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Stem Cells in Periodontal Regeneration

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Abstract: *Periodontitis is an inflammatory disease which results in clinical loss of supporting periodontal tissues including the periodontal ligament, cementum and alveolar bone. For decades, periodontologists have sought various surgical and non-surgical procedures to repair the damage. But, the ultimate aim of regeneration has not been achieved. This review is about the application of stem cells in periodontal regeneration. The triad inclusive of cells, signalling molecules and scaffold plays a significant role in achieving regeneration.*
Keywords: *Periodontal ligamentstem cells, regeneration, scaffold, signalling molecules, tissueengineering,*

I. Introduction

Periodontitis is a disease of the periodontium characterized by irreversible loss of connective tissue attachment and supporting alveolar bone[1]. It is a highly prevalent chronic inflammatory disease[2]. Various surgical and nonsurgical treatment procedures were followed since 1950s which had resulted in arresting the progression of periodontitis and had helped in tissue healing. But the ultimate goal of regeneration of lost periodontal structures remains questionable.

Periodontal regeneration aims at complete restoration of the lost tissues to their original architecture and function by recapitulating the crucial wound healing events associated with their development [2]. This entails the reformation of all the components of the periodontium, gingival connective tissue, periodontal ligament, cementum, and alveolar bone. This had led to the introduction of stem cells in periodontal regeneration.

1993, Langer and Colleagues[3] proposed tissue engineering as a possible technique for regenerating lost tissue and restoration of various human tissues and organs in starting to become a reality.

II. Stem Cells

1. History of stem cells:

Stem cell refers to a clonogenic, undifferentiated cell that is capable of self-renewal and multi-lineage differentiation [4]. They form the origin of life. They are unique and form the basis of development, growth and survival of a living organism. Stem cells are the foundation cells of every organ and tissue in the body including the periodontium [5, 6].

The term stem cell appeared first in the literature during 19th century [7]. Birth of stem cell research took place way back in 1953 when Leroy Stevens identified teratoma like cells in testicles of inbred mice. The concept that stem cells may reside in the periodontal tissues was first proposed approximately 20 years ago by Melcher, who queried whether the three cell population of the periodontium (cementoblasts, osteoblasts, and periodontal ligament fibroblasts) were derived from a single population of ancestral cells or stem cells [8]. The most compelling evidence that these cells are present within the periodontal tissues has been provided by the studies of Mc Culloch et al (1987) who identified small population of progenitor cells adjacent to blood vessels within the periodontal ligament[9].

II. Stem cells-types[10-12]:

2.1. Embryonic stem cells
2.2. Foetal stem cells
1.3. Adult stem cells- Haematopoietic stem cells
Non haematopoietic stem cells (bone
Marrow stromal stem cells or
Mesenchymal stem cells)

2.4. Humanderived mesenchymal stem cells (dental origin)
- dental pulp derived stem cells
- stem cells from exfoliated human deciduous teeth
- Adult periodontal ligament stem cells

- Root apical papilla stem cells
- dental follicle stem cells
- Mesenchymal stem cells from gingiva

2.5. Human derived mesenchymal stem cells (non-dental origin)

- Bone marrow derived mesenchymal stem cells
- Adipose derived stem cells

III. Terminologies [13]:

3.1 Progenitor cell: It is an undifferentiated precursor cell with the capacity to undergo differentiation into specialised cell types; unlike putative stem cells they do not retain the capacity for self-renewal.

3.2 Totipotent stem cell:they are cells derived from the first few divisions of the fertilised egg which have the potential to give rise to all the differentiated cells of the fully developed organism.

3.3 Pluripotent stem cell:they are cells capable of self-renewing and differentiating into any of the germ layers(ectoderm, endoderm, mesoderm)

3.4Multipotent stem cell: cells that self-renew and differentiate into several different specialised cell types, often within a tissue (e.g. haematopoietic stem cells)

2. Differences between :

EMBRYONIC STEM CELLS	ADULT STEM CELLS
• Totipotent and pluripotent cells	• Show multipotent differentiation
• Immortal in nature	• Mature and finite life span
• Greater differential potential	• Capable of differentiation into only limited number of cell types
• Can be isolated from embryo with relative ease.	• Found low in numbers in the human body. Isolation of these cells is challenging • Do not expand readily in cultures
• Unlimited ability to self-renew and proliferate in culture in huge numbers. • Remarkably broad therapeutic potential	• Very few adult stem cells exhibit stem cell plasticity
• Subjected to ethical controversy and legal restrictions	• No such restrictions present.

3. Ethical concerns:

Although stem cell population are present in foetus during gestation, their roles in normal development have been widely studied, their possible clinical usefulness has barely been explored, owing to the ethical issues of using cells from the foetus in treating disease and risks to pregnancy associated with intrauterine procedures[14]

4. Stem cell banking:

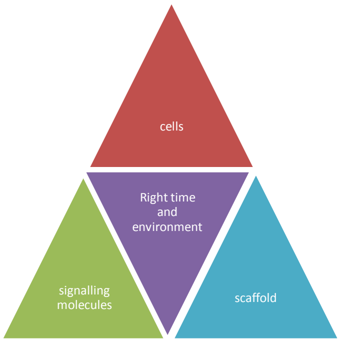
In 2005, the National academics [15] issued a report, cord blood establishing a National haematopoietic stem cell bank program, which recommended that a national cord blood bank be established to harness the medical potential of these sources of stem cells. Research in recent times indicates that umbilical cord blood is rich in "stem cells" [16]. Those cells have important advantages compared to the bone marrow stem cells. The major advantage that umbilical cord blood stem cells are easier to gather that stem cells from the bone marrow. They have a unique ability to regenerate, reproduce into over 200 types of tissues. Above all, such stem cells can be collected from the umbilical cord of child can be frozen and kept in a tank; which can be used later [17].

The first ever cord blood bank in the world was started in New York's Milstein National cord blood Centre. Today, there are over 40 cord blood banks worldwide, both public and private [16]

III. Tissue Engineering

It is a specialised field of science based on principles of cell biology, developmental biology and biomaterials science to fabricate new tissues to replace lost or damaged tissues [18-20].

1. Triad of tissue engineering:



The tissue engineering approach to bone and periodontal regeneration combines 3 key elements to enhance regeneration [21]

1.1 Cells

1.2. Conductive scaffold

1.3. Signalling molecules

1.1. Cells:stem cells are considered as a major component of tissue engineering process. Stem/progenitor cells contribute to regeneration process. Different types of stem cells used in this process includes

1.1.1 Periodontal ligament derived mesenchymal stem cells:

They are first isolated from the periodontal ligament tissues of extracted human third molar teeth, followed by the periodontal ligament from the root surface following extraction, periodontal ligament remaining in the alveolar bone surfaces of the extraction sockets. These cells are multipotent and can differentiate into osteoblasts, fibroblasts and periodontal ligament like tissues.

1.1.2. Root apical papilla stem cells:

They are obtained from the tips of growing tooth roots which represent a unique population of dental stem cells (SCAP). They have the capacity to differentiate into adipocytes ,odontoblasts and osteoblasts in vitro.

1.1.3Dental follicle cells:

They are multipotent and contain progenitors for cementoblasts, periodontal ligament and osteoblasts.

1.1.4 Dental pulp stem cells:

They have the ability to terminally differentiate into odontoblasts like cells to form

Bone, representing a potential stem cell sources for stem cell therapy.

1.1.5 Human gingiva

Tomas I. Mitrano et al in 2010 studied if gingival connective tissue could be a reservoir of MSCs that could be used in regenerative procedures based on tissue engineering [22]. The results clearly demonstrated that it is possible to isolate MSCs from the gingival connective tissue and obtain their differentiation into osteoblasts, cartilage and adipose cells in the same way that has been described regarding samples obtained from the bone marrow [22].

1.1.6 Stem cells of non- dental origininclusive of bone marrow derived mesenchymal stem cells and adipose derived stem cells.

1.2 Conductive Scaffold:

The role of scaffold is to provide support for delivering cells and growth factors to the proposed site of tissue regeneration. Regeneration of any tissue requires a physical support to the cells. They should

- Be biodegradable. The rate of degradation should coincide with rate of tissue formation [23].
- Should be porous for the diffusion of cells and nutrients [24]. Allow appropriate differentiation of cells without affecting their progeny.
- They should ideally mimic the natural environment of tissues.
- They should be biocompatible and non –immunogenic [25].

They are available in both natural and synthetic forms. Natural biomaterials used as scaffold includes collagen, chitosan, alginate and fibrin, agarose, gelatin, hyaluronic acid and pectin.

Synthetic biomaterials includes polygycolicacid, poly lactic acid, and their copolymers

1.3 Signalling molecules:

The availability of cells and substrate alone do not serve the purpose of tissue engineering. Here comes the Role of instructive messages in a prefabricated 3-dimensional construct (signalling molecule).

Growth factors and enamel matrix proteins have a proven role in controlling the behaviour of cells within the periodontal tissues. The most studied growth factors in periodontal regeneration include platelet derived growth factor (PDGF), epidermal growth factor (EGF), FGF, IGF and different BMPs.

PGDF seems to have a positive effect in periodontal healing and regeneration [26-29]. A wide range of evidence from periodontal regeneration studies indicate that BMPs are capable of inducing formation of new alveolar bone and cementum [30-32]. The rationale for the potential use of enamel matrix proteins in periodontal tissue regeneration therapies is justified by the initial cementum formation during the normal development of tooth attachment apparatus [33, 34]. Commercially available emdogain have been suggested to stimulate the formation of root cementum [35]. It also acts a signalling molecule which can regulate the activity of follicle cells, periodontal ligament cells, odontoblasts, gingival fibroblasts and cementoblasts [36-41].

IV. Current Advances:

1. Bio patch:

They are Nano-sized plasmids carrying the genetic instructions (DNA) for making bone.It is a non-viral gene delivery system for bone regeneration wherein collagen scaffold is utilised to deliver polyethylenimine (PEI) - plasmid DNA (pDNA) encoding platelet derived growth factor-B(PDGF-B) complexes [42].

2. PRF membrane: The second generation platelet rich fibrin has many uses in periodontal therapy as a graft,in management of intrabony defects, recession coverage, and in ridge augmentation. But recently, it could also be used as scaffold for stem cell therapy. For the first time, platelet rich fibrin membrane was used as a scaffold for periosteal tissue regeneration (invitro) [43]. PRF preparations are known to contain platelets, growth factors such as PDGF, TGF- β, IGF-I which promotes cell proliferation [44]. It is a biocompatible natural scaffold with signalling molecule at a lower cost.

3. **Hertwig's epithelial root sheath / Epithelial cell rests of malassez in periodontal regeneration**

Epithelial cell rests of malassez are the only odontogenic epithelial population in the periodontal ligament. Studies had proved that the combination of Hertwig's epithelial root sheath/epithelial cell rests of malassez and dental mesenchymal stromal/stem cell populations give rise to better outcomes in periodontal regeneration [45-47].

Dental pulp cells in combination with porcine epithelial cell rests of malassez can differentiate into ameloblast like cells and generate enamel like tissues, *invivo*, as shown by positive amelogenin staining [47].

Co-culture of dental follicle cells and Hertwig's epithelial root sheath cells significantly increase bone/cementum related gene expression [45].

V. Conclusion:

Tremendous research in stem cell therapy is in the path of making it a realistic alternative in periodontal regeneration. The availability of stem cells, scaffold and signalling molecules will give rise to a predictable outcome in the near future. Further research is still needed regarding appropriate signalling molecules coding for individual tissues in periodontal attachment apparatus.The delivery of right signals at the right time mimicking normal embryological development can only pave the way for a successful regeneration.

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