Review

CONTEMPORARY APPROACHES OF RESEARCH IN CLINICAL PERIODONTOLOGY

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Abstract
Periodontitis leads to destruction of tooth attachment apparatus and hence periodontal regenerative procedures are focused much in the research field of periodontology. In the past decades, various regenerative therapies have been introduced in the field of periodontology which includes bone grafts, growth factors, stem cells and their combination using matrix-based scaffolds and proteonomics. The current review discusses recent progresses of periodontal regeneration using tissue-engineering and regenerative approaches and focuses on advances in protein and gene based regenerative procedures and role of 3-D printing in periodontal regeneration.
Key words: Tissue engineering, Gene Therapy, Proteonomics, Polymicrobial synergy.

Introduction

Sir Arthur Kennedy once quoted that "If necessity is mother of invention, scientifically developed production is the mother of scientific research." The scientific evidence that has been emerging over the last few decades brought in a loop several new advancements. Research in the field of periodontics has gained an upgrade in last two decades introducing newer innovations in mythology and armamentarium. The way to current research included tissue engineering and regeneration, Bacterial peptides, Protein based therapy, Gene therapy, Polymicrobial Synergy and Dysbiosis and Nanotechnology which include the 3D printing.

TISSUE ENGINEERING AND REGENERATION

Tissue engineering being a rapidly evolving discipline integrates the biology and engineering together to create products which may be tissue or cellular in nature to develop biological substitutes to better manage, restore, maintain and improve the functions of various organs.[1]

Cell therapy is an emerging cure with high potential in which the cellular substances are used for treatment. Cell sources for the treatment includes mesenchymal stem cells (MSCs) and mature somatic cells. MSCs include cells from bone marrow, dental tissue and adipose tissue. Somatic cells are the cells which can be reprogrammed to Induced Pluripotent Stem Cells (iPSCs) or directly to desired cell type.[2]

CELLS INVOLVED IN PERIODONTAL TISSUE ENGINEERING:

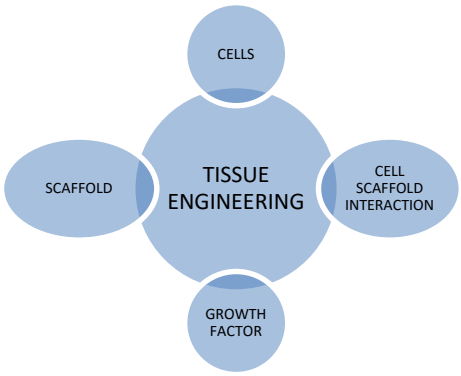
a) Bone Marrow- derived MSCs (BM-MSCs)- They were identified by Friedenstein for the first time. They have a direct role in tissue regeneration and also impacts wound healing via paracrine mechanism. They are the most potent source of cells in the field of tissue engineering.[3]

b) Pulp Stem Cells from tooth (DPSCs): The pulpal stem cells have the potential of self-renewal and multi-potential properties. These cells can differentiate into various cell types such as osteoblasts, odontoblasts, adipocytes, chondrocytes etc.[3]

c) Periodontal Ligament Stem Cells (PDLSCs): These are specialised connective tissue cells that help in establishing the attachment between the alveolar bone and the tooth. These can divide and develop into various cell types including neurons, chondrocytes and osteoblasts and have a potential to regenerate periodontal ligament, blood vessels and alveolar bone.[3]

d) Stem Cells from Human Exfoliated Deciduous Tissue (SHED): These are also known as unique cell type due to their increased production rate and plasticity for multi-potent differentiation.[3]

e) Dental Follicle Stem cells (DFSCs): The cells are collected from the dental follicle and has



an important role for development of tooth. DFSCs can differentiate into periodontal ligament fibroblasts, cementoblasts or osteoblasts. These are easy source of cells and can be taken from third molars.[3]

f) **IPSCs**: The cells are generated from somatic stem cell and have a potential for regeneration. Cell therapy will constantly remain a focus during research in periodontal regeneration with increasing evidence from 3-D printing and scaffold designing technology.[3]

II. Protein/Peptides based Therapies for Periodontal Regeneration

In few years, considerable improvements have been made in using various proteins (biological) for the treatment of periodontal diseases and till now a few proteins been approved by FDA for the use as a commercially available product which chiefly include recombinant human platelet derived growth factor (rhPDGF), enamel matrix derivative (EMD) and P-15 peptides.[3]

A) EMD

It is the first ever protein derived agent marketed as EMDOGAIN for periodontal regeneration. EMD is a mixed fraction of protein which is derived from enamel of piglet with a propylene glycol alginate carrier. The main purpose of EMD is to have an effect on the behaviour of different cell types such as cementoblasts, osteoblasts, MSCs, T-cells and acts by enhancing cell adhesion and promoting cell proliferation, osteogenesis, cementogenesis, angiogenesis and synthesis of ECM. There are evidences which proved that EMD in the field of periodontology is a single therapeutic agent which can be used for regeneration in infrabony defects, furcation defects and recession defects.[4]

B) Platelet derived growth factor (rhPDGF)

It is an important key factor released during blood coagulation and also has a potent role in angiogenesis, enhances cell recruitment and proliferation of periodontal ligament cells and bone. It is approved by FDA and is commercially available as GEM21S which is a combination of rhPDGF-BB and beta tricalcium phosphate. In periodontology, it is indicated for treatment of intrabony defects and it also supports periodontal regeneration.[5]

C) PEPGEN-15(P-15)

P-15 is a polypeptide which contains 15-AA that impersonates the cell binding domain of collagen type-1 and promotes the attachment with the cell thus enhancing osteogenesis. P-15 is approved by FDA and is now available as a mixture of P-15 with anorganic bone matrix. Clinically it is used as a bone graft material with similar or superior qualities when compared with other grafting materials. It is used for regeneration in infrabony defects, histological evaluation reflected its role in periodontal regeneration.[6]

PROTEIN BASED THERAPIES IN CLINICAL EVALUATION

i) Recombinant human fibroblast growth factor-2(rhFGF-2):

FGF-2 has a role in binding with heparin and acts in various healing and growth-related processes of the body. It acts as a potent stimulator of angiogenesis in osteoporosis. Clinically high doses of rhFGF-2 significantly improve bone fill and helps in periodontal regeneration. It is a safe protein therapy and provides good surgical outcomes.[7]

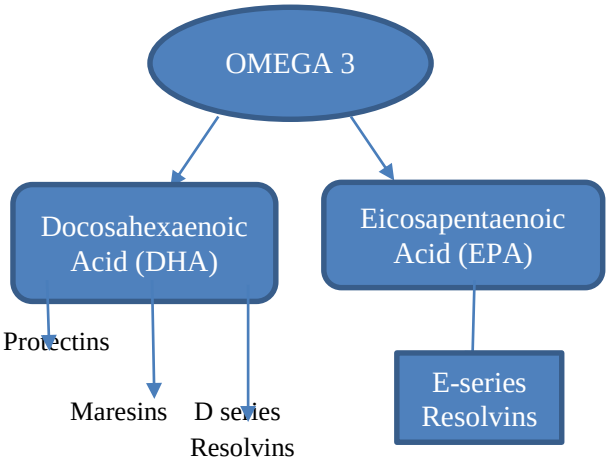
ii) Teriparatide Peptides: It is a bio-synthetic protein of parathyroid hormone which works as an anabolic agent and helps in the treatment of osteoporosis. It is used for the treatment of osteoporosis and it improves both cortical bone cancellous bone structure. Systemic administration of these peptides helps in modulating bone and periodontal wound healing.[8]

RESOLVINS

Resolvins are autocoids which are derived from OMEGA-3 (Fig.3) fatty acids and play a role in regulating the resolution phase of acute inflammatory response. In periodontal disease, resolvins helps to resolve inflammation through various processes within the lesion which chiefly involves prevention of neutrophil penetration followed by phagocytosis and clearance of the lesion thus resolving inflammation and promoting tissue regeneration.[9]

ROLE OF GENE THERAPY IN PERIODONTOLOGY

The latest establishment of already existing and current advancement of gene based applied science has permitted individuals to get a closer review of a disease. The requirement for newer gene-based



diagnostic techniques that are capable of measuring various analysis is concurrently becoming very important. The determination of particular genetic variation that can be aimed by specific drugs has become important in the present environment.

Gene therapy a reconstructive approach

A wider definition of gene therapy is the genetic alteration of cells for treatment purposes. Scaffolds made and used as carrier for proteins, gene and cell, delivery have confirmed its potential by providing biomaterials that can interact smartly with the cells, and bioactive factors. A crucial task that has been less contemplated is the modulation of the exuberant host response to microbial contamination that torments the periodontal wound microenvironment. Periodontal regeneration has for quite some time been the definitive objective in periodontal treatment. Nonetheless, treating and re-building the diseased periodontium's unique structure, properties, and capacity establish a noteworthy challenge. Various extraordinary approaches have been proposed however the quantity of regenerated tissue is regularly constrained and hard to predict. Regeneration, infers the reconstruction of the cementum, periodontal ligament, alveolar bone in a particular temporal sequence and spatial distribution is based on a number of essential factors:

i) **Protein associated approach** – factors like PDGF, b FGF, BMP-2,6,7,12, TGF- β and VEGF etc are taken in account for reforming periodontal tissues.

ii) **Cell associated approach** – Use of stromal stem cells have been useful in reconstitution of bone defect that are too wide to resolve immediately.

iii) **Gene transport approach** - Gene therapy encodes that the growth factor is utilized to stimulate tissue regeneration and to control the short half-lives of growth factor peptides in vivo.[10]

- **Additional methods in periodontal tissue regeneration with gene therapy**

Transcription factor and regulators, Wnts (the fly wingless gene), Bone sialoprotein, NTF-hydrogel therapy, periodontal vaccine.

PROTEOMICS IN PERIDONTOLOGY

Polypeptides are the functioning part of mortal somatikos. Nearly each organic particle in the body is either a protein or an out turn of protein activity. The term proteomics was coined in 1977, which is characterized research of all proteins including their relative abundance, distribution, functions in a given cell or organism within a given environment. It has given much more understanding of organisms than genomics.[11]

Proteomics and Dentistry

Dental proteomics have prospered in two particular areas which are salivary analysis i.e. oral fluid diagnostics or oral fluid biomarkers and proteomics of bone and enamel structures, especially dental enamel. Extensive research and recognition of the protein constituents in human saliva is an imperative initiation towards the determination of saliva protein markers for human disease detection in specific for oral cancer providing a diagnostic and therapeutic significance.[11]

Proteomics and Periodontics

Periodontal ligament fibroblast protein articulation has been deliberated using immunological methods. Certain proteins have been recognised from PDL fibroblasts which can serve as a reference map for later clinical studies as well as primary probe.[11]

i) **Periodontal Pathogen:** Proteomics, this branch of genetics suggests a deal to understand the thorough swift taking place in oral pathogens which adapt to habitat change in their domain i.e. oral cavity. *P.gingivalis* a periodontal pathogen, undergoes changes from its commensal status in healthy individuals to an extremely intriducent intracellular pathogen in patients suffering from periodontitis. Extensive study done on this pathogen in terms of its structural variability, and the proteins responsible for their upregulation and adaptation in the epithelial cell environment which is induced by the considerable alteration in the protein complement of the organism.[12]

- **Stem Cell Research & Genetics** The proteomic and transcriptomic examination provides a radical perception of protein expression, regulation, and cellular biology of mesenchymal stem cells.[12]

The Future of Protein genetic research[12]

One of the most hopeful evolution to come from this study of human genes and proteins has been recognised as a potential new drug for curing disease. This depends on genome and proteome details to recognise proteins associated with a disease, which computer software can then use as targets for new drugs.

Development of Biomarkers[13]

The developed, of "Oral Fluid Nano Sensor Test (OFNASET) is predicted to be a hand held comfortable to use instrument that practitioners could use to quickly determine complex salivary protein and nucleic acid target.

The polymicrobial symbiosis and dysbiotic bacterial relationship[14]

The oral cavity is inhabited by variety of microflora which is composed of 500 species. However, this entity may become virulent leading to pathogenesis of infectious oral disease, example dental caries and periodontal disease. The human microbes and the host co-advanced to have a harmonious or reciprocal relationship. The resident microorganisms contribute to nutrition, digestion, differentiation of host mucosa, development of immunity, colonization and upregulation and take up nutritious natural surroundings around the host. Robust commensal bacterial colonization prevents the pathogenic bacterial colonization by the process known as colonization resistance.

Dysbiosis means disharmony with the symbiotic state of the organisms in the tissue. It generally happens in case of pathological changes in the cell. Periodontitis is a dysbitoic disease resulting from deviation insub- gingival gram-positive bacteria to gram negative bacteria.

The development of a periodontal dysbiosis occurs over broadened timeframe, which steadily turns symbiotic association of host and microbe to pathogenic.

THE POLYMICROBIAL SYNERGY AND DYSBIOSIS MODEL[14]

A recent paradigm of periodontitis progression has been postulated which challenges the traditional concept of periodontitis being induced by few particular periopathogens such as belonging to Red complex, but by a more comprehensive dysbiotic-synergistic community. These heterogenous microbiota inhabiting the periodontium or distinct gene integrations execute discrete functions that shape and stabilizes the infection eliciting pathogens Hence, the complete comprehension of the pathogenesis of periodontitis is based on the polymicrobial synergy and dysbiosis model which describes the newer and better therapeutic interventions. The causation of periodontitis by the diverse bacteria in gingival sulcus as explained by the polymicrobial synergy and dysbiosis model. Hence periodontitis to a certain extent is caused by a deflection from the harmonious symbiotic bacterial community to a dysbiotic one.

Three D Print ready Biopolymeric substances for periodontic complex reformation.[15]

This development and fabrication of scaffolds for tissue regeneration by material- direct printing systems are an advancement in the field of periodontology to have a newer vision of regeneration. It's uncomplicated assembly with further expected properties, synthetic polymer materials are commonly employed with diverse manufacturing systems: fused deposition modelling (FDM) and selective laser sintering (SLS). In particular, bone scaffolds are produced by FDM using PCL and mustered to spinned PCL membrane for PDL cell sheets for periodontal compound neogenesis.

Three D technology for preclinical architectural periodontal regeneration[15] The exposed dentinal root surface is scanned using microcomputed tomography to initiate the image data. According to figure representation defect-adaptable scaffolds are outlined. Operational restorations of PDLs are explored using periostea mien, and 3D-printed, fiber-guiding scaffolds that could support PDL unification to the teeth with cementum-like tissues and stimulate periodontal complex formation. Based on a design for periodontal regeneration, 3D customized fiber-guiding scaffolds are lately evolved with accompanying with geographical reshaping to the one-wall defect using the canine model. A solvent casting method, PCL scaffolds are investigated for habituation to tooth-root structures using the 3D-printed models and analysed quantitatively.

Three D Scaffolding mechanism for reformative Medicine.[16]

Bio substances better monitored for defect adaptation and bio resorption features have much considerable claim in the clinics. The latest blueprint may permit further swift chairside. Additionally, utilization of combination or mixed therapies (cells, genes, and/or biologics) with these latest biomaterials may produce more bioactive constructs thus upgrading the regenerative outcomes. 3D bioprinting can provide inactivation of these reparative entities onto its exterior succour in the finer scheduling of cells for the advancement of new tissue formation.

CONCLUSION

So, analysts must carry on to evolve and magnify their resolution skills, evaluate parameters that affect diagnosis and prognosis, plan an extensive treatment plan, provide suitable treatment and judge the outcome when periodontal care is indicated.

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