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Biomimetics in dentistry, review and recent update

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Introduction: Jack Steele in 1960 coined the word 'BIONICS' which means taking ideas from nature. Biomimetics is defined as the study of the formation, structure or function of biologically produced substances and techniques especially for the purpose of synthesizing similar products by artificial mechanisms which mimic natural ones. It can be categorised as

1. Tissue engineering triad which includes stem cell, scaffold ,signalling molecule.
2. Enamel like a)Invasive - Composites / ceramicsb)Non Invasive - CCP ACP / Novamin

c)Future-Self assembling peptides

3. Dentin like

4. Root end filling materials : PRP / DFDBA

5. Regenerative endodontics : Revascularization

Stem Cell TherapyPulp Implantation

Scaffold Implantation3-D Cell PrintingGene Therapy Bio Engineered Tooth

I. STEM CELLS: Three approaches are being used for creation of new tissues by mimicking natural ones, which form the tissue engineering triad. The concept of using stem cells for dental tissue engineering was explored by Paul Sharpe & associates. Three important stem cells are found to be associated with dental pulp. They are,

a) ***Dpsc :*** Dental Pulp tissue is extracted from the teeth recovered during routine dental procedure throughout the life and these teeth are the most convenient and valuable source. DPSCs can be differentiated by modulation with growth factors, transcriptional factors, extracellular matrix proteins and receptor molecules into different cell types including odontoblast, osteoblast, chondrocyte, cardiomyocytes, neuron cells, adipocyte, corneal epithelial cell, melanoma cell and insulin secreting Beta cells.[1,2,3]

b) ***Shed****:* SHED were first isolated in 2003 from exfoliated human deciduous incisors. But they differ from DPSC with respect to their higher proliferation rate, sphere-like cell-cluster formation, and differentiation capacity.[4]Also, SHED present higher levels of osteocalcin production and alkaline phosphatase activity than DPSC during osteogenic differentiation.

c) ***Scap:*** It is likely that SCAP resides in the apical papilla in close approximation to the periapical tissues. Therefore, after endodontic disinfection, under the influence of the survived HERS, these cells give rise to primary odontoblasts to complete the root formation.

II. SCAFFOLD / ECM: It acts as a scaffold for cell attachment & to modulate cell proliferation & differentiation. It plays an important role in odontoblast differentiation and dentin repair. Bone & Dentin ECM proteins consist primarily of Type 1 collagen, acidic proteins & proteoglycans. Collagen protein forms lattice for deposition of calcium & phosphate whereas non collagenous proteins control initiation & growth.

III. SIGNALLING MOLECULES: They are extracellular secreted molecules and play a key role in regeneration & repair. They are classified into

a) Growth factors : TGF –β / BMP / PDGF

i) TGF-β: they are derived from plasma cells. They are anti inflammatory in nature and promote mineralization as well as wound healing.

ii) BMP: they comprise of more than 20 related proteins including collagen, fibronectin, polysaccharide, hyaluronic acid, proteoglycans. They are produced from bone matrix. Among them, BMP-2,4,7 are expressed in dental epithelium during tooth morphogenesis .

iii) PDGF: PDGF plays a role in embryonic development, cell proliferation, cell migration, and angiogenesis.

b) Inflammatory cytokines : IL-1 / IL-6 / TNF-α

iv) IL-1: In terms of clinical use, because of its characterization as a hematopoetic factor, IL-1 was given to patients after bone marrow transplantation to improve the engraftment.

v) IL-6: It can be secreted by macrophages in response to specific microbial molecules, referred to as pathogen-associated molecular patterns (PAMPs) IL-6 is responsible for stimulating acute phase protein synthesis, as well as the production of neutrophils in the bone marrow. Inhibitors of IL-6 (including estrogen) are used to treat postmenopausal osteoporosis. During exercise, it is thought to act in a hormone-like manner to mobilize extracellular substrates and/or augment substrate delivery

vi) TNF-ALPHA: Tumor necrosis factor-α (TNF-α) which is a member of the TNF ligand superfamily and a multifunctional cytokine, regulates various cellular reactions such as proliferation, differentiation, maintenance of a differentiated phenotype, and

apoptosis in various types of cells. TNF-α challenged pulp cells exhibited increased mineralization & increased expression of DPP, DSP & DMP-1. This is due to P-38, a mitogen activated protein kinase which regulates DSP, DPP & MMP-1 expression & mediates mineralization.TNF-α in turn stimulates differentiation of dental pulp cells towards increased mineralization which helps in reparative dentin formation.

ENAMEL: Dental enamel is a biological ceramic and is the most highly mineralized of all skeletal tissues. During its development EMP (enamel matrix protein) forms-self assembling supermolecular structures which controls deposition & morphology of Hydroxyapatite. Researchers have identified and cloned the major enamel gene – Amelogenin , Sheathlin or ameloblastin , Enamelin & Tuftelin which also control enamel growth and maturation.

i) CCP-ACP: The casein phosphopeptide has a remarkable ability to stabilize calcium phosphate in solution as amorphous calcium phosphate nanocomplexes, thereby allowing the formation of small casein phosphopeptide amorphous calcium phosphate clusters.The role of CCP-ACP has been described as localization of ACP on the tooth surface, which buffers the free calcium and phosphate ion activities, helping to maintain a state of supersaturation with respect to the enamel by suppressing demineralization and enhancing remineralization.

ii) NovaMin is a known component made of bio-active glass particulates with a median size of less than 20 microns. It is indicated that when NovaMin comes in contact with saliva or any aqueous media, its active ingredient, inorganic chemical calcium sodium phosphor silicate, binds to the tooth surface in order to initiate the remineralization process on the tooth enamel. Thus, it remineralizes hard tooth structure while occluding dentinal tubules [5]

iii) SAP- Peptide treatment significantly increased net mineral gain due to a combined effect of increased mineral gain and inhibition of mineral loss. Self-assembling peptides undergo well-characterised hierarchial self-assembly into three-dimensional fibrillar scaffolds in response to specific environmental triggers[6,7] . Such scaffolds offer a new generation of well-defined biopolymers with a range of potential applications.

DENTIN contains 3 unique proteins: DSP ; DPP ; DMP-1. Among noncollagenous proteins, dentin sialophosphoprotein (DSPP) is the most abundant ECM in dentin and is processed into three major forms: dentin sialoprotein (DSP), dentin glycoprotein (DGP) and dentin phosphoprotein (DPP)[8]. Among them, DSP and DPP are chiefly expressed in odontoblasts and dentin.[9,10,11]Both DSP and DPP play unique roles in dentinogenesis. Mutations of either the

DSP or DPP domain cause dentinogenesis imperfecta type II and III (DGI-II and III) and dentin dysplasia type II (DD-II), the most common dentin genetic disorder. DSP is a sialic acid-rich, glycosylated protein1 and is involved in the initiation of dentin mineralization[12,13,] whereas DPP contains abundant aspartic acid and serine, comprising approximately 70–80% of the total amino acid residues and facilitates the maturation of dentin[14,15.]

i) Pulp capping agents: Currently calcium hydroxide , MTA & Biodentin are widely accepted as pulp capping agents. Recent materials include EMDOGAIN / TNF-α / COB cement STATIN / P R F / Lasers.

ii) Emdogain/emd gel - produced from enamel matrix derivative and secreted from HES. It contains proteins like Amelogenin, Enamelin, Tuftelin, Amelin & Ameloblastin and has the capacity to induce rapid reparative dentin formation. Often used in periodontal therapy. It can be utilized for tissue engineering supported regeneration. Nakamura et al in a similar study found that in the EMD treated teeth, pulp showed, a bridge of new hard tissue abutted by a layer of odontoblast like cells features of classic wound healing.

iii) Castor oil bean (cob): It is a polymer derived from Castor oil plant – Ricinus Comminus. The Castor Bean Polyurethane cement is composed of 81-96% triglyceride of ricinoleic acid. It result in osseointegration by formation of micronuclei. It has been successfully used as an endodontic sealer as well as root end filling in apical surgery

iv) Statin is the first line drug for hyperlipidemia . Statin improves osteoblast function via BMP-2 pathway & supresses osteoclastic activity.

v) Lasers : CO_2, Erbium, Neodynium have varying effect on different tissues. Laser irradiation might stimulate release of HSP which are induced by stress from heat & chemical stimuli. Of specific interest is HSP - 47 which is a collagen specific molecule (CHAPERONE). It binds to collagen & plays an essential role in collagen production .Moritz et al & Melcer et al reported use of high power CO_2 laser on exposed pulp surfaces in direct pulp capping and found neo-dentin bridge formation.

ROOT END MATERIALS **:** various materials have been suggested for use in periapical surgeries to facilitate faster healing. Examples include are DFDBA ,PRP. PRP is an autologous source of platelet-derived growth factors and transforming growth factors that is obtained by sequestering and concentrating platelets by centrifugation PRP is a storage vehicle for growth factors especially PDGF, TGF-B both of which influence bone formation All this form a scaffold where osteogenic cells in periapical granulation tissue participate in bone regeneration. It is generally believed that

inflamed soft tissue in periapical lesions should be completely removed during surgery. However recent reports have noted that if a scaffold is provided such as PRP, it can result in wound healing through clot formation & release of growth factors. This in turn will increase the quality of new bone and reduce the time needed for bone regeneration.

DFDBA: it is an allograft between individuals of the same species but of disparate genotype; types of donors are cadaveric, living related, and living unrelated[16,17]. It allows osteoconduction when the bone graft material serves as a scaffold for new bone growth that is perpetuated by the native bone.

REGENERATIVE ENDODONTICS:

i.Revascularization: Revascularization is a new treatment method for immature necrotic permanent teeth. It allows the stimulation of the apical development and the root maturation of immature teeth[18,19,20]. Two pulp revascularization techniques are used in the literature, one using calcium dihydroxide and the second using a triple antibiotic paste.

ii.Stem cell therapy: Stem-cell therapy is the use of stem cells to treat or prevent a disease or condition. The molecules and exosomes released from stem cells are also being studied in an effort to make medications.[9]

iii.Pulp implantation: In pulp implantation, replacement pulp tissue is transplanted into cleaned and shaped root canal systems. The technique for creating replacement pulp tissue is using a three-dimensional cell printing technique.

iv.Scaffold Implantation : Tissue engineering is based on that fact that by cultivating postnatal dental stem cells (DSCs) on a well-designed bioengineered three dimensional scaffold, it is possible to regenerate tooth organogenesis.

v.3D cell printing is the process of creating cell patterns in a confined space using 3D printing technologies, where cell function and viability are preserved within the printed construct. Bioprinting can be used to print tissues and organs to help research drugs and pills.[4][5][6] In addition, 3D bioprinting has begun to incorporate the printing of scaffolds.[7] These scaffolds can be used to regenerate joints and ligaments.

vi.Gene therapy can enhance osteoinduction via expression of growth factors, induce osteoblast differentiation and facilitate the production of osteoid matrix and utilize an osteoconductive apparatus.

vii.Bio Engineered Tooth :The procedures include induction of iPSCs or epithelial derived stem cells into epithelial (epi.) sheets and induction of iPSCs or dental mesenchymal

(mes.) stem cells into mesenchymal masses with odontogenic potential and tissue recombination. This is followed by in vitro organ culture of the recombinants to the late bud or early cap stage, implantation of bioengineered tooth germs into the lost tooth sites of patients, and regeneration of functional replacement teeth.

Conclusion: Future biomimetic materials and regenerative Endodontic methods for regeneration of lost tooth or its structures can only be achieved with such procedures. Thus, these methods have the potential for regenerating both pulp & dentin offering an alternative method to save teeth. Biomimetic materials & methods will revolutionize future endodontics with advances in signalling pathways underlying morphogenesis & lineage of stem cells.

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