Regenerative Biomaterials in dentistry

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Abstract: There is an onset of age of regeneration and biomaterials. Mankind is advancing beyond the ability to create inanimate object, towards the capability of replacing and regenerating our own living body tissues. The amalgamation of bioengineering and dentistry has resulted in explosion of knowledge that has enhanced our understanding and started a new era of dentistry, with the introduction of biomaterials which are biologic therapeutic agents and which leads to replacement, repair, maintenance, and enhance the lost tissue function.

Pulp therapy with biomaterials is biologically based procedures designed to replace damaged structures, including dentine and root structures, as well as cells of pulp - dentine complex. Regenerative dental procedures include the development of the application of Platelet rich plasma (PRP), Emdogain, Recombinant human bone morphogenic protein, Growth factor, and cell that has the ability to continuously divide and produce progeny cells i.e. Stem cells & various other biomaterials for pulp therapy.

Key words: Regeneration, Pulp Therapy, Platelet rich plasma PRP, Bone morphogenic protein BMP.

Introduction

The goal of dentistry is to functionally and esthetically restore lost tooth structure, with a material available which can mimic all the physical, mechanical and esthetic properties of enamel and dentine. There is need of development of novel techniques which can regenerate enamel and dentine, as opposed to replacing lost tooth structure, with artificial material which would have significant benefits of regeneration. Regenerative procedures have a long history originating around 1952 when Dr B. W. Hermann introduced the application of calcium hydroxide as a regenerative material for vital pulp amputation [1]. But due to its drawback of causing internal resorption and incomplete dentinal bridge formation, its use is not further recommended.

In 1965, Urist, introduced a family of proteins i.e. bone morphogenic proteins (BMP) which have bone inductive properties. The biologic properties and putative role of BMP in dentine led to several studies to determine effect of these molecules on dentine repair and it was concluded that BMPs induce reparative dentine formation.

Discussion -

Bone morphogenic proteins (BMP)

Bone morphogenic proteins (BMPs) are a generic term for a family of proteins which have bone-inductive properties. It was observed as early as in 1965 by Marshell Urist [2] that demineralized bone matrix was capable of stimulating bone formation when implanted in ectopic sites. They have a pivotal role in regulation of bone induction maintenance & repair. Like

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bone, demineralized dentine also has an intrinsic capability to induce mineralization. When applied directly to areas of pulp exposure, demineralized dentine induces the local formation of mineralized tissue [3]. This reparative dentine forms superficial to and not at the expense of pulp tissue. Thus, recombinant bone morphogenic protein's use in pulp procedures leads to the the emergence of a new paradigm in the field of dentistry [4].

Clinical Applications of BMP's [5]

a. Periodontal regeneration was achieved when BMP was applied to the defect site which results in decrease depth of the defect site brought about by stimulating vertical bone growth and regenerating the periodontal attachment.
b. Application in oral surgical procedures like: Rigid augmentation, Sinus elevation procedures, Placement in extraction socket. Placement around implants to accelerate osseointegration.
c. Recombinant BMP regenerate original alveolar bone height and periodontal attachment apparatus as well when used in periodontal osseous defects.
d. As therapeutic agents for treatment of bone fractures.
e. In preventing bone defects.
f. Treating periodontal bone defects.

Mechanism of action - Nakashima in 1990 [6] demonstrated that BMP affect by induction of a layer of reparative dentine. This protection is provided via two mechanisms:Firstly, they stimulate proliferation of pulp stem cells and induce their differentiation into odontoblast to enhance healing potential and rapid dentine formation. Secondly, they act by increasing the thickness of remaining dentine and reducing direct connection between tubules of primary dentine and the reparative dentine .The permeability of the dentine to transportable irritants is reduced.

Platelet rich plasma (PRP)

Although with the discovery of bone morphogenic protein a new chapter has been opened in reconstructive and regenerative sciences. But the relative effectiveness and the successful application of bone morphogeniç proteins (BMPs) depends on elucidation of the optimal therapeutic dosage, delivery system, and local conditions for repair and this led to introduction of platelet rich plasma (PRP) .

Mechanism of action of Platelet Rich Plasma: [5]

Platelet rich plasma has been found to work via three mechanisms:

1. Release of Growth Factors increases local cell division (producing more cells).
2. Inhibition of excess inflammation (decreased early macrophage proliferation).
3. Degranulation of the agranules in platelets, which contain the synthesized and prepackaged growth factor.

Emdogain (enamel matrix protein)

Emdogain was introduced by Hammartson (Sabbarini J, Mohamed A, et al 2008) facilitate regenerative procedures. Amelogenins are the main component of enamel matrix protein participates in differentiation and maturation of odontoblastic cells and leads to early dentine formation. Enamel matrix derivative (EMD) in the form of Emdogain (commercially available enamel matrix protein) incite natural regenerative processes in mesenchymal tissues. The EMD induced processes mimic normal odontogenesis and participate in reciprocal ectodermal – mesenchymal signaling that control these processes [7, 8]. Emdogain is a purified acidic extract of developing embryonal

enamel derived from six month-old piglets. It acts as a tissue-healing modulator that mimics the events that occur during root development and to help stimulate regeneration.

The use of Straumann Emdogain offers a treatment option with capabilities to regenerate periodontal tissue as shown in several pre-clinical, human histological case reports and randomly controlled clinical trials. To date, over 3,000 defects treated with Straumann Emdogain have been evaluated through more than 400 published clinical studies, demonstrating its clinical effectiveness [9].

Composition of Enamel Matrix Protien - [10]

It consists of three types of proteins:

1) **Amelogenins:** Amelogenins participate in the differentiation of odontoblast and subsequent predentine formation. Recent studies show that hydroxyapatite crystals grown in the presence of amelogenins develop into characterically long crystals associated with enamel formation.

2**) Enamelins**: It is the second largest component of enamel matrix protein. It contains serum proteins and are termed as non -amelogenin. It includes proline-rich enamelin, tuftelin and tuft proteins. This protein is expressed prior to the onset of mineralization. The function of tuftelin in tooth development is that it functions at the level of ameloblast differentiation and/or extracellular matrix secretion.

3**) Sheathlin**: It is also known as ameloblastin or amelin. It has osteoinductive fraction of enamel extracts .This protein is present in the secretory stage of enamel formation and plays a role in enamel biomineralization. Ameloblastin is also detected in pulpal mesenchymal cells and Hertwig's Root sheath.

Mechanism of action of Enamel Matrix Derivative (EMD): **[10]**

EMD when applied to exposed pulp tissue enhances morphogenic events in repairing of dental pulp i.e. rapid fibro dentine matrix formation and subsequent reparative dentinogenesis. It forms superficial layer or scab consisting of extracellular matrix proteins and necrotic cell remnants overlying a zone of chronic inflammatory cell infiltrate. Subjacent to that EMD induce a large amount of dentine like tissue at the interface between the wounded and unharmed pulp tissue [11]. The induction of dentine by EMD is via intracellular cyclic –AMP signal in exposed cell which leads to autocrine growth factor secretion in orchestrated cascade [12].

The involvement of enamel proteins in root formation was first suggested in 1974. The function of enamel proteins in root formation is in following ways:

a)They serve in attachment of cementum to root dentine (Ten Cate 1996).

b)They help to initiate cementogenesis (Heritier 1982).

c) They serve as an inducer of dental follicle cells to differentiate into cementoblasts (L. Hammarstrom 1997; Hammarstrom 1996).

Clinical applications: Root end induction, Periodontal regeneration , Correction of infrabony pockets, Correction of intraosseous defects, Treatment of Furcation and recession defect, Reimplantation, Pulpotomy

Stem cells

Duailibi et al. (2006) defined stem cells as "Quiescent cell populations present in low numbers in normal tissue, which exhibit the distinct characteristic of asymmetric cell division, resulting in the formation of

two distinct daughter cells - a new progenitor/ stem cell and another daughter cell capable of forming a differentiated tissue" [13]. All tissues originate from stem cells. A stem cell is commonly defined as a cell that has the ability to continuously divide and produce progeny cells that differentiate into various other types of cells or tissues.

Classification of Stem Cells:

Stem cells are classified as :

1 Embryonic or fetal stem cell : They are derived from in vitro fertilization where embryo is formed from the fertilized eggs and are 4-5 days old also called as blastocyst .

2. Adult or post natal stem cell : These are undifferentiated cells that typically generate the cell type of the tissue in which they reside. They can renew themselves and their primary role in a living organism is to maintain and repair the tissues in which they are found [14]. Based on plasticity of stem cell which defines its ability to produce different tissues .stem cells are subdivided as .

1 Totipotent : It has the potential to give rise to any and all human cells, such as brain, liver, blood or heart cells. It can even give rise to an entire functional organism.

2 Pluripotent Stem Cell : These are the inner cell mass of the blastocyst in the developing zygote and embryonic stem cell in culture, capable of giving rise to all embryonic cells and tissues .

3 Multipotent fetal stem cell : These are cells derived from the three germ layers (ectoderm, mesoderm, ectoderm) that generate cells as organs and tissues are formed.

4 Multipotent adult stem cell : These are tissue specific and form all type of cell .

5 Unipotent stem cell : These are cell in adult organism that are capable of differentiating only one lineage

Mechanism of action of stem cell in dentine regeneration :

Stem cells retain the ability to respond to mild environmental stimuli and focally up regulate their secretory activity during reactionary dentinogenesis leading to dentinal regeneration. The dental pulp contains a population of stem cells, called pulp stem cells or, in the case of immature teeth, stem cells from human exfoliated deciduous teeth (SHED). Pulp stem cells are called odontoblastoid cells, because these cells appear to synthesize and secrete dentin matrix like the odontoblast cells they replace. After severe pulp damage or mechanical or caries exposure, the odontoblasts are often irreversibly injured beneath the wound site. It was proposed that the cells within the subodontoblast cell–rich layer or zone of Howl adjacent to the odontoblasts differentiate into odontoblastoids [14].

Shi S., et al. (2003) [15] found that two type of stem cells were identified in adult human dental pulp (dental pulp stem cells (DPSC), and human primary teeth (stem cells from human exfoliated deciduous teeth (SHED).

Dental pulp stem cells (DPSC) :

DPSCs has the ability to regenerate a dentin-pulp-like complex that is composed of mineralized matrix with tubules lined with odontoblasts, and fibrous tissue containing blood vessels in an arrangement similar to the dentin-pulp complex found in normal human teeth (**Gronthos S., et al. 2003)**. DPSCs possess the properties of high proliferative potential, the capacity of self-renewal, and multi-lineage differentiation. **(**Gronthos S., et al.2005).

Mechanism of action of DPSC: (Miura M., et al 2003)

Following physiological stimulation or injury, such as caries and operative procedures, stem cells in pulp can proliferate and differentiate into dentin-forming odontoblasts (Nakashima et al., 1994; Gronthos et al., 2000, 2002). Replace damaged odontoblasts by newly generated populations of odontoblasts [16].

Stem cells from human exfoliated deciduous teeth (SHED):

The dental pulp contains a population of stem cells, called pulp stem cells. Miura M., et al. in 2003 identified a population of highly proliferative, clonogenic cells capable of differentiating into a variety of cell types including neural cells, adipocytes, and odontoblasts. And named these special cells as SHED. After in vivo transplantation, SHED was found to be able to induce bone formation, generate dentin, and survive in mouse brain along with expression of neural markers(Miura et al 2003).

Adult dental pulp stem cells (DPSC) Adult dental pulp contains precursors capable of forming odontoblasts under appropriate signals; among these signals are the calcium hydroxide or calcium phosphate materials, which constitute pulp-capping materials used by dentists for common dental treatments .

Stem cells from the apical part of the papilla (SCAP)- Stem cells from the apical part of the human dental papilla (SCAP) have been isolated and their potential to differentiate odontoblasts was compared to that of the periodontal ligament stem cells (PDLSC) Hargreaves et al., 2008.

Stem cells from the dental follicle (DFSC) have been isolated from the third molars' follicle of humans and used to express the stem cell markers: Notch1, STRO-1 and nesting.

Periodontal ligament stem cells (PDLSC) (Anil Dhingra et al 2011) PDL contain STRO-1 positive cells that maintain certain plasticity since they can adopt adipogenic, osteogenic and chondrogenic phenotypes *in vitro* [13].

Conclusion

The advent of biomaterials is allowing dentistry to move forward in the use of regeneration as an underlying principle for the treatment of dental diseases. The introduction of biomaterials strongly suggests newer strategies to replace tissues lost during the process of caries or trauma and will lead to a new era of dentistry.

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