of special importance in the success of the delivery systems.

It was observed that when 3D scaffolds are used with the carriers of the molecules to deliver, the signaling molecules it should be combined within the 3D structure or on the surface of the scaffolds, so the therapeutic molecules are released to the surrounding tissues and then act to regulate cellular functions. Thus presently, nanosized particles are the most common form of delivery carriers because these carriers are often intended to enter the cell membrane and sometimes even to the nucleus[22,23].

The treatment for periodontal diseases is based on two main approaches: the elimination of bacteria to avoid the progression of the disease and the regenerative therapy that may allow the regeneration of the damaged tissue[24]. To this end, BMPs have been often used since they are involved in the osteogenic differentiation of stem cells showing the ability to regenerate PDL, cementum, as well as alveolar bone when administered from biomaterials[25-27].

Nanoparticles has been explored to deliver therapeutic molecules for periodontal regeneration. In an in vitro study[28], PLGA nanoparticles were developed to encapsulate minocycline for periodontal infections. The nanoparticles of size 85-424 nm have showed an entrapping efficiency of up to 29.9% and the release was shown to be sustained for several weeks, which resulted in a considerable antibacterial effect compared to the minocycline-

free nanoparticles. Similar nanoparticles composed of PLGA and poly (lactic acid) showed higher entrapment efficiencies of up to 63.8%, and their implantation in dogs showed that the nanoparticles loaded with triclosan were able to penetrate through the junction epithelium[14,29].

A more osteoconductive vehicle for the delivery of tetracycline was developed using calcium-deficient HA nanoparticles with varying Ca/P ratios. The loaded drug showed sustained release of up to 88% over a period of 5 days and considerable antibacterial effect. Furthermore, when the drug-loaded nanoparticles were placed in contact with PDL cells, the cell proliferation increased, suggesting that the use of HA nanoparticles as local drug delivery agents in periodontal treatment may be a good option[30].

Growth factors have also been used for their therapeutic action in dental tissues. Compared to the common drug molecules, growth factors require water-based solutions in the nanoparticle processing. For this purpose, glycydil methacrylate, derivative dextran, and gelatin nanoparticles were prepared with a size of 53.7 nm to encapsulate BMP, which showed a sustained release of more than 12 days. Furthermore, the nanoparticles were shown to be biocompatible and could be used as a promising vehicle for the delivery of active molecules to the periodontium[31].

Nanodiamonds, which are carbon nanoparticles of 4-5 nm, have also been used as a growth-factor carrier for the alveolar ridge augmentation. These have been shown to effectively physisorb and simultaneously deliver BMP2 and fibroblast growth factor and are able to induce the differentiation and proliferation of osteoblasts[29].

Owing to some concerns related to the lack of continuous supply of growth factors, gene therapy has been proposed as a possible solution. For the delivery of genetic molecules, the carriers should be positively charged to enable complexes with highly phosphorylated nucleic acids. NanosizedCaP particles were developed with 30-50 nm in size to load the platelet-derived growth factor gene. Results showed significantly higher PDL fibroblast proliferation when placed in contact with the gene-complexed nanoparticles[32].

Alveolar bone regeneration has also been achieved through the delivery of polymeric nanoparticles that carry siRNA molecules for the interference of Sema4d, which is considered as a target gene for osteoporosis. The results showed, after injection in mice, that the siRNA-loaded nanoparticles were able to increase significantly the formation of bone in the osteoporotic alveolar bone[33].

The nanoparticles are often incorporated into the 3D matrices to allow scaffolding roles while maintaining the controlled and sustained release of the encapsulated molecule. In an In-vitro study[34], tetracycline-loaded nanoparticles of size around 130 nm were prepared using an ionic gelation method, which was then incorporated in a calcium sulfate cement matrix. The release pattern was sustained and presented an antibacterial effect as well as an enhanced ALP activity of human PDL cells.

In a similar study, chitosan loaded with tetracycline was prepared as nanoparticles by a solution nebulization method, which was then incorporated into polycaprolactone (PCL) nanofibers. The release pattern of the drug from naked nanoparticles actually showed a burst with ~70% of release initially, which, however, was sustained significantly when incorporated within the PCL nanofiber structure[35].

In an *In-vivo* and *In-vitro* study[36], For the regeneration of mandible defects, the nanohydroxyapatite/collagen scaffolds were developed to deliver BMP2-derived peptides. The nanocomposite scaffolds showed sustained and controlled release of the peptide molecules as well as enhanced osteogenic capacity of marrow stromal cells[36]. Also, Nanocomposite scaffolds of HA nanoparticles with PCL were also reported to deliver BMP2 and have an excellent ability to regenerate the mandibular bone defect in rabbits[37].

The BMP2-loaded nanohydroxyapatite/collagen/ poly (lactic acid) constructs also showed a slow release of BMP2, which resulted in high osteogenic signaling of dental pulp stem cells. Furthermore, when the BMP2-loaded scaffolds in combination

with dental pulp stem cells were implanted in rabbits, the bone formation was similar to that of autologous bone, proving that BMP2 was able to promote higher differentiation of the loaded stem cells, which in turn enhanced bone regeneration[38].

Nanofibers have often been shown to be excellent matrices for the sustained delivery of drugs mainly due to their high surface area. For PDL regeneration, nanofibers composed of PCL effectively encapsulated metronidazole benzoate and presented a low burst and sustained release of the drug up to 19 days[39]. Similarly, doxycycline was encapsulated into PLGA nanospheres, which were then incorporated into PLLA nanofibrous scaffolds. The drug release was strongly dependent on the physical and chemical composition of the nanospheres, showing a complete release up to 6 weeks and a strong antibacterial effect[40].

In an elegant study for the mandibular reconstruction, PLGA nanofibers-incorporated FTY720, which is a targeted agonist of S1P receptors 1 and 3 and is used as a cell recruiter to enhance bone regeneration, was explored .The in vivo results showed that the loaded nanofibers were able to enhance blood vessel growth and the recruitment of macrophages, therefore proving their ability to regenerate critical size defects by recruiting specific macrophages and bone healing cells[41].

Collectively, the delivery of therapeutic molecules, including drugs, growth factors, and genes, has been realized in the disease treatment or repair of dental tissues, with the use of different types of nanomaterials, including nanotopological scaffolds, nanoparticulate carriers, or combination of them. For the controllable and effective delivery of these bioactive molecules and the physicochemical properties of the carrier materials, the loading and compartment of the cargo molecules should be controlled at the molecular level, which ultimately is in great need of nanotechnology and nanoscale tailoring approach.

Gene therapy

Growth factors have significantly enhanced periodontal therapy outcomes with a high degree of variability, mostly due to the lack of continual supply for a required period of time. Gene therapy is an effective method to overcome this barrier. The findings of Chen R *et al*[42] suggested that transfection of genes through ultrasound and nano/microbubbles results in high gene expression, facilitating gene therapy for periodontal disease involving alveolar bone resorption. Also recently, low inherent toxicity of other calcium phosphate nanoparticles, have been reported and have been proposed for periodontal regeneration[32,43].

3D Bioprinting

Recently Ma Y and colleagues[44] proposed a bioprinting-based approach to generate nano-liter sized 3D cell-laden hydrogel array with gradient of ECM components, through controlling the volume ratio of two hydrogels, such as gelatin methacrylate (GelMA) and poly (ethylene glycol) (PEG) dimethacrylate. The resulting cell-laden array with a gradient of GelMA/PEG composition was used to screen human PDLSC response to ECM. The behavior (e.g., cell viability, spreading) of human PDLSCs in GelMA/PEG array were found to be depended on the volume ratios of GelMA/PEG, with cell viability and spreading area decreased along with increasing the ratio of PEG. The developed approach would be useful for screening cell-biomaterial interaction in 3D and promoting regeneration of functional tissue.

CONCLUSION

Utilization of nanotechnology for therapeutics more generally in dentistry medicine offers significant opportunities as the requirements can be limited in their complexity and thus the therapeutic can be more readily realized. One factor that should be taken into consideration when developing nanotechnologies is the cost of the device or therapy being developed. There are numerous complex therapies being developed to treat a wide range of diseases, not only in dentistry but also in biomedicine more broadly, but they will never see clinical use as they will be too expensive to synthesize and thus too expensive for purchasers to

procure. Cost is an important factor that is often forgotten in the development of new therapies and devices, but is ultimately the hurdle that will decide if it progresses or fails.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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