ORIGINAL RESEARCH PAPER
Volume-9 | Issue-1 | January-2020 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

STEM CELL THERAPY IN DENTISTRY-AN OVERVIEW

Pathology

Dr. Bijo Alexander	MDS, Professor, Oral & Maxillofacial Pathology, Noorul Islam Dental College, Thiruvananthapuram
Dr. Rajeev. R*	MDS, Additional Professor, Dept. of Oral & Maxillofacial Pathology, Govt. Dental College, Thiruvananthapuram *Corresponding Author
Dr. Vivek V. Nair	MDS, Professor, Dept. Of Prosthodontics, Govt. Dental College, Thiruvananthapuram
Dr. Anand. R. Krishnan	MDS, Assistant Professor, Dept. Of Orthodontics, Govt. Dental College, Thiruvananthapuram
Dr. Rohini P. V	MDS,Senior Resident., Oral & Maxillofacial Pathology, Govt. Dental College, Thiruvananthapuram

ABSTRACT

The emergence of stem cell therapy has given a great fill up for the future of tissue regenerative medicine. Dental stem cells have great potential because of its accessibility, plasticity and proliferative ability. Various studies have shown that stem cells are primarily found in 'niches' and dental tissues are a rich source of mesenchymal stem cells that are useful for tissue engineering application. Several types of dental stem cells have been identified including those from human dental pulp, primary exfoliated deciduous teeth, periodontal ligament, third molar follicles etc. Many studies are still in nascent stages but it is imperative that stem cells and tissue engineering will give rise to a separate branch of regenerative dentistry which will leave an indelible print in future of dental practice.

KEYWORDS

dental stem cells, tooth regeneration, regenerative dentistry.

INTRODUCTION:

The human body is made up of three basic categories of cells: germ cells, somatic cells and stem cells. Stem cells are undifferentiated cells with the ability to divide and give rise to identical undifferentiated cells. The stem cells are divided into two groups; the embryonic stem cells and adult stem cells. The adult stem cells are located in human tissues like bone marrow, dental pulp, skin and adipose tissue [1]. The stem cells residing in the oro-facial region have been classified as mesenchymal stem cells, adult stem cells and tissue stem cells [2].

The loss of teeth can occur due to various conditions like dental caries, periodontitis, trauma and developmental anomalies. Replacement of lost teeth is mandatory for both functional and aesthetic reasons. Stem cell research aims to replace the conventional prosthetic procedures by aiming to provide stimulus to the organism to regenerate the tissue from inside or to develop the tissue externally which could be transplanted as natural tissue [3]. It is based on the ability of cells to proliferate and differentiates as well as through cells and scaffold interaction [4].

Stem cell characteristics:

1. Totipotent stem cells can differentiate into embryonic and extra embryonic cell types and therefore produce all types of cells as well as germ layers.
2. Pluripotent stem cells can differentiate into cells from any of the three germ layers except embryonic membrane cells.
3. Multipotent stem cell can differentiate into more than one adult cell.
4. Oligopotent stem cells can differentiate into only a few cells like lymphoid or myeloid stem cells.

Classification of stem cells:

Stem cells can be classified as embryonic stem cells and adult stem cells.

Embryonic stem cells are derived from the blastocyst during embryonic development and are either totipotent or pluripotent in nature. They can give rise to all the three primary germ layers: ectoderm, endoderm, and mesoderm [26].

Adult stem cells exist throughout the body in different tissues including the bone marrow, skin, peripheral blood, liver, retina, brain, blood vessels, pancreas, muscle, adipose tissue, and dental tissues. They can divide and give rise to another cell like itself but have a limited differentiation potential to other cell types [26].

Induced pluripotent stem cell (IPSS) is an evolving concept in which 3–4 genes found in the stem cells are transfected into the donor cells using appropriate vectors. The stem cells thus derived by culturing will have properties almost like these cells. Yamanaka and Takahashi in 2006 cultivated first IPSS from adult mouse cells in their research laboratory. They succeeded in growing it from human adult cells in 2007 [26].

Based on their source, stem cells can be again classified as ***autologous stem cells*** which are cells obtained and used in the same individual, ***allogeneic stem cells*** which are cells obtained from a donor belonging to the same species and ***xenogenic stem cells*** obtained from a donor belonging to the different species [25].

Mesenchymal stem cells are a prospective source of adult stem cells. They are actually non-hematopoietic, multipotent cells that can proliferate and differentiate into cells of mesodermal origin like adipocytes, chondrocytes as well as representative lineages of three germ layers [6]. The main source for mesenchymal stem cells is bone marrow. Mesenchymal stem cells constitute only 0.001-0.01% of the cells in the bone marrow as they are actually the non-hematopoietic (blood) stem cells in the bone marrow. They are also called as skeletal stem cells as these cells can generate all the cell types that are found in the skeleton that include bone, cartilage and fat in the marrow cavity of bones. "Skeletal" stem cells actually provide a "niche" for the other type of stem cell, the hematopoietic (blood) stem cells.Other than bone marrow, the sources of mesenchymal stem cells include umbilical cord blood, adipose tissue, muscle, joints and teeth.

Stem cells in oro-facial region:

Dental Pulp Stem Cells (DPSC)

Permanent tooth pulp is the commonest site for dental pulp stem cells. They have a moderate proliferation rate with better immunological acceptance. It has multipotentiality and has odontogenic, myogenic, adipogenic, angiogenic and osteogenic potential and can form complete dentin pulp complex. Bone and CNS regeneration, reversal of liver fibrosis and corneal reconstruction are some of the prospective contributions that are being explored [8]. It has also been stated that dental pulp stem cells can induce immunologic tolerance by suppressing t-cell proliferation and thereby prevent alloreactivity in case of solid-organ or hematopoietic allogenic transplantation [24].

Stem Cells from Human Exfoliated Deciduous Teeth (SHED)

The source is pulp of exfoliated deciduous teeth. SHED was identified to be a population of highly proliferative clonogenic cells capable of differentiation into a variety of cell types including neural cells, adipocytes and odontoblasts. After *in-vivo* transplantation, SHED was found to induce bone formation and generate dentin. It is however unable to form dentin pulp complex *in-vivo*. Thus exfoliated teeth may be an unexpected unique source for autologous stem cell transplantation and tissue engineering [9]. Stem cells from exfoliated deciduous teeth has immunomodulatory activity. They maintain the ratio between t-reg. and t-helper cells .This can be utilized in treatment of certain autoimmune diseases like systemic lupus erythematosus [24].

Periodontal Ligament Stem Cells (PDLSC)
Periodontal ligament stem cells reside in the perivascular space of the periodontium and are a promising tool for periodontal regeneration. PDLSC could differentiate into periodontal ligament, alveolar bone, cementum, peripheral nerves and blood vessels *in vivo* after transplantation into mice. They contain multiple stem cell lineages and their utility is yet to be fully explored [10].

Dental Follicle Stem Cells (DFSC)
Dental follicle is a loose connective tissue that surrounds the developing tooth and can be a source for mesenchymal stem cells. They are present in impacted teeth. DFSC can be isolated and grown under defined tissue culture conditions and can be used in periodontal and bone regeneration [11].

Stem Cells from Apical Papilla (SCAP)
SCAP is usually obtained from wisdom teeth which are extracted for orthodontic reasons etc. Apical papilla is the immature mostly uncalcified precursor of tooth with more undifferentiated cells. SCAPS can differentiate osteogenically, adipogenically and odontogenically *in -vitro*; while *in -vivo* it differentiate into odontoblasts and osteoblasts [12].

Immature Dental Pulp Stem Cells (IDPSC)
Human immature dental pulp stem cells were isolated from pulp of primary teeth. These cells can be induced to undergo uniform differentiation into smooth and skeletal muscles, neurons, cartilage and bone *in-vitro*. In-vivo transplantation into immunocompromised mice showed engraftment in various tissues. Easy availability and expression profile of various markers make IDPSC a great tool for regeneration [13].

Human Periapical Cysts-Mesenchymal Stem Cells (Hpcy-mscs)
Tatullo and his team were the first to demonstrate the existence of human periapical cyst-mesenchymal stem cells (hpcy-mscs). These human periapical cysts-mesenchymal stem cells resides inside the inner layer of the periapical inflammatory cyst wall and can easily be isolated from a discarded tissue. It has been shown that as Hpcy-mscs can differentiate into functional dopaminergic neurons, they can be used in the treatment of Parkinson's disorders. Hpcy-mscs have the ability to differentiate into various cell types such as adipocytes, osteoblasts and neurons. It can be easily collected from the surgically-removed periapical cysts [24].

Oral Epithelial Stem Cells (OESCS)
Oral mucosal epithelium contains a large reservoir of epithelial stem cells necessary for tissue homeostasis. They are unipotent stem cells with clonogenicity located in basal layer of oral mucosa. They can form a well organized graft but cannot differentiate into mesenchymal cell lineages [14].

Gingiva Derived Stem Cells (GMSCS)
Gingiva derived stem cells have similar stem cell like properties, immunosuppressive and anti-inflammatory functions as human bone marrow derived mesenchymal stem cells.They are isolated and characterised from gingival lamina propria. GMSCS retain a potent capacity for multilineage differentiation, its related gene expression and *in vivo* bone formation. They have demonstrated osteoblastic, chondrocytic, endothelial and neural directions when incubated in *in-vitro* inductive culture conditions [15].

Tooth Germ Progenitor Stem Cells (TGPSC)
Human tooth germ progenitor stem cells derived from wisdom teeth are suitable for endothelial and epithelial transformation in dental tissue regeneration approaches. They have high proliferative activity and can differentiate in to lineages of three germ layers including osteoblasts, neural cells and hepatocytes [16].

Bone Marrow Stem Cells (BMSCS)
Bone marrow stem cells are derived from bone marrow of mandible or maxilla and have low odontogenic potential. Recent studies have demonstrated that BMSCS from both mice and humans have the ability to cross lineage boundaries and to form functional components of other tissues expressing tissue specific proteins in organs such as heart, skeletal muscle and vascular endothelium in oro-facial region. However the volume of collectable amount of cells is limited [17].

Epithelial Stem Cells (EPSC)
Epithelial stem cells are located in cervical loop of rodent incisors and third molars of newborns or juvenile animals. They are unipotent and possess clonogenic properties. Third molar stem cells are useful for both tooth formation and regeneration but require donation from children. Cells from rodent incisors cannot be used because of introduction of rodent cells into the oral cavity [18].

Periosteum derived stem cells. (PSCS)
Periosteum is a specialised connective tissue that covers outer surface of bone tissue.Periosteal stem cells display multipotentiality at single stem cell level and a higher proliferation while retaining the ability to differentiate *in-vitro*. They can differentiate into osteoblasts, adipocytes and a chondrocytes [19].

Salivary Gland Stem Cells (SGSC)
Derived from stroma of salivary glands and can be guided for osteogenic,chondrogenic and adipogenic differentiation. Isolation of SGSC is very difficult. In the future, these cells have the potential to reduce radiotherapy induced salivary dysfunction in patients [20].

Aging of stem cells:
In vitro mesenchymal stem cells lose their stemness after 120 days. Various changes occurring in stem cells during culturing. Stem cells gradually lose its proliferation index due to shortening of telomere [27].

Storage of stem cells:
Storage of these stem cells can be done by cryopreservation in liquid nitrogen (−196°c). These cells will survive at such low temperatures only if they are suspended in cryopreservatives/ cryoprotectants. Dimethyl sulfoxide is the standard cryoprotectant used as it prevents freezing damage to living cell [27].

Advantages of Dental Stem Cells
The advantages of stem cells from oral and maxillofacial region are that;
1. They have got multiple lineages.
2. Their store life is better under cryopreservation.
3. They show good interaction with scaffold and growth factors.
4. Easy surgical access.
5. The very low morbidity of the anatomical site after the collection of the pulp [26].
6. It has some advantages over umbilical cord stem cells; it can be harvested at any point in later years of life unlike umbilical cord stem cells which should be collected at the time of birth [30]
7. Cost effective for banking compared to cord stem cell banking [28].

Limitations of Dental Stem Cells:
1. Volume of tissue collected is minimal and hence limited availability of stem cells [30].
2. Very limited studies in humans have been done [28].

Stem cells storage and transport:
Tissue samples containing stem cells are placed in a screw top vial containing an appropriate media, which nourishes it during transport and it should reach the processing storage facility before 40 hours. In the laboratory, the samples are trypsinized and passaged to yield colonies of stem cells. Adequate inductive signals and appropriate growth factors are added in stem cells to get the required cell type [26].

Stem cell markers and scaffold:
Before transplantation of cultured stem cells into the patient the correct lineage should be confirmed by using stem cell markers like OCT4, NANOG, SSEA4, TRA-1-60 andTRA-1-81. Also microbial contamination should be ruled out by using compulsory endotoxin test. Stem cells are transplanted along with a suitable carrier called "scaffold"which can be of different shapes, pattern and biomaterials. Depending upon the necessity it can be biodegradable or non biodegradable. Materials used include poly lactic acid, polyglycolic

acid, polyethylene terapthalate, polypropylene fumarate, hydroxyapatite/tricalcium phosphate, fibrin, alginates, and collagen [26].

Application and challenges of dental stem cell therapy:

Regenerative dentistry aims to regenerate the damaged dental tissue and to fully restore teeth function and anatomy. Dental stem cells may create a repair conductive microenvironment stimulating the recruitment of endogenous stem cells or progenitor at injury site. Regeneration of craniofacial structures, dentin, cementum, salivary glands, pulp and even whole teeth regeneration, TMJ reconstruction, cleft lip and palate repair, cancer therapy, cancer models for cancer biology, oral mucosal models for study of oral mucosa, forensic dental profiling, correlation and collection of ante-mortem and post-mortem data are the other possibilities that can be explored. However several studies in other organs exploring the possibility of repairing tissues with exclusive usage of scaffolds impregnated with chemotactic or growth factors gave uncertain results by formation of irregular and fibrotic appearance of regenerated tissue [22].

Other than in oro-facial region, the applications of dental stem cells include:

1. Certain *in-vitro* experiments have shown that dental pulp stem cells can stimulate angiogenesis/vasculogenesis, providing applications in cell-based treatments of ischemic diseases [24].
2. Dental stem cells can be used in treatment of orthopedic problems and spinal cord damage.
3. Dental pulp cells were found out to be able to form islet-like aggregates which may be a greater discovery in treatment for type 1 diabetes patients [28].
4. Experimental studies have proven that dental pulp stem cells can differentiate into active neurons which can be utilized in the management of degenerative disorders such as Alzheimer's and Parkinsonism [30].
5. The oral stem cells show their capability in corneal regeneration [29].

Even though the cells may be identified, isolated and grown, the body's immune system may identify the transplanted cells as foreign bodies and can generate an immune reaction and rejection of new cells [23].

CONCLUSION:

Since considerable heterogeneity exists between individual cells isolated from same dental pool, identification and purification of stem cell sub populations with improved potency is a necessary step before application of cell based treatment in dental clinics. The health of tissues surrounding the delivery site and delivery methods in stem cells plays a key role. The fate of stem cells after transformation into pulp or periodontal ligament is still uncertain. Even though many studies have been done on animal models, human clinical trial is still limited or practically nonexistent. Technical, safety, regulatory and ethical considerations exist. Stem cell based regenerative approaches in dentistry is still in the nascent stages but continued development can benefit millions of potential patients globally.

REFERENCES

1. Lymperi S, Ligoudistianou C, Tarasila V et.al.Dental stem cells and their applications in dental tissue engineering. The open dent J.2013; 7:76-81.
2. Jamal M, Chogle S, Goodis H,Karam SM.Dental stem cells and their potential role in regenerative medicine Med Sci 2011;4(2):53-61.
3. Khetan S, Burdick J.Cellular encapsulation in 3D hydrogels for tissue engineering.JoVE 2009 ; (32).1590-1600.
4. Schnider RK, Puellen A, Kramann R et.al.The osteogenic differentiation of adult bone marrow and perinatal umbilical mesenchymal stem cells and matrix remodeling in three dimensional collagen scaffolds. Biomaterials 2010;31(3):467-80.
5. Desai VD,Varma B,Maheswari S, et.al.Tooth Regeneration by Stem Cells: An Innovative Approach.Asian J Pharm.Hea Sci 2012;2(3):433-7.
6. Sunil, P.M., Manikandhan, R., Muthu, M.S. and Abraham, S., 2012. Stem cell therapy in oral and maxillofacial region: An overview. Journal of oral and maxillofacial pathology: JOMFP, 16(1), p.58.
7. Silva, L.B., Neto, A.P.D.S., Pacheco, R.G.P., Júnior, S.A., de Menezes, R.F., Carneiro, V.S.M., Araújo, N.C., da Silveira, M.M.F., de Albuquerque, D.S., de Martinez Gerbi, M.E.M. and Álvares, P.R., 2016. The promising applications of stem cells in the oral region: literature review. The open dentistry journal, 10, p.227.
8. Prockop DJ.Marrow stromal cells as stem cells for nonheamopoetic tissues. Science 1997; 276(5309):71-74.
9. Barfoot, J., Doherty, K. and Blackburn, C.C., 2017, October. EuroStemCell: A European infrastructure for communication and engagement with stem cell research. Seminars in cell & developmental biology (Vol. 70, pp. 26-37). Academic Press
10. Suchanek J,Soukup T,Visek B,Ivancakova R ,Kucerova L,Mokry J.Dental pulp stem cells and their characterization. Biomed Pap Med Fac Univ Palacky Olomouc Czech Republic.2009; 153(1):31-36.
11. Spagnuolo, G., Codispoti, B., Marrelli, M., Rengo, C., Rengo, S. and Tatullo, M., 2018. Commitment of oral-derived stem cells in dental and maxillofacial applications. Dentistry journal, 6(4), p.72.
12. Miura M, Gronthos S,Zhao M et al.SHED:Stem cells from human exfoliated deciduous teeth.Proeedings of National Academy of Sciences USA .2003 May 100(10),5807-5812.
13. Wenjun Zhu and Min Liang.Periodontal Ligament Stem cells: Current Status, Concerns and Future Prospects.Stem Cells International.Vol 2015.
14. Honda MJ, Imaizumi M et.al.Dental follicle stem cells and tissue engineering.J Oral Sci.2010 Dec; 52(4):541-552.
15. Cantore S, Bellini A, DeVito D et.al. Characterization of human apical papilla derived stem cells.Journal of biological regulators and homeostatic agents.2017 Oct-Dec; 31(4):901-910.
16. De Souza Valves FB,Costa Ayub CL et.al. Human Immature dental pulp stem cells(hIDPSCs),Their application to Cell Therapy and Bioengineering: An analysis by Systemic Revision if Last decade of Literature. The Anatomical Record (Hoboken) .2013 Dec; 296:1923-8.
17. Kyle B Jones and Ophir D Klein. Oral epithelial stem cells in tissue maintenance and diseases: the first step in a long journey.Int.J.Oral Sci.2013:5(3):121-129.
18. Fawzy EL-Sayed, Dorfer CE.Gingival mesenchymal cells/progenitor cells.a unique tissue engineering gem.Stem Cells Int.2016.
19. Hu B, Nadiri A,Kuchler Bopp S et.alTissue engineering of tooth crown, root and periodontium.Tissue Eng 2006:12(8);2069-2075.
20. Krause DS.Plasticity of marrow derived stem cells.Gene Ther .2002;9(11):754-758.
21. Marcella La Nice, Francesca Paino et.al.Dental pulp stem cells:state of the art and suggestion for a true translation of research into therapy.Journal of Dentistry Vol 42, Issue 7, July 2014:761-768.
22. Concetta Ferreti and Monica Matholi-Belmonte.Periosteum derived stem cells for regenerative medicine proposals: Boosting current knowledge.World J Stem Cells.2014 July 26; 6(3):266-277.
23. Nanduri LSY, Maimets M,PringleSA et.al.Radiother Oncology 2011 Jun 99(3):367-372.
24. Seki, T. and Fukuda, K., 2015. Methods of induced pluripotent stem cells for clinical application. World journal of stem cells, 7(1), p.116.
25. Sloan AJ, Smith AJ. Stem cells and the dental pulp: Potential role in dentin regeneration and repair.Oral Dis 2007 March 13(2):151-157.
26. Lee JS, Hong JM, Moon GJ et.al. A long term follow up study of intravenous and autologous mesenchymal stem cell transplantation in patients with ischaemic stroke.Stem cells.2010 Jun 28 (6):1099-1106.
27. Spagnuolo G., Codispoti, B., Marrelli, M., Rengo, C., Rengo, S. and Tatullo, M., 2018. Commitment of oral-derived stem cells in dental and maxillofacial applications. Dentistry journal, 6(4).
28. Samuel A.R. and Gounder, R., 2017. Role of Stem Cells in Prosthodontic Rehabilitation. Journal of Pharmaceutical Sciences and Research, 9(4).
29. Giordano G., La Monaca, G., Annibali S., Cicconetti, A. and Ottolenghi, L., 2011. Stem cells from oral niches: a review. Annali di stomatologia, 2(1-2).
30. Mitsiadis TA,Orsini G,and Jimenez -Rojo L.Stem cell based approaches in dentistry. European cells and Materials. Vol 30:2015:248-257.