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Recent Approaches in Biomimetic Dentistry: A Review

Ruchi Gupta[1], Anil K Tomer[2], Arvind Bhatheja[3]
[1] *Professor, Dept of Conservative Dentistry and Endodontics, Divya Jyoti College of Dental Sciences and Research, Modinagar, Ghaziabad*
[2] *Professor and Head, Dept of Conservative Dentistry and Endodontics, Divya Jyoti College of Dental Sciences and Research, Modinagar, Ghaziabad*
[3] *PG Student, Dept of Conservative Dentistry and Endodontics, Divya Jyoti College of Dental Sciences and Research, Modinagar, Ghaziabad*
Corresponding Author:Dr Ruchi Gupta

Abstract: *Biomimetics is the study of the formation, structure, or function of biologically produced substances and materials and biological mechanisms and processes especially for the purpose of synthesizing similar products by artificial mechanisms which mimic natural ones. It is a challenge to design and fabricate new biomimetic materials like enamel, dentin, cementum, pulp, bone and periodontal ligament. Biomimetics provide new strategy that translates our knowledge of biological system and create new synthetic pathways to mimic biological processes. Three approaches are being used for the creation of new tissues by mimicking natural ones which includes the tissue engineering triad; the Cells, Mediators and a biocompatible matrix.*

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I. Introduction

Biomimetics is gaining popularity in the field of medicine, especially in skin regeneration. Bioartificial skin is being produced using patients own cells. Likewise autograft heart valves and ear cartilage can also be produced.

It is a challenge to design and fabricate new biomimetic materials like enamel, dentin, cementum, pulp, bone and periodontal ligament. Biomimetics provide new strategy that translates our knowledge of biological system and create new synthetic pathways to mimic biological processes. Three approaches are being used for the creation of new tissues by mimicking natural ones which includes the tissue engineering triad; the Cells, Mediators and a biocompatible matrix.

Biomimetics *is defined as the* study of the formation, structure, or function of biologically produced substances and materials and biological mechanisms and processes especially for the purpose of synthesizing similar products by artificial mechanisms which mimic natural ones.

Strategies for Tissue Engineering

1. **Injection of cells** Stem cells are injected directly to the site of injury.
2. **Guided Tissue Regeneration** By placing physical barrier undesirable cells are prevented from entering the injured site.
3. **Cell induction**- Circulating cells are induced to change into a desirable phenotype by injecting growth and differentiating factors into the injured site.
4. **Cells in a scaffold matrix-** Scaffolds seeded with the desired cells are implanted into the injured site.

Dental pulp has the capacity to differentiate into odontoblastic cells. When any noxious stimuli act on pulp, the progenitor/stem cells within the pulp tissue will migrate to the injured site. These progenitor/stem cells proliferate and differentiate into odontoblasts by the morphogens present in the dentin and pulp and reparative dentin is formed.Hence the triad required for tissue regeneration are,

1. Stem/Progenitor cells.
2. Signaling molecules or morphogens.
3. Scaffold or extracellular matrix.

Regenerative dentistry, including endodontics, periodontics and maxillofacial surgery is a new field that seeks the concepts of tissue engineering.

DEMINERALIZED DENTIN MATRIX

The repair of bone defects resulting from trauma, infections, neoplasias or developmental abnormalities represents a challenge for maxilla-mandibular complex surgeries. Several researches have presented some materials that have osteopromotive potential for osteogenesis including demineralized dentin matrix.

The importance of decalcified dentin matrix is based on its osteoinductive property. The chemotactic, mitogenic and osteogenic potential of dentin matrix is associated with bone morphogenetic protein according to Gomes and coworkers. Dentin matrix is also rich in other factors like transforming growth factor-beta, fibroblast growth factor, platelet derived growth factor and epidermal growth factor.

Uses:
Demineralized dentin matrix is proposed to be used as:

1. An implant biomaterial

The dentin matrix used as implant biomaterial has osteogenic and chemotactic potential. Kawai and Urist MR have reported that autogenous demineralized dentin matrix slices (DDM) stimulated bone neoformation.

This phenomenon is probably controlled by complex molecular interactions, cellular messages of short or long extension, affecting the speed and duration of the osteoblastic and osteoclastic activity, as well as proliferation, differentiation, and chemotaxis of special cells. The cellular proliferation begins with local stimulating factors such as bone morphogenic proteins (BMP). In addition to BMP, DDM slices are also rich in other growth factors such as transforming growth factor-beta (TGF-β), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF) and epidermal growth factor (EGF).

Demineralized bone matrix (dBm), in contact with mesenchymal cells, induce chondrogenesis followed by osteogenesis when implanted in muscle, bone marrow, tendon, lung, pericardium, and periodontal ligament sites. The potential of dBm to elicit differentiation of mesenchymal cells obtained from embryonic muscle, bone marrow, spleen, and thymus into cartilage has also been confirmed in vitro. Demineralized dentin matrix (dDm) has the same effect as when dBm is implanted in muscle, skin, bone marrow, and periodontal ligament sites, or incubated in contact with mesenchymal cells obtained from the above tissues. The transformation of mesenchymal cells into osteoblasts or chondroblasts induced by dBm or dDm is due to a non-collagenous portion of the matrices and is dependent on the levels of vascular-derived oxygen.
It has also been clarified that demineralized dentin originating from various mammals induces undifferentiated mesenchymal cells to differentiate into osteogenic cells and then into cartilage and bone.

2. An apexification agent
Zhi performed a study to identify the clinical effects of demineralized dentin matrix (DDM) as an apexificating agent. The findings suggested that DDM can be used as a new apexificating agent.

3. Pulp capping agent
Tziafas D and Kolokuris I reported the effect of dDm or dentin matrix constituents on dental pulp or papilla cells. Anneroth and Bang used allogenic demineralised and lyophilized dentin as a pulp-capping agent and found hard-tissue barrier formation. Irregular dentin formation was also observed in contact with fragments of dentin that penetrated the pulp tissue during mechanical pulp exposure.

4. Scaffold for bone regeneration:
DDM may be a useful bone substitute that serves as a scaffold for bone regeneration by inducing a high level of new bone formation soon after surgery.
DDM has advantages such as high bioaffinity, easy harvesting, osteoinduction and no risk of infection, and thus can be considered as a safe grafting material that may be used instead of autogenous bone graft.

II. Approaches To Stem Cell Technology

Several major areas of research have been identified that might have application in the development of regenerative endodontic techniques. These techniques are

(a) Root canal revascularization via blood clotting,
(b) Postnatal stem cell therapy,
(c) Pulp implantation,
(d) Scaffold implantation,
(e) Injectable scaffold delivery,
(f) Three-dimensional cell printing
(g) Gene delivery

These regenerative endodontic techniques are based on the basic tissue engineering principles already described and include specific consideration of cells, growth factors and scaffolds.

III. Root Canal Revascularization Via Blood Clotting

Revascularization is the procedure to re-establish the vitality in a nonvital tooth to allow repair and regeneration of tissues. The rationale of revascularization is that if a sterile tissue matrix is provided in which new cells can grow, pulp vitality can be re-established. Revascularization protocols are derived from the

observations of re-implanted and autotransplanted teeth in experimental animals in which necrotic pulp, if free of infection, provides a matrix into which the cells from the periapical tissues could grow and re-establish pulp vascularity eventually slowly replacing the necrotic tissue. In immature, infected, nonvital teeth, infection control is achieved with minimal instrumentation, depending more on aggressive, copious irrigation with sodium hypochlorite, chlorhexidine, or povidone-iodine. Some authors have suggested the use of ciprofloxacin and metronidazole paste or $Ca(OH)_2$ paste to control the infection.

Use of intracanal irrigants (NaOCl and chlorhexdine) along with the placement of antibiotics (e.g. a mixture of ciprofloxacin, metronidazole, and minocycline paste) for several weeks is an important aspect of revascularization. This particular combination of antibiotics effectively disinfects root canal systems and increases revascularization of avulsed and necrotic teeth, suggesting that this is a critical step in revascularization. The selection of various irrigants and medicaments is worthy of additional research, because these materials may confer several important effects for regeneration in addition to their antimicrobial properties. For example, tetracycline enhances the growth of host cells on dentin, not by an antimicrobial action, but via exposure of embedded collagen fibers or growth factors. However, it is not yet known if minocycline shares this effect and whether these additional properties might contribute to successful revascularization.

Elimination of microorganisms and necrotic tissues from the root canal system is the key factor in a successful revascularization. Instrumentation is contraindicated in revascularization treatment. Root dentinal walls are so thin that any instrumentation makes them weaker and more susceptible to future fractures, and also formation of a smear layer could occlude the dentinal walls and tubules.

Human dentin contains several angiogenic growth factors that can promote tissue regeneration in the root canal space. Therefore, it is safe to assume that the blood clot in the disinfected empty root canal space that contains platelet-derived growth factors along with growth factors derived from dentinal walls plays the role of a protein rich scaffold that might be crucial for successful population and differentiation of stem cells and, ultimately, root development.[18]

The importance of a bacteria-tight coronal seal for successful revascularization is well documented. A majority of reported studies have used a double seal over the blood clot formed inside the canal, MTA and a resin-bonded restoration. Sealing ability and biocompatibility of MTA has been documented in several studies.

Advantages of revascularization:

1. The main advantage of revascularization technique over traditional apexification or artificial barrier technique in endodontic treatment of immature necrotic teeth includes continuation of root development and strengthening the root structure.
2. After control of infection, it can be completed in a single visit.
3. It is also very cost-effective, because the number of visits is reduced, and no additional material (such as TCP, MTA) is required.
4. Obturation of the canal is not required unlike in calcium hydroxide– induced apexification, with its inherent danger of splitting the root during lateral condensation.
5. Also, the regeneration of tissue in root canal systems by a patient's own blood cells avoids the possibility of immune rejection and pathogen transmission from replacing the pulp with a tissue engineered construct.
6. However, the biggest advantage is that of achieving continued root development (root lengthening) and strengthening of the root as a result of reinforcement of lateral dentinal walls with deposition of new dentin/hard tissue.

Limitations of revascularization:

There are only a few limitations of revascularization:

1. Long-term clinical results are not yet available.
2. It is possible that the entire canal might be calcified, compromising esthetics and potentially increasing the difficulty in future endodontic procedures if required.
3. In case post and core are the final restorative treatment plan, revascularization is not the right treatment option because the vital tissue in apical two thirds of the canal cannot be violated for post placement.

POST-NATAL STEM CELL THERAPY

The simplest method to administer cells of appropriate regenerative potential is to inject postnatal stem cells into disinfected root canal systems after the apex is opened. Postnatal stem cells can be derived from multiple tissues, including skin, buccal mucosa, fat, and bone. A major research obstacle is the identification of a postnatal stem cell source capable of differentiating into the diverse cell population found in adult pulp (e.g., fibroblasts, endothelial cells, odontoblasts).

Technical obstacles include the development of methods for harvesting and any necessary ex vivo methods required to purify and/or expand cell numbers sufficiently for regenerative endodontic applications.

One possible approach would be to use dental pulp stem cells derived from autologous (patient's own) cells that have been taken from a buccal mucosal biopsy, or umbilical cord stem cells that have been cryogenically stored after birth or an allogenic purified pulp stem cell line that is disease- and pathogen-free; or xenogenic (animal) pulp stem cells that have been grown in the laboratory. It is important to note that no purified pulp stem cell lines are presently available, and that the mucosal tissues have not yet been evaluated for stem cell therapy.

Advantages:
There are several advantages to the approach of using postnatal stem cells.
1. Autogenous stem cells are relatively easy to harvest and to deliver by syringe, and the cells have the potential to induce new pulp regeneration.
2. This approach is already used in regenerative medical applications, including bone marrow replacement.

Disadvantages:
There are several disadvantages related to the delivery method of injecting cells:
1. The cells may have low survival rates.
2. The cells might migrate to different locations within the body, possibly leading to aberrant patterns of mineralization. A solution for this latter issue may be to apply the cells together with a fibrin clot or other scaffold material. This would help to position and maintain cell localization.

IV. Pulp Implantation

This involves the use of many biodegradable membrane filters which are rolled together to form a three dimensional pulp tissue structure from two-dimensional cell cultures. This can then be implanted into disinfected root canal systems. These aggregated sheets of cells are more stable than dissociated cells in the support of cellular proliferation.

In pulp implantation, replacement pulp tissue is transplanted into cleaned and shaped root canal systems. The source of pulp tissue may be a purified pulp stem cell line that is disease or pathogen-free, or is created from cells taken from a biopsy, that has been grown in the laboratory. The cultured pulp tissue is grown in sheets in vitro on biodegradable polymer nanofibers or on sheets of extracellular matrix proteins such as collagen I or fibronectin. So far, growing dental pulp cells on collagens I and III has not proved to be successful, but other matrices, including vitronectin and laminin, requires investigation.

Advantages:
The advantage of having the cells aggregated together is that it localizes the postnatal stem cells in the root canal system. Also, the cells are relatively easy to grow on filters in the laboratory.

Disadvantages:
The disadvantage of this technique includes:
1. Implantation of sheets of cells may be technically difficult.
2. The sheets are very thin and fragile, so research is needed to develop reliable implantation techniques.
3. The sheets of cells also lack vascularity, so they would be implanted into the apical portion of the root canal system which requires a coronal delivery of a scaffold capable of supporting cellular proliferation.
4. Cells located more than 200 μm from the maximum oxygen diffusion distance from a capillary blood supply are at risk of anoxia and necrosis.

The development of this endodontic tissue engineering therapy appears to present low health hazards to patients, although concerns over immune responses and the possible failure to form functioning pulp tissue must be addressed through careful in vivo research and controlled clinical trials.

V. Scaffold Implantation

To create a more practical endodontic tissue engineering therapy, pulp stem cells must be organized into a three-dimensional structure that can support cell organization and vascularization. This can be accomplished using a porous polymer scaffold seeded with pulp stem cells.

A scaffold should contain growth factors to aid stem cell proliferation and differentiation, leading to improved and faster tissue development. The scaffold may also contain nutrients promoting cell survival and growth, and possibly antibiotics to prevent any bacterial in-growth in the canal systems. In addition, the scaffold may exert essential mechanical and biological functions needed by the replacement tissue.

In pulp-exposed teeth, dentin chips have been found to stimulate reparative dentin bridge formation. Dentin chips may provide a matrix for pulp stem cell attachment and also be a reservoir of growth factors. The

natural reparative activity of pulp stem cells in response to dentin chips provides some support for the use of scaffolds to regenerate the pulp-dentin complex.

INJECTABLE SCAFFOLD DELIVERY

This approach makes use of hydrogels that are injectable scaffolds and can be delivered by a syringe. This allows tissue engineered pulp tissue to be administered in a soft three-dimensional scaffold matrix, such as a polymer hydrogel. Hydrogels are injectable scaffolds that can be delivered by syringe. Hydrogels have the potential to be non-invasive and easy to deliver into root canal systems. In theory, the hydrogel may promote pulp regeneration by providing a substrate for cell proliferation and differentiation into an organized tissue structure. Past problems with hydrogels included limited control over tissue formation and development, but advances in formulation have dramatically improved their ability to support cell survival. Despite these advances, hydrogels are at an early stage of research, and this type of delivery system, although promising, has yet to be proven to be functional in vivo. To make hydrogels more practical, research is focusing on making them photopolymerizable to form rigid structures once they are implanted into the tissue site.

THREE-DIMENSIONAL CELL PRINTING

The final approach for creating replacement pulp tissue may be to create it using a three-dimensional cell printing technique. In theory, an ink-jet-like device is used to dispense layers of cells suspended in a hydrogel to recreate the structure of the tooth pulp tissue. The three-dimensional cell printing technique can be used to precisely position cells, and this method has the potential to create tissue constructs that mimic the natural tooth pulp tissue structure. The ideal positioning of cells in a tissue engineering construct would include placing odontoblastoid cells around the periphery to maintain and repair dentin, with fibroblasts in the pulp core supporting a network of vascular and nerve cells.

Theoretically, the disadvantage of using the three-dimensional cell printing technique is that careful orientation of the pulp tissue construct according to its apical and coronal asymmetry would be required during placement into cleaned and shaped root canal systems. However, early research has yet to show that three-dimensional cell printing can create functional tissues in vivo.

GENE THERAPY

Genes can stimulate or induce a natural biological process by expressing a molecule involved in regenerative response for the tissue of interest. Precise delivery and efficient transfer of genes into target tissue cells, prompt assessment of gene expression at required times and appropriate levels and/or minimization of undesirable systemic toxicity are essential prerequisites for successful gene therapy. Either viral or non-viral vectors are used to enable the cellular uptake and expression of genes. Viral vectors are genetically altered to eliminate their disease-causing ability. The viruses can replicate genes of interest together with their own genome, through the use of host cell genetic machinery.

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