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PERIODONTAL LIGAMENT STEM CELLS: REDEFINING THE FUTURE OF TISSUE REGENERATION

***Dr. Deepthi Cherian and Dr. M.M Dayakar**

K V G Dental College, Sullia, Karnataka, India.

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***Correspondence for Author**
Dr. Deepthi Cherian
K V G Dental College, Sullia, Karnataka, India.

ABSTRACT

The goal of periodontal therapy is the arrest of periodontal disease progression and regeneration of structures that are lost to disease. Osseous grafting and Guided Tissue Regeneration (GTR) are widely used techniques. The success of these approaches has been limited as a result of insufficient biocompatibility, resorption of bone and donor-site morbidity. Tissue engineering provides an alternative approach to current treatments. It regenerates living and functional dental structures. A critical component of it is the choice of stem cell population. Stem cells are the cells that are capable of self replicating and are able to differentiate into atleast two different types of cells. In dental structures, mesenchymal stem cells are obtained from the dental pulp , gingiva, dental follicle and periodontal ligament. Stem cells of periodontal ligament are activated following damage to the periodontium. They undergo terminal differentiation into ligament forming cells which secure the connections between the cementum and the adjacent alveolar bone. Periodontal ligament cells were found to generate clonogenic adherent cell colonies. Differentiation assays suggests that these cells exhibit unique properties compared with other mesenchymal stem cells. In this article an overview of periodontal ligament stem cells and its potential for use in periodontal regeneration is discussed.

KEY WORDS: periodontal ligament stem cells, tissue engineering.

INTRODUCTION

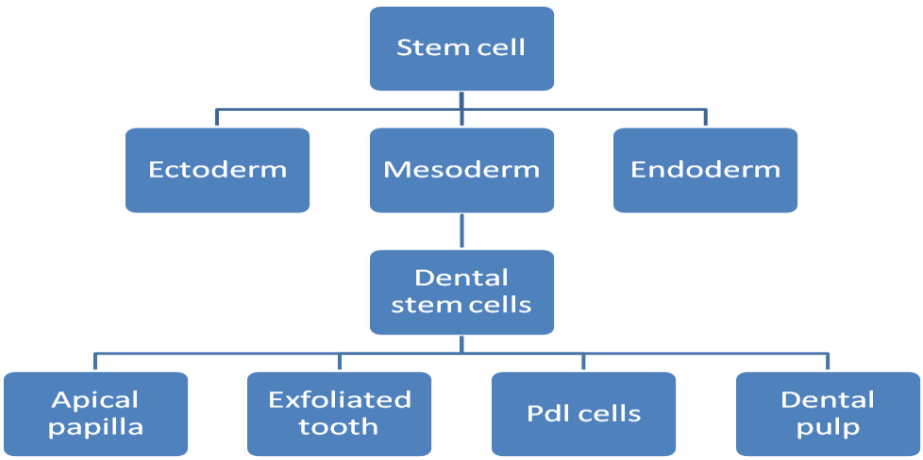
Periodontal regeneration represents the ultimate goal of periodontal therapy and entails the re-formation of all components of the periodontium: gingival connective tissue, periodontal ligament, cementum and alveolar bone. It aims to restore these lost tissues to their original

form and function by recapitulating the crucial wound healing events associated with periodontal development.[1] To compensate for the bone loss incurred as a result of periodontal disease, numerous approaches have been used to stimulate bone formation at the site of the defect. These include the introduction of alloplastic materials, autografts, allografts and xenografts, GTR which have resulted in some gain in clinical attachment levels. However, histological analyses of these treatments have shown minimal osteoinductive capacity as most grafts become encased in a dense fibrous connective tissue .The success of these approaches has been limited as a result of insufficient biocompatibility, resorption of bone, limited graft quantity and donor-site morbidity .As a consequence, current research trends have been directed towards developing cell-based techniques for periodontal regeneration.[2] Tissue engineering is an interdisciplinary field of study that applies the principles of engineering to biology and medicine toward the development of biological substitutes that restore, maintain, and improve normal function.[3] Tissue engineering is a novel and exciting field that aims to re-create functional, healthy tissues and organs in order to replace diseased, dying, or dead tissues. Tissue engineering will likely have its most significant impact in dentistry via bone tissue engineering and regeneration. The emerging discipline of tissue engineering and regenerative medicine endeavors to use a rational approach based on morphogenetic signals for tissue induction, responding stem/progenitor cells and the scaffold to maintain and preserve the microenvironment. The most critical component for tissue engineering is the choice of stem cell population.[3] The term ‘‘stem cell’’ first appeared in the literature during the 19th century. A ‘‘stem cell’’ refers to a clonogenic, undifferentiated cell that is capable of self-renewal and multi-lineage differentiation. In other words, a stem cell is capable of propagating and generating additional stem cells,while some of its progeny can differentiate and commit to maturation along multiple lineages giving rise to a range of specialized cell types. Depending on intrinsic signals modulated by extrinsic factors in the stem cell niche, these cells may either undergo prolonged self-renewal or differentiation.[1]

Stem cell characteristics that make them good candidates for cell-based therapy are: [4]

1. Potential to be harvested from patients
2. High capacity of cell proliferation in culture
3. Ease of manipulation to replace existing nonfunctional genes via gene splicing methods
4. Ability to migrate to host target tissues (homing)
5. Ability to integrate into host tissues and interact with the surrounding tissues.

Mesenchymal stem cells are one of the most highly studied types of adult stem cells. Mesenchymal stem cells demonstrate a lower developmental potential and a shorter lifespan than pluripotent embryonic stem cells, which have the ability to proliferate indefinitely in vitro and the potential to differentiate into all cell types present in the body. MSC show the property of adherence to plastic; a specific surface-antigen expression pattern; and multipotent differentiation potential. Studies have identified mesenchymal stem cell-like cells from trabecular bone, periosteum, articular cartilage, synovium, synovial fluid, skeletal muscle, adipose tissue, tendons, blood, blood vessels, umbilical cord vasculature , placental tissue ,fetal tissues and skin.[2] Stem cells have also been isolated from many dental tissue. Five types of dental stem cells have been established: dental pulp stem cells, stem cells from exfoliated deciduous teeth, stem cells from apical papilla, periodontal ligament stem cells, and dental follicle progenitor cells. The main characteristics of dental stem cells are their potential for multilineage differentiation and self-renewal capacity. Dental stem cells can differentiate into odontoblasts, adipocytes, neuronal-like cells, glial cells, osteoblasts, chondrocytes, melanocytes, myotubes, and endothelial cells.[5] Constructing complex structures like a periodontium, which provides the functional connection between a tooth or an implant and the surrounding jaw, could effectively improve modern dentistry. Dental precursor cells are attractive for novel approaches to treat diseases like periodontitis, dental caries or to improve dental pulp healing and the regeneration of craniofacial bone and teeth.



Periodontal ligament stem cells

Periodontal ligament tissue originates from cranial neural crest-derived ectomesenchymal cells .The dental follicle that are derived from Cranial Neural Crest differentiate into periodontal ligament cells and are also believed to contain the progenitor cells that differentiate into cementoblasts and osteoblasts. Thus, the DF plays a crucial role in forming

the PDL tissue, namely the fabrication of the periodontium.[6] The concept that stem cells may reside in the periodontal tissues was first proposed almost 20 years ago by Melcher, who queried whether the three cell populations of the periodontium were ultimately derived from single population of ancestral cells or stem cells.[7] Small population of progenitor cells has been identified by in vivo cell kinetic studies.9 These progenitor cell populations within the periodontal ligament appear to be enriched in locations adjacent to blood vessels and exhibit some of the classical cytological features of stem cells, which include small size, responsiveness to stimulating factors and slow cycle time. In the event of injury to the periodontium these mesenchymal stem cells could be activated towards terminal differentiation and tissue repair or regeneration.[8]

Population of Periodontal ligament stem cells that express the characteristics of MSCs are present in the extracted tooth.They are also isolated within the granulation tissue of periodontitis-affected intra-bony defects Periodontal ligament stem cells obtained from inflamed tissues within periodontal defects during periodontal flap surgery are an easily accessible source of multipotent adult stem cells for use in clinical and research work without the need to extract third molars or to access the dental pulp.[9]

To generate enriched, homogenous epithelial and mesenchymal DSC populations for tooth tissue engineering applications, the two most commonly used approaches are as follows. The first is based on the ability to sort stem cells using antibodies that recognize the antigen, STRO-1, a carbohydrate moiety present on many types of stem cells . Heterogeneous tooth bud cell populations can be incubated with magnetic beads to which anti– STRO-1 antibody is linked covalently. The cells that express STRO-1 become bound to the magnetic beads, whereas the STRO-1 negative non–stem cells are washed off. The STRO-1 expressing stem cell populations then are released from the magnetic beads, resulting in an enriched PNDSC population.A second approach to generating enriched DSC populations is to perform Hoechst 33342 dye profiling, taking advantage of the ability of certain stem cells to exhibit the capacity to efflux the dye, whereas non–stem cells retain the dye . After labeling, the cells are sorted by flow cytometry to generate enriched populations of Hoechst 33342 negative (stem) cells, and Hoechst 33342 retaining (non–stem cell) populations. Once sorted, clonal epithelial and mesenchymal SP and non-SP cells can be expanded in vitro.[10]

Using cloning techniques, a large number of cells of differing phenotype have been isolated from the periodontal ligament.Postnatal PDL stem cells express mesenchymal surface

markers, such as Stro-1, CD105 (Endoglin, SH2 antigen), CD146 (MUC 18), and CD166 (ALCAM, SB10 antigen), alkaline phosphatase,bone sialoprotein,osteocalcin and have a multipotent capacity to differentiate into adipocyte, osteoblast- like, and cementoblast-like cells in vitro and to form cementum/PDL–like tissue.[11] The basic roles of a scaffold in bone tissue engineering is to act as a carrier for cells and to maintain the space and create an environment in which the cells can proliferate and produce the desired bone matrix.[10] Several natural, synthetic and hybrid scaffolds are used that enhance regeneration by increasing the recruitment ,migration, proliferation and mineralization of PDLSC. The materials used are polyesters such as polyglycolic acid (PGA), polylactic acid (PLA) and polylacticcoglycolic acid (PLGA). Polymer scaffolds are coated with a uniform, dense, nano-crystalline apatite coating. These apatite-coated macroporous scaffolds combine the osteoconductve properties of apatites with the strength and versatility of degradable polymers.they include Hybrid calcium hydroxyapatite scaffolds, like nanohydroxyapatite / chitosan , nanohydroxyapatite/collagen and hydroxyapatite/gelatin components and GEM.In vitro studies have shown that biomimetic apatites coated onto synthetic polymers promote maturation of osteogenic precursors, with upregulation of osteocalcin and bone sialoprotein in MC3T3-E1 cells cultured on such surfaces.[10] Akizuki and coleagues used autologous periodontal ligament cells obtained from extracted tooth roots to fabricate cell sheets using a temperature-responsive cell-culture approach based on cell-sheet engineering. A special culture dish, in which the dish surface is hydrophobic under normal culture conditions at 37’C , allowing cells to attach themselves to it and grow but becomes hydrophilic at 20’C so that cells detach themselves spontaneously, was used .This process enabled the collection of the confluent cell cultures as a single sheet in which the deposited extracellular matrix and cell-cell junction proteins remained intact, in contrast to traditional enzymatic treatments for cell detachment, which damage the cultured cells. Cell Sheet were implanted into experimental dehiscence defects in dog molars. After 8 weeks, significantly improved periodontal tissue regeneration was observed.[10]

Advantages of pdlsc over other stem cell sources

1. PDLSCs could be successfully isolated from inflamed PDL tissue obtained during flap surgery, and they retained the regenerative potential to form cementum and related PDL tissues. [9]
2. Periodontal ligament derived cells were found to generate clonogenic adherent cell colonies that are capable of developing into adipocytes, osteoblast- and cementoblast-like

cells in vitro and demonstrate the capacity to produce cementum and periodontal ligament-like tissues in vivo.[10]

3. The incidence of fibroblastic colony-forming units was greater than that reported for bone marrow stem cells and dental pulp stem cells.[8]
4. The level of expression of scleraxis by PDLSC, which was higher than in bone marrow stem cells and dental pulp stem cells, suggests that periodontal ligament stem cells may exhibit unique properties compared with other mesenchymal stem cells.[2]
5. PDLSC have the ability to differentiate into neuronal precursors.[1]
6. Cryo-freezing does not seem to alter the properties of PDLSCs and this will have significant relevance should ‘‘banking’’ of these cells become a clinical necessity.[1]

Despite biological evidence showing that regeneration can occur in humans, complete and predictable regeneration still remains an elusive clinical goal (especially in advanced periodontal defects). Culture conditions are not sufficiently developed to mimic the cell microenvironment in vivo and to ensure that both cell proliferation and differentiation can be performed safely and consistently. Cell cultures may not be completely free of pathogens and infectious risks are a concern. Karyotypic instability and gene mutations of the cells after prolonged culture can also limit their usefulnessas there is a greater likelihood for genetic or epigenetic changes in stem cells. Clinical challenges in stem cell-based periodontal therapy relate to immune rejection after administration, oncogenic properties of stem cells and functional integration of transplanted tissues into the host. Immunosuppressive effects of MSCs both in vitro and in vivo.[11]

CONCLUSION

PDL contains stem cells that have the potential to generate cementum/PDLlike tissue in vivo. Transplantation of these cells, which can be obtained from an easily accessible tissue resource and expanded ex vivo,might hold promise as a therapeutic approach for reconstruction of tissues destroyed by periodontal diseases. [12] PDLSCs could be successfully isolated from extracted tooth or inflamed PDL tissue, and they retained the regenerative potential for cementum and related PDL tissues.It is expected that a multilevel approach involving cell biologists, matrix biologists, pharmacologists, biomaterials scientists / engineers and nanotechnologists will be required to prove that Periodontal Ligament Stem Cells can redefine the future of tissue regeneration.

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