Nanotechnology in Periodontal Regeneration: A Review

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Abstract

Periodontitis involves destruction of the periodontal ligament and supporting structures. It ranges from a simple inflammation of gums to major damage resulting in loss of bone. Multiple conditions like trauma, periodontal disease, reconstructive surgery, ageing, osteoporosis and neoplastic pathology, have a common characteristic feature being loss of bone and tissue. The regenerative procedures that are currently practiced aim to regenerate the lost tissue via means of grafting, placement of membranes and many more, but have been accompanied with a set of limitations and major disadvantage being graft rejection. Periodontal regeneration still endures to be a partially unsolved algorithm. In dentistry, a new arena of development is being exploited to set a new approach for regeneration that is Nanotechnology. This branch involves tissue engineering which aims to regenerate the lost tissues via manufacturing scaffolds which transport signaling cells and molecules. These scaffolds possess magnificent physical as well as chemical properties and biomimetic features that act as a substitute of the highest standard offering innumerable benefits for promoting cell growth and tissue regeneration via tissue engineering.Nanomaterials because of their refined physiochemical characteristics and biomimetic attributes serve as a scope worthy substitute that offers several advancements for stimulation of cell growth and tissue regeneration. This review provides an insight to basic information about nanotechnology, the various nano particles having application in periodontal regeneration, the advanced regenerative procedures fabricated on the principles of nanotechnology, their applications, the clinical studies highlighting the achievements so far, supremacy over the conventional method and limitations.

Keywords: *Nanotechnology, periodontal regeneration, nanomaterials, tissue regeneration, bone augmentation*

Introduction

Periodontal tissue regeneration serves to be the pioneer for the lost tooth and the supporting structures. The regenerative and augmentative procedures are multiplex in nature and therefore challenging for the maxillofacial and periodontal surgeons. Variousailments liketrauma, periodontal disease, reconstructive surgery, ageing, osteoporosis and neoplastic pathology, have a common characteristic feature being loss of bone and tissue. Due to increased consumption of tobacco and betelnut, the prevalence rates of periodontitis are quite high in India.[1] Currently, many approaches exist in tissue regeneration and bone augmentation, but they are not efficient enough to deliver consistent results.[3] This is where nanotechnology comes into picture as it has manufactured and processed an entity called nano scaffolds. These scaffolds possess magnificent physical as well as chemical properties and biomimetic features

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that act as a substitute of the highest standard offering innumerable benefits for promoting cell growth and tissue regeneration via tissue engineering. Hence, the paramount of this literature-based article is to bring for than outline of diverse nanoscale scaffolds as vital elements in tissue engineering and regenerative medicine prototype used for alveolar bone regeneration and bone augmentation.

Tissue Regeneration and Bone Augmentation: Present view: At present, autografts, allografts, xenografts and synthetic graft materials are currently used for tissue regeneration and bone augmentation.[4,5] But they have their own set of limitations.[6–8]Tissue engineering is a process where the wound healing is manipulated to achieve tissue regeneration.[9] This process broadly covers three key components: the signaling molecules, scaffolds and cells.[10,11] Tissue engineering shows improved results with the use of advanced materials such as "enamel matrix derivatives (EMD)" for treatment of infra-bony defects, "platelet derived growth factor (PDGF)" and "transforming growth factor-β (TGF-β)" are the growth factors that are effective for periodontal regeneration."Guided tissue regeneration (GTR)"and "laser-assisted new attachment procedure (LANAP)" can also be considered for new attachment, but requires further clinical trials.[12,13]

Tissue engineering demands the cells to stay alive inside the human body and continue to perform the function, which becomes difficult due to poor biomechanical and physico-chemical properties of the traditional scaffolds.[14] Hence, nanotechnology set the ball rolling on the evolution of tissue regeneration and bone augmentation.

What is Nanotechnology?: Nanotechnology is an arena of scrutiny and novelty concerned with fabricating things on the extent of atoms and molecules and has reached to all areas of science. A nanometer is one-billionth of a meter that is ten times the diameter of a hydrogen atom. This field offers advanced alternative solutions for scientific and medical problems. It involves manipulation of atoms and molecules to form larger nano structures, this is called the bottom approach. Whereas, larger structures or pieces are broken down to generate nanostructures from them, this is the top-down approach.[15,16] Nanotechnology has been exploited on a large scale over the last twenty to thirty years in various fields. For example, in dentistry use of submicron grained size ceramics for production of all-ceramic restorations improves its appearance, aesthetics and mechanical properties, increase the resistance to wear and increase strength.[17]

Nano biomaterials for tissue engineering and bone augmentation: In oral biology, the main purpose of practicing these procedures is to restore the functionality of the lost tissue and the tissue itself that take place during alveolar and periodontal tissue genesis, with the help of scaffolds carrying signaling molecules and cells.[2,14] This technology has outlooked to integrate scaffold matrix technologies with the regenerative potential of stem cells which are in close proximity, mainly to dental pulp, periodontal ligament (PDL) and alveolar tissue.[18] Therefore, an ideal biomaterial prospective should involve a scaffold that is functionally categorized where the chemical constituents and 3-D construct of each recess should match the detailed framework, biochemical components and mechanical attributes. Additionally, the matrices are supposed to degrade at a suitable rate so as to meet the regeneration pace of the tissues.[19,20]A study stated that there has been development of a scaffold which is a "3-layered construct" for concurrent regeneration of hard and soft tissue structures of the periodontium, like cementum, alveolar bone and PDL.[21]

Nano scaffolds: The current developments in nanotechnology have been cutting edge because of their ability to cause osteogenic enhancement.[22]It has acknowledged remarkable advancement of these scaffolding materials to propose distinctive 3-D matrix conditions for cells and tissues.[23] Nano scaffolds show superior most attributes in every dimension than various conventional approaches that are practiced for the purpose of tissue regeneration and bone augmentation.[24,25] The existing examples of scaffolds like "3-layered construct" suggest the nanomaterials that are used often should be multi-layered for multi tissue regeneration as this helps in exacting reproduction of even the minute characteristics of the structures that are to be regenerated.[26]

Nanoparticles, due to their reduced size, aid in quick reaction to extraneous stimulants such as ultrasounds, magnetic fields, X-ray and pH exposure. Delivery by nanoparticles which is controlled, depends mainly upon their reduced size and subsequent high surface area. The topography of nanoparticles is such that it imparts definitive physicochemical signals to cells such that it becomes easy for the cells to adhere and differentiate.

Besides, various active molecules and biological proteins are usually amalgamated along with the scaffolding materials to employ therapeutic efficiency and structurally control the cellular activity at nanoscale level. This is how nano tissue engineering succeeds in achieving structures that mimic their native tissue and develop structures of equivalency to the dentin, cementum, pulp, PDL and alveolar bone.

Role of extracellular matrix [ECM] in tissue regeneration: Extracellular matrix is an elaborate molecular complex made of three major constituents: protein, glycoconjugate and glycosaminoglycans. These elements along with cell adhesion receptors interact to form a complex in which cells live in tissues and organs. These receptors send cues to the cells from ECM which regulates manifold and paramount procedures like, proliferation, metastasis, growth and differentiation.

The ECM mainly contains collagen fibers which are produced via self-computing of smaller subunits. These self-computed fibers of collagen result in the mineralization of hydroxyapatite nanocrystals in a highly organized way. This bottom-up approach creates a structure of fine architecture that mimics the native tissue with accurate details. This can provide an engineered entity with distinctive mechanical properties. This enables amelogenesis and dentinogenes is induction in the matrix protein.

Hence, manipulation of nano construct of native tissue has been the matter of contention in current research era of tissue engineering scaffolds.

How are nano scaffolds produced?: Nano scaffolds are commonly produced by approaches such as: phase separation, peptide synthesis and electrospinning approach. Nanofibrous scaffolds which are built of poly-l-lactide acid (PLLA) can be incorporated through the "phase-separation" as well as "porogen leaching method." These scaffolds, in human dental pulp cells, manifest the stimulation of odontogenic differentiation in contrast to solid-walled PLLA scaffolds.

In recent times, scientists have invented scaffolds made up of biopolymers in combination with bioactive glass, known as nanocomposite nanofibrous scaffolds. These nanoparticles play a key role in upgrading mineralization and remineralization of mutilated dentin matrices. Furthermore, a study reported incorporation of magnesium phosphate into nanofibrous scaffolds, where they helped in enhancing the rate of differentiation of pulp stem cells.

Nanoparticles: A nanoparticle (NP) is a minuscule particle which usually ranges between 1 to 100 nanometers in diameter. They have peculiar physicochemical properties to their material counterparts of comparatively larger size. They are classified as nanospheres and nanocapsules. Nanospheres are those nanoparticles that have a matrix type of construct where a drug is dispersed. Nanocapsules have a membrane wall construct with an oil core in the center containing the drug. Several applications use nanospheres in delivery of drugs, genetic material and growth factors. These include controlled drug delivery using porogens for reinforcement of a mechanically weak scaffold as bioreactors of microscopic nature helping in the formation of hydroxy apatite crystals, followed by mineralization using microspheres for providing the sites for cell adhesion and preparation of formulations like suspensions, colloidal gels and injectables to be used in minimal invasive surgery.

Inorganic Nanoparticles

i. Synthetic Polymers: The ones customarily used are "poly-α-hydroxyesters [poly-glycolic acid (PGA), poly-lactic acid (PLA), poly-lactic-glycolic acid (PLGA) and poly-caprolactone (PCL)]" for biomedical applications. They are available at reasonable cost, easy to adapt and have a high safety index. Major disadvantage is hydrophobicity and degrade via autocatalysis.Various combinations of TGA/PLA/PLGA/PEG/PCL have been tested for alveolar bone regeneration and have shown positive results.

ii. Ceramic NPs: Ceramic materials are "synthetic crystalline, solid, inorganic non-metallic materials". Bioceramics include "bioactive glass, bioactive glass–ceramic, calcium phosphate groups and alumina." These have been used to refine the morphology and performance of the scaffolds. For example, calcium phosphate, mineral trioxide aggregate (MTA) and bioactive glass.

iii. Silica NPs: These can be integrated as bioparticles, either core or shell silica NPs and mesoporous silica nanoparticles (MSNPs). They have been used in biomedical field and for drug delivery because of their unique structure and increased pore volume and surface area. The limitation of silica NPs is variable toxicity.

iv. Metallic NPs: They are the safest and most commonly used is gold NPs because of their ability to be drawn into variable shapes such as rods, cages or spheres. Thus, can be implemented in drug delivery, bio-imaging, photo-thermal therapy and biosensing. The combination of gold and silver NPs along with chitosan have shown successful outcomes for bone regeneration, mineralization and osteointegration of implants. They are biocompatible NPs with less cytotoxicity.

v. Magnetic NPs: They show paramagnetic properties of long duration and non-invasive tracking. Therefore, in biomedical field, cobalt, nickel, iron and their subsequent oxides have been used for cell tracking, drug delivery, as biosensors, 3-D cell organization and imaging procedures.

Organic nanoparticles:

i. Liposomes: Liposomes are mostly used in imaging and drug delivery. They are bilayer structures made up of phospholipids. Their properties vary because of their size, composition, surface charge and preparation and are used in imaging and drug delivery.

ii. Natural Polymeric NPs: These are classified as proteins and polysaccharides. They are biocompatible and bio-degradable materials that possess bulk physical characteristic features.NPs hold high capability for drug loading,have a flexible synthesis and their structure constitutes of polymer chains which show a broad variety in terms of composition and characteristics. Collagen, gelatin, alginate, chitosan and fibrin are some of the natural polymericNPs.

iii. Carbon:

a. Carbon nanotubes (CNTs)- these are cylindrical structures made of carbon allotropes. They are mechanically and chemically stable with conducive electrical properties.Usually come eitherin the form of a single or multi-walled tubular architecture. CNTs show effective performance on bone and tissue regeneration, also aid in multiplication of cells and bone integration.

b. Graphene and its derivatives: A film which is single layer,1 atom thick and is arranged with carbon atoms in 2-D hexagonal construct which shows similarity to honeycomb.They constitute large variation of graphene derivatives like, graphene oxide(GO) and reduced form of it, called as reduced graphene oxide(rGO).

Composite Scaffolds: Combinations of various organic as well as inorganic particles have been evaluated as composite scaffolds, which in turn improve the properties and decreases the limitations of singular components. Many researchers have experimented with varied composite scaffold designs of different combinations such as, nHA with high molecular-weight polymers, nHA with PLA, PCL[88], PLGA, chitosan, collagen, coralline and polyamide. Most of these combinations have come up with ameliorated mechanical strength and scaffold biocompatibility.

Hazards of Nanotechnology: Although there are many potential advantages of using nanotechnology, it ought to be countervailed against the risks. The physical and chemical properties have enormous ramifications in many ways via which these nanoparticles interrelate with biotic constituents, their uptake, accretion and excretion through the body and interact with environs at large. The interplay between nanoparticles and human tissue can be physical or chemical. The physical interactivity mostly leads to disintegration of membranes and its activities such as "protein folding, aggregation and various transport processes."Whereas, the chemical interactions result in oxidative damage and formation of reactive oxygen species. Besides these, environmental reactions also determine the nanomaterial toxicity.

It is difficult to avoid the exposure to nanoparticles, being airborne in nature. Humans are exposed to these, knowingly through nanotherapy or unknowingly through natural/human-induced particles leading to multiple entry routes due to high reactivity, which aggravates the condition.[98]Interaction of nanoparticles with proteins, enzymes, molecular structures DNA, RNA in a reversible or irreversible manner may lead to devastation in biological systems resulting in emergence of new diseases. This warrants detailed studies to evaluate the toxicity of nanoparticles before using them for therapeutic purpose.

Future prospects: This multidisciplinary domain of science is undergoing colossal development and has grown immensely in the past few years, thus exhibiting a step aheadof existing practice in the healthcare sector. The research and development has paved its way in the field of nanoengineering which will change the practice of dentistry, medicine and day to day life, moulding it into a better future.Like other technologies, nanotechnology also has the aptitude to be exploited and misused on a large scale.

In the field of dentistry, nanotechnology will give a superiorperception to preventive management, which is the latest trending treatment approach along with advantages like early detection of the disease and treatment of oral cancer.

Conclusion

One of the recent exploitations in periodontology has been the use of nanoparticles in oral biology. Periodontal regeneration still endures to be a partially unsolved algorithm. The purview of periodontal tissue regeneration in nanotechnology is to rejuvenate the lost structure using tissue engineering, in conjunction with materials called "nanoscaffolds" which manipulate the physiological and biological processes for an improved performance of the objective. This will revolutionize the province of periodontal tissue regeneration. In the subsequent wave of research and innovation, the underlying fundamental mechanism of interactions conducted in vivo between nanoparticles and cells at a molecular scale will remarkably facilitate the evolution of this domain.

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