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Review Article

STEM CELLS: NEWER APPROACH FOR PERIODONTAL REGENERATION

Jaiman Girija[1*], Devraj CG[2], Yadav Ashish[3], Sharma Swati[4]

[1]Post Graduate student, Department of Periodontics and Implantology, Mahatma Gandhi Dental College, Jaipur, India
[2]Professor & Head, Department of Periodontics and Implantology, Mahatma Gandhi Dental College, Jaipur, India
[3]Reader, Department of Periodontics & Implantology, Mahatma Gandhi Dental College, Jaipur, India
[4]Senior Lecturer, Department of Periodontics and Implantology, Mahatma Gandhi Dental College, Jaipur, India

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*Corresponding Author: **Dr. Girija Jaiman**
D/O Suraj Bhan Jaiman, C-293, Vaishali Nagar, Jaipur, Rajasthan, 302004, Email: girijajaiman@gmail.com

ABSTRACT

Stem cells are the foundation cells for every tissue and organ in the body, including the periodontium. Periodontitis is a periodontal tissue destructive disease and the most common cause for tooth loss in adults. There is no ideal therapeutic approach to cure periodontitis and achieve optimal periodontal tissue regeneration. Periodontal regeneration approaches used till now are not able to regenerate periodontium completely to its pre-existing levels. Periodontal regeneration using stem cells is a promising field of tissue engineering for periodontal regeneration, but the feasibility of concept is still in clinical pipeline and research has long way to go.

Keywords: Stem Cells; Periodontium; Regeneration; Tissue Engineering

INTRODUCTION

Stem cells are the foundation cells for every organ and tissues in the body including periodontium. Stem cells are uncommitted entities capable of both self – renewal and differentiation into multiple cell lineages[1]. A stem cell refers to a clonogenic, undifferentiated cell that is capable of self renewal and multi-lineage differentiation[2] with varying degrees of potency and plasticity[3]. Stem cells are unspecialized cells that develop into the specialized cells that make up different types of tissues in the human body[4]. The isolation, culture, and partial characterization of stem cells isolated from human embryos were reported in the November; 1998[4]. Literally, stem cell has been defined in the Merriam Webster's Collegiate Dictionary as "an undifferentiated cell that gives rise to differentiated cells."

A stem cell has two defining characteristics[5,6]:

(i) The ability for indefinite self-renewal to give rise to more stem cells; and[7]

(ii) The ability to differentiate into a number of specialized daughter cells to perform specific function(s)[2,8]

A stem cell can divide asymmetrically, in which case one of the two daughter cells retains the stem cell characteristics while the other is destined for specialization under specific conditions[6].

The periodontium is an unusually complex tissue comprised of two hard (cementum and bone) and two soft (gingiva and periodontal ligament) tissues. Once damaged, the periodontium has a limited capacity for regeneration. Tissue regeneration can be defined as reproduction or reconstitution of a lost or injured part and periodontal regeneration is restoration of lost periodontium. New cementum formation, remodelling of the periodontal ligament and new bone formation has been observed during orthodontic tooth movement, but it is classified more as a physiological response rather than true repair or regeneration of pathologically damaged tissue. Periodontitis is slow going destructive process and therefore phases of minor regeneration can also be observed during the early stages of periodontal disease. But once periodontitis is established, therapeutic intervention can only induce regeneration[9]. Periodontal regeneration is a complex process and it requires recruitment of locally derived progenitor cells to the site. These cells can subsequently differentiate into periodontal ligament-forming cells, mineral-forming cementoblasts, or bone-forming osteoblasts[10].

TYPES OF STEM CELLS

In general, there are certain types of stem cell populations those are identified from embryonic and postnatal tissues[1]. Embryonic stem cells (early, germ line stem cells) are derived from mammalian blastocytes and theoretically have the ability to generate differentiated cell types arising from the three germ layers: mesoderm, ectoderm and endoderm[1,4]. Postnatal stem cells (adult, somatic stem cells) are tissue specific,

committed precursors capable of developing into a restricted number of cell lineages[1].

The use of embryonic stem cells generates many ethical concerns regarding the consumption of blastocystes[8]. This makes post-natal stem cells a more feasible approach for translation into clinical dental practice[11].

Bone marrow stromal stem cells (BMSSCs) are also known as mesenchymal stem cells. These cells have been identified as a population of organized hierarchical postnatal stem cells with the potential to differentiate into osteoblasts, chondrocytes, adipocytes, cardiomyocytes, myoblasts and neural cells[1].

Friedenstein and colleagues in 1976 first time identified mesenchymal stem cells in aspirates of adult bone marrow[12]. These cells were identified by their capacity to form clonogenic clusters of adherent fibroblastic-like cells or fibroblastic colony-forming units with the potential to undergo extensive proliferation in vitro and to differentiate into different stromal cell lineages[13,14,15].

Based on their ability to differentiate, stem cells can be classified into three broad categories[16].

1. Totipotent stem cells are found only in early embryos. Each cell can form a complete organism (e.g., identical twins).
2. Pluripotent stem cells exist in the undifferentiated inner cell mass of the blastocyst and can form any of the over 200 different cell types found in the body.
3. Multipotent stem cells are derived from foetal tissue, cord blood, and adult stem cells. Although their ability to differentiate is more limited than pluripotent stem cells, they already have a track record of success in cell-based therapies.

Classification of stem cells according to their differentiation potential[6]

•Embryonic stem cells – Pluripotent; derived from the inner cell mass (blastocyst) of the pre – implantation embryo.

•Embryonic germ cells – Pluripotent; derived from primordial germ cells isolated from the embryonal gonad (foetus).

•Embryonal carcinoma cells – Pluripotent; derived from primordial germ cells in embryonic gonads and usually found as components of testicular carcinoma in adults.

•Adult stem cells – Multipotent; derived from the ectodermal and endodermal organs of the adults.

•Adult cells that has undergone nuclear transformation -- Tutipotent.

•Adult stem cells that can be induced to an embryonic stem cell phenotype —Inducible pluripotent

STEM CELLS OF DENTAL ORIGIN

The majority of craniofacial structures are derived from mesenchymal cells which in turn are originated from the neural crest. During development these cells migrate, differentiate, and participate in the morphogenesis of all craniofacial structures (bone, cartilage, musculature, ligaments, teeth, and periodontium) working synergistically with mesodermal cells. Mesenchymal cells undergo asymmetric division with one offspring cell differentiating toward an end-stage cell while the other one replicates into an offspring mesenchymal cell, keeping its stem cell status. Residual mesenchymal cells upon completion of morphogenesis continue to reside inside various tissues and are called mesenchymal stem cells. In the adult those cells maintain physiologically necessary tissue turnover and, after injury or disease, differentiate & launch tissue regeneration[7].

Stem cells are found to be present in following periodontal tissues.

- Dental pulp stem cells (DPSCs)[17]
- Stem cells from exfoliated deciduous teeth (SHED)[18]
- Periodontal ligament stem cells (PDLSCs)[19]
- Stem cells from apical papilla (SCAP)[20]
- Dental follicle progenitor cells (DFPCs)[21]

These dental ectomesenchymal stem cells can be classified in two different groups with respect to their major differentiation potential.

- The first group is associated with the dental pulp, consisting of DPSCs, SHEDs and SCAPs.
- The second group contains PDL stem cells and dental follicle progenitor cells and is related to the periodontium periodontal ligament stem cells (PDLSCs) and dental follicle progenitor cells (DFPCs).

Dental Mesenchymal Stem Cells[22]:

Dental tissues are specialized tissues that do not undergo continuous remodeling as shown in bony tissue therefore, dental-tissue derived stem/progenitor cells may be more committed or restricted in their differentiation potency in comparison with BMMSCs. Additionally, dental mesenchyme is termed 'ectomesenchyme' due to its earlier interaction with the neural crest. From this perspective, ectomesenchyme-derived dental stem cells may possess different characteristics similar to those of neural crest cells.

Dental Pulp Stem Cells (DPSCs)[16]:

One important feature of pulp cells is their odontoblastic differentiation potential. Human pulp cells can be induced in vitro to differentiate into cells of odontoblastic phenotype, characterized by polarized cell bodies and accumulation of mineralized nodules. In addition to their dentinogenic potential, subpopulations of hDPSCs also possess adipogenic and neurogenic differentiation capacities by exhibiting adipocyte- and neuronal-like cell morphologies and expressing respective gene markers[23]. More recently, DPSCs were also found to undergo osteogenic, chondrogenic and myogenic differentiation in vitro.

Dental follicle precursor cells[24]:

The human dental follicle is a tissue of the tooth germ, which can easily be isolated after wisdom tooth extraction. Like, bovine dental follicles, cells of the human dental sac develop into the mature periodontium consisting of alveolar bone, the PDL and cementum. The dental follicle contains ectomesenchymal cells which are derived from the neural crest. DFPCs, like BMSCs, are plastic adherent and colony forming cells, and they can differentiate into osteoblast like cells under in vitro conditions. According to *Morsczeck* et al 2005[25] similar to PDL stem cells, DFPCs can also differentiate, form robust connective tissues and produce clusters of mineralized tissue.

Stem cells from apical papilla[20]:

A new class of dental stem cells was isolated from the dental papilla of wisdom teeth or incisors of 4 month old mini-pigs (SCAP, stem cells from apical papilla). *Jo YY* et al in 2007 has

stated that the dental papilla is an embryonic-like tissue that becomes dental pulp during maturation and formation of the crown. Therefore, SCAPs can only be isolated at a certain stage of tooth development. However, SCAPs have a greater capacity for dentin regeneration than DPSCs because the dental papilla contains a higher number of adult stem cells compared to the mature dental pulp.

Stem Cells of Human Exfoliated Deciduous Teeth (SHED)[21]:

Furthermore, ectomesenchymal stem cells of human exfoliated deciduous teeth (SHEDs) were isolated from the dental pulp of exfoliated incisor[18]. These cells could be cultivated either as fibroblast-like, adherent cells, or like neural stem cells as neurospheres. SHEDs are capable of differentiation into odontoblast, adipocytes and neural cells. They induced bone formation and produced dentin under in vivo conditions; and they were able to survive and migrate in murine brain after transplantation into immunocompromised animal.

PERIODONTAL LIGAMENT STEM CELLS

The periodontal ligament, which is a highly fibrous and vascular tissue, has one of the highest turnover rates in the body[24,25]. *Mc Culloh* et al in 1987 has reported that many cells are present in the periodontal ligament including cementoblasts, osteoblasts, fibroblasts, myofibroblasts, endothelial cells, nerve cells and epithelial cells[25]. In addition to these, a smaller population of progenitor cells has been identified by in vivo cell kinetic studies. 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, including small size, responsiveness to stimulating factors and slow cycle time[10,26].

The concept that stem cells may reside in the periodontal tissues was first proposed by *Melcher AH* in 1985[27] who queried whether the three cell populations of the periodontium (cementoblasts, alveolar bone cells and periodontal ligament fibroblasts) were ultimately derived from a single population of ancestral cells or stem cells.

*Berkovitz et a*l 1995[28] have stated that gingival fibroblasts maintain the synthesis and integrity of the gingival connective tissue, periodontal ligament fibroblasts have specialized functions that are concerned with formation and maintenance of periodontal ligament, including repair or regeneration following damage. Although both gingival and periodontal ligament fibroblasts are similar in appearance when grown in culture, they have very important functional difference, thus in animal studies, it has been found that when tooth roots were covered with periodontal ligament cells grown in culture and then reimplanted in vivo they acted as progenitor cells and gave rise to the formation of new periodontal ligament tissue (*Bokyo et al* 1981[29]; *Van Dijk et al* 1991[30]; *Lang et a*l 1995[31]). In marked contrast, gingival fibroblasts failed to produce new tissue. Also, the total protein and extracellular matrix protein production have been shown to be higher in periodontal ligament compared to gingival fibroblasts as observed by *Somerman et al* 1989[32]], *Kuru et al 1998*[33]. Moreover the response of these two cell types to attachment factors, extracellular matrix proteins and growth factors have found to be different[34,35].

In addition, some of the periodontal ligament cells have been shown to possess osteoblast like chacterstics, including the production of osteonectin[36], osteoclacin, and higher levels of alkaline phosphatise[37]. These studies indicate that phenotypically distinct and functional sub-populations of cells of both fibroblasts and osteoblast cementoblast lineage exist in the periodontal ligament, and these cells probably include some stem and precursor cells important in repair and regeneration.

The periodontal ligament and marrow spaces of the alveolar bone contain stem cells, which function as the precursor cells, for the more specialized cells in the mesenchymal cell population that is continually renewing under physiological conditions due to cell death and terminal differentiation[28].

A number of recent studies have investigated the origin and location of the progenitor cell population in the periodontal ligament. It has been suggested that, after the embryonic development of the periodontal ligament from undifferentiated mesenchymal cells, some progenitor cells remains in the mature tissue[38].

Lekie and McCulloh (1996) suggested that the progenitor cell population is located perivascularly, adjacent to blood vessels[39].

In this regard, in a wound healing model, *Gould et al* found that, following the partial removal of periodontal ligament, the proportion of "H-dymidine"-labelled perivascular cells in the adjacent periodontal ligament increased fivefold. The majority of such cells have been found to reside in the central part of the ligament, and further it was suggested that they may give rise to periodontal ligament fibroblasts and also migrate towards the bone and cementum surfaces, where they may differentiate into osteoblasts or cementoblasts respectively[39].

The cells present in the vascular channels of the alveolar bone, which migrates toward the periodontal ligament, may be another source of progenitor cells. This suggestion was supported by a study in which root slices were cultured in vitro with cells derived from the rat clavaria. It has been suggested that, it is also possible that separate precursor cells may be present for each distinct mature cell type. This precursor population plays a major role in periodontal homeostasis and regenerative healing process.

The most compelling evidence that these cells are present within the periodontal tissues has been provided by the in vivo and histological studies of *McCulloch and co-workers*[25,10].

IDENTIFICATION OF PERIODONTAL LIGAMENT STEM CELLS

Bartold et al (2006)[10] used the same criteria; used by *Friendestien et al*[12] to identify Bone marrow mesenchymal stem cells; to identify cells classified as mesenchymal stem cells, also obtained from the adult periodontal ligament (periodontal ligament stem cells). When plated under the same growth conditions as described for bone marrow stromal stem cells, these periodontal ligament stem cells demonstrated the ability to produce clonogenic adherent cell colonies[40.]

Fibroblastic colony-forming units were defined as aggregates of 50 cells or more[1] *Bartold et al* reported the incidence of fibroblastic colony-forming units obtained from periodontal ligament (170) was greater than that that reported for bone marrow stromal stem cells[41] per 105 cells plated. It is not

known that this is indicative of a propensity for stem cells to be present within periodontal ligament tissue or whether it is a reflection of a difference in stromal tissue turnover in periodontal ligament vs. bone marrow.

CHACTERSTICS OF PERIODONTAL LIGAMENT STEM CELLS

Earlier cloning of periodontal ligament fibroblasts has been done through viral transfection to immortalize clonogenic cell lines[40].

- *Bartold et al 2006*[10], using specific cell culture conditions have been able to establish some clones with high proliferative capacity as well as determine that the majority of individually isolated colonies (>80%) failed to proliferate beyond 20 population doublings. It implies that high proliferating periodontal ligament stem cells are representative of only a minor proportion of the cells which can be expanded in vitro over successive cell passages.
- They reported that periodontal ligament stem cell cultures demonstrated about 30% higher rates of proliferation in comparison to the growth of cultured bone marrow stromal stem cells. Apparently these cells retain their capacity for higher growth potential beyond the 100 population doublings before in vitro senescence is detected. Whereas, in vitro senescence occurs after approximately 50 population doublings for bone marrow stromal stem cells[10].
- These periodontal ligament stem cells go through senescence and thus have a finite lifespan, even though they demonstrate a high proliferative potential. Undergoing senescence seems to be a characteristic of most postnatal stem cells that particularly distinguishes them from embryonic stem cells, which are essentially immortal[10].
- Enzyme telomerase play a significant role in maintaining telomere lengths and chromosomal stability during cellular division. Embryonic stem cells are known for their high expression of the enzyme telomerase, and it is associated with their immortal nature. In many mesenchymal stem cells, telomerase activity is absent. This absence may contribute to prolonging cellular senescence by controlling a number of key cell cycle regulators, which subsequently allow progression within the cell cycle from G1 to S phase, resulting in increased proliferation potential and survival rate. The lifespan of bone marrow stromal stem cells increases almost threefold when they are induced to express active telomerase[10].
- Stem cell marker, STRO-1, to isolate and purify bone marrow stromal stem cells. This same marker is also expressed by human periodontal ligament stem cells and dental pulp stem cells[10].
- Periodontal ligament stem cells share expression of the perivascular cell marker CD146 in common with bone marrow stromal stem cells. The coexpression by these cells of alpha-smooth muscle actin and/or the pericyte-associated antigen, 3G5. These bone marrow stromal stem cells and periodontal ligament stem cells arise from different embryonic origins as independently unique stem cell populations, they inhabit a common environment in the perivascular niches in their respective tissues[10].
- Hematopoietic markers CD14 (monocyte/macrophage), CD45 (common leukocyte antigen) and CD34 (hematopoietic stem/progenitor cells/endothelium) are not expressed by periodontal ligament stem cells or bone marrow stromal stem cells[10].
- Tendon and periodontal ligament tissues share some morphological and functional features such as dense collagen bundles and the capacity to absorb mechanical forces of stress and strain. *Bartold et al*. used semiquantitative reverse transcription-polymerase chain reaction to evaluate the expression levels of scleraxis, a tendon-specific transcription factor, in cultured human periodontal ligament stem cells. The results indicated that periodontal ligament stem cells expressed quantitatively higher levels of scleraxis transcripts compared to bone marrow stromal stem cells. From this they concluded that periodontal ligament stem cells probably symbolize a unique population of postnatal stem cells that are different from bone marrow-derived mesenchymal stem cells[10].

STEM CELL THERAPY

Stem cell therapy is a treatment that uses stem cells, or cells that come from stem cells, to replace or to repair a patient's cells or tissues that are damaged including the periodontium that is damaged by inflammation[41]. All stem cells no matter what their source are unspecialized cells that give rise to more specialized cells. Stem cells can become one or more than 200 specialized cells in the body. They serve as the body's repair system by renewing themselves and replenishing more specialized cells in the body. Stem cells now can be grown and transformed into specialized cells with chacterstics consistent with cells of various tissues such as muscles or nerves though cell culture. Highly plastic adult stem cells from a variety of sources, including umbilical cord blood and bone marrow, are routinely used in medical therapies. Embryonic cell lines and autologous embryonic stem cells generated through therapeutic cloning have also been proposed as promising candidates for future therapies. Potency specifies the differentiation potential (the potential to differentiate into different cell types) of the stem cells, such as totipotent, pluripotent, multipotent, oligopotent and unipotent[5].

PERIODONTAL REGENERATION

Till now, restoration of damaged or diseased periodontal tissues has relied almost entirely on the use of implantation of structural substitutes, often with little or no reparative potential. These efforts focus almost exclusively on regenerating lost alveolar bone and have included the use of autografts (cortical/cancellous bone, bone marrow), allografts (demineralized freeze-dried/freeze-dried bone) and alloplastic materials (ceramics, hydroxyapatite, polymers and bioglass). Due to issues such as the variability in safety, clinical effectiveness and stability over time of these agents, their use for periodontal regeneration has been questioned. More recently, biological approaches based on the principles of

tissue-engineering have emerged as prospective alternatives to conventional treatments. Such approaches have included gene therapy and the local administration of biocompatible scaffolds with or without the presence of selected growth factors[42]. These new approaches based on an understanding of the cell and molecular biology of the developing and regenerating periodontium, offer interesting alternatives to existing therapies for the repair and regeneration of the periodontium[10].

Periodontal regeneration can be considered a recreation of the developmental process which includes morphogenesis, cytodifferentiation, extracellular matrix production and mineralization. These processes affirm the theory that some mesenchymal stem cells remain within the periodontal ligament and thus promote tissue homeostasis; they provide a source of renewable progenitor cells which generate cementoblasts, osteoblasts and fibroblasts during adult life[10].

If injury occurs in the periodontium, the mesenchymal stem cells may be stimulated to initiate terminal differentiation and regeneration or repair of tissues. A great number of cells of differing phenotype have been isolated from the periodontal ligament and regenerating periodontal tissue with the use of cloning techniques. Various clonal cell lines were reported to have characteristics of stem cells based on the results of preliminary investigations, thus justifying further studies of these properties and their application for cell-based periodontal regenerative therapies[10]. *Bartold et al.* reported, the identification and characterization of cell populations derived from adult human and sheep periodontal ligament that have the morphological, phenotypic and proliferative characteristics consistent with adult mesenchymal stem cells. The identification of mesenchymal stem cell populations located in the periodontium has inspired interest in the clinical utility of stem cell-based therapies to treat tissue injury resulting from trauma or periodontal disease[41].

PERIODONTAL TISSUE ENGINEERING

Tissue engineering is a contemporary area of science based on the principles of cell biology, developmental biology and biomaterials science to develop new procedures and biomaterials to replace lost or damaged tissues. The main requirements for producing an engineered tissue are appropriate progenitor cells, signalling molecules, an extracellular matrix or carrier construct and an adequate blood supply[1]. For successful periodontal regeneration, it is necessary to use and recruit progenitor cells that can differentiate into specialized cells with a regenerative capacity, followed by proliferation of these cells and synthesis of the specialized connective tissue that they are attempting to repair.

Tissue engineering approach for periodontal regeneration will need to utilize their regenerative capacity of cells residing within the periodontium, their isolation and proliferation within a 3-dimensional (3D) frame work with implantation into defect[10].

In wound healing, tissue scaring or repair is the result of natural healing process. Using tissue engineering this scarring would be replaced by tissue regeneration[5]. This will require the presence of three key elements – the signalling molecule, scaffold, or supporting matrices[43].

Signalling molecules -- Various signalling molecules that can be used are platelet derived growth factors, fibroblast growth factor – 2, bone morphogenetic proteins, enamel matrix derivatives, transforming growth factor -- beta, insulin like growth factor[24].

Scaffold material -- Hydroxyapatite, Beta tricalium phosphate. Titanium mesh, Alpha hydroxyl acids (polyglycolic acid, poly lactic acid, copolymers), Alginate, Hyaluronate, Chitosan, Collagen, Synthetic hydrogels, Extracellularmatrix.

Both in vitro and in vivo studies have used dental stem cells to achieve periodontal regeneration both. In these studies, progenitor cells were seeded directly onto biomaterial scaffolds (e.g. polyglycolic acid, calcium phosphate material, collagen sponges) followed by transplantation into periodontal defects in animal models (such as mice, rats, dogs, pigs and sheep). Seeding of tooth bud cells (which presumably include some progenitor cells) on biodegradable scaffolds resulted in the formation of new periodontal ligament and bone tissues after implantation into the omentum of adult rat hosts and at the site of previously lost teeth. A novel study by *Synder EY et al 1992*[44], have reported the combination of swine stem cells from the apical papilla with periodontal ligament stem cells to regenerate root and periodontal structure in minipigs. The swine stem cells from the apical papilla were seeded into a root-shaped scaffold that was then wrapped with gel foam containing porcine periodontal ligament stem cells. After a three-month healing period, periodontal ligament tissue was noted to form around this bio-root structure and appeared to have a natural relationship with the surrounding bone. Regenerated root structure containing new cementum and periodontal ligament has been reported by *Kuo et a*l in 2008[45] to occur by culturing swine dental bud cells on a cylinder scaffold and then grafting it back into the alveolar socket. These promising results reported in animal models using dental stem cells are paving the way for human regenerative periodontal therapy[6].

CONCLUSION

First isolated in 2004; periodontal ligament stem cells have been shown to give rise to adherent clonogenic clusters resembling fibroblasts. They are capable of developing into adipocytes, osteoblast-like cells and cementoblast-like cells in vitro as well as producing cementum-like and periodontal ligament-like tissues in vivo. Recent studies have also shown the ability of stem cells to differentiate into neuronal precursors. They also express an array of cementoblast and osteoblast markers as well as the STRO-1 and CD146 antigens, which are found on dental pulp stem cells and bone marrow mesenchymal stem cells. These findings indicate that periodontal ligament stem cells have properties similar to those of dental pulp stem cells and bone marrow mesenchymal stem cells, and represent another mesenchymal stem cell-like population. These periodontal ligament stem cells along with a matrix scaffold, together with the introduction of various signalling molecules in an orderly sequence provide promising approaches for periodontal regeneration. Because approximately 70% of the human population has impacted third molars, periodontal ligament cells can be an accessible alternative source for adult stem cells in the regeneration of

periodontal tissue. Further in depth research is required to achieve complete regeneration of periodontium using periodontal ligament stem cells.

REFERENCES

1. Gronthos S, Akintoye SO, Wang C & Shi S. Bone marrow stromal stem cells for tissue engineering. Periodontology 2000. 41; 2006: 188–195
2. Smith A. A glossary of stem cell biology. Nature 2006; 441: 1060.
3. Robey PG. Stem cells near the century mark. J Clin Invest. 2000; 105(11):1489-1491
4. Thomson JA; Itskovitz – Eldor J, Shapiro SS, Waknitz MA, Sweirgiel JJ, Marshal VS et al. Embryonic stem lines derived from human blastocytes. Science 1998; 281: 1061-2.
5. Saina R., Saina S., Sharma S. Therapeutics of stem cells in periodontal regeneration. J of Natu Sci, Bio and Med. 2011; 2:38-42.
6. Lin NH, Gronthos S. & Bartold PM. Stem Cells and Future Periodontal Regeneration, Periodontol 2000. 2009: 51 239–251.
7. Nedel F, André DA, Oliveira IO, Cordeiro MM, Casagrande L, Tarquinio SBC, Nor JE, Demarco FF. Stem Cells: Therapeutic Potential in Dentistry. J Contemp Dent Pract. 2009; (10) 4:090-096.
8. National Institutes of Health (NIH). Stem cells: scientific progress and future research directions. Bethesda: NIH, 2001. 23-42.
9. Glossary of periodontal terms, 2001, 4th edition. p.44.
10. Bartold PM., Shi S. & Gronthos S. Stem cells and periodontal Regeneration. Periodontol 2000. 40; 2006: 164–172.
11. Krebsbach PH, Robey PG. Dental and Skeletal Stem Cells: Potential Cellular Therapeutics for Craniofacial Regeneration. J Dent Educ. 2002; 66(6):766-773.
12. Friedenstein AJ. Precursor cells of mechanocytes. Int Rev Cytol 1976: 47: 327–359.
13. Bartold PM, McCulloch CA, Narayanan AS, Pitaru S. Tissue engineering: a new paradigm for periodontal regeneration based on molecular and cell biology. Periodontol 2000. 2000: 24: 253–269.
14. Bartold PM, Narayanan AS. Periodontal regeneration. In: Biology of the periodontal connective tissues, Chapter 11. Chicago: Quintessence Publishing, 1998: 5-10.
15. Conrad C, Huss R. Adult Stem Cell Lines in Renegerative Medicine and Reconstructive Surgery. J Surg Res. 2005; 124(2):201-208.
16. Madan N., Madan N., Bajaj P., Gupta N., Yadav S. : Stem Cells – A Scope For Regenerative Medicine. Inter J Bioeng. 2011; 4: 2-6.
17. Gronthos S, Mankani M, Brahim J, Gehon Robey P, Shi S. Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo. PNAS. 2000; 97(25):13625-13630.
18. Miura M, Gronthos S, Zhao M, Lu B, Fisher LW, Robey PG, Shi S. SHED: Stem cells from human exfoliated deciduous teeth. Proc Natl Acad Sci U S A. 2003; 100(10):5807–5812.
19. Seo BM, Miura M, Gronthos S, Bartold PM, Batouli S, Brahim J, Young M, Robey PG, Wang CY, Shi S. Investigation of multipotent postnatal stem cells from human periodontal ligament. Lancet. 2004; 364(9429):149-55.
20. Jo YY, Lee HJ, Kook SY, Choung HW, Park JY, Chung JH, Choung YH, Kim ES, Yang HC, Choung PH: Isolation and characterization of postnatal stem cells from human dental tissues. Tissue Eng. 2007; 13: 767–773.
21. Morsczeck C, Got W, Schicrholz J, Zeilhaer F, Kuhn U, Muhl C et al. Isolation of precursor cells (PCs) from human dental follicle of wisdom teeth. Matrix biol 2005; 24:155-165.
22. Sonayama W, Liu Y, Fang D, Yamaza T, EO hang C, et al. Mesenchymal Stem cell – Mediated functional tooth regeneration in Swine. PLosONE 1 2006; 1: e79.
23. Trubani O, Orsini G, CaputiS, Piatelli A. Adult mesenchymal stem cells in dental research: a new approach for tissue engineering. Int J Immunopathol pharmacol. 2006 ;19(3):451-60.
24. Grover V, Malhotra R, Kapoor A, Verma N, Sahota JK. Future of periodontal regeneration. J Oral healt Comm Dent. 2010; 4 (spl): 38-47
25. Sodek J. A new approach to assessing collagen turnover by using a microassay. A highly efficient and rapid turnover of collagen in rat periodontal tissues. Biochem J 1976: 160: 243–246.
26. McCulloch CA, Nemeth E, Lowenberg B, Melcher AH. Paravascular cells in endosteal spaces of alveolar bone contribute to periodontal ligament cell populations. Anat Rec 1987: 219: 233–242.
27. Melcher AH. Cells of periodontium: their role in the healing of wounds. Ann R Coll Surg Engl 1985: 67: 130–131.
28. Berkovitz BMB, Moxham BJ. and Newman HN. Periodontal ligament in health and disease. 1995; 2 nd edition, Barcelona: Mosby – Wolfe; pg 83-106.
29. Boyko GA., Melcher AH. and Brunette DM. Formation of new periodontal ligament by periodontal ligament cells implanted in vivo after culture in vitro. A preliminary study of transplanted roots in dogs. J clin periodontol 1981; 19: 615 – 624.
30. Van Dijk L.J., Schakenraad J.M., Van der Voort, H.M. et al. Cell – seeding of periodontal ligament fibroblasts. A novel technique to create new attachment. A pilot study. J Clin Periodontol. 1991; 18: 196–199.
31. Lang H., Schuler, N., Arnhold, S et al. Formation of differentiated tissues in vivo by periodontal cell populations cultured in vitro. J Dent Res. 1995; 77: 1219 – 1255.
32. Somerman MJ, Foster RA, Imm GR. et al. Periodontal ligament cells and gingival fibroblasts

responds differently to attachment factors in vitro. J Periodontol. 1989; 60: 73 – 77.
33. Kuru, L., Griffiths, GS., Parkar, M.H. et al. Flow cytometery analysis of gingival and periodontal ligament cells. J Dent Res.1998; 77: 555 – 564.
34. Giannopoulou, C. and Cimasoni, G. Functional chacterstics of periodontal and gingival fibroblasts. J Dent Res. 1996; 75: 895 – 902.
35. Denninson DK., Vallone DR., Pinero GJ. et al. Differential effects of TGF-β1 and PDGF on proliferation of periodontal ligament cells and gingival fibroblasts. J Periodontol. 1994; 65: 641 – 648.
36. Notchu RM., Mc Cauley, LK. Shigeyama, Y. and Somerman, M.J. Expression of mineral – associated proteins by periodontal ligament cells; in vitro vs in vivo. J Periodontal Res. 1996; 31: 369 – 2.
37. Kawase T, Sato S. Miake, K. and Saito S. Alkaline Phosphatase of human Periodontal ligament fibroblasts – like cells. Adv Dent Res.1998; 2: 234 – 239.
38. Hassell, TM. Tissues and cells of Periodontium. Periodontol 2000; 3: 9 – 38
39. Lekic P., Sodek, J. and McCulloh. CAG. Relationship of cellular proliferation to expression of osteopontin and bone sialoprotein in regenerating rat Periodontium. Cell tissue res. 1996; 285: 491 – 500.
40. Ivanovski S, Haase HR, Bartold PM. Expression of bone matrix protein mRNAs by primary and cloned cultures of the regenerative phenotype of human periodontal fibroblasts. J Dent Res. 2001; 80: 1665–1671.
41. Bartold PM, McCulloch CA, Narayanan AS, Pitaru S. Tissue engineering: a new paradigm for periodontal regeneration based on molecular and cell biology. Periodontol 2000. 2000: 24: 253–269.
42. Giannobile WV, Lee CS, Tomala MP, Tejeda KM, Zhu Z. Platelet-derived growth factor (PDGF) gene delivery for application in periodontal tissue engineering. J Periodontol. 2001: 72: 815–823.
43. Kao RT, Murkami S, Beirne OR. The use of biologic mediators and tissue engineering in dentistry. Periodontol 2000. 2009: 50:127-53.
44. Snyder EY, Deitcher DL, Walsh C, Arnold-Aldea S, Hartwieg EA, Cepko CL. Multipotent neural cell lines can engraft and participate in development of mouse cerebellum. Cell 1992: 68: 33–51.
45. Kuo TF, Huang AT, Chang HH, Lin FH, Chen ST, Chen RS, Chou CH, Lin HC, Chiang H, Chen MH. Regeneration of dentin–pulp complex with cementum and periodontal ligament formation using dental bud cells in gelatine chondroitin- hyaluronan tri-copolymer scaffold in swine. J Biomed Mater Res A 2008: 86: 1062–1068.

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