International Journal of Psychosocial Rehabilitation, Vol. 24, Issue 08, 2020
ISSN: 1475-7192

A Novel Paradigm in Dentistry- Stem Cell Therapy: A Comprehensive Review

*[1]Dr. Shivangi Singh ,[2]Dr.Nidhi Puri ,[3]Dr. Upasana Sethi Ahuja ,[4]Dr. Manu Dhillon
[5]Dr. Akshay Rathore ,[6]Dr. Seema Ahuja ,[7]Dr. Nidhi Puri

ABSTRACT--*Stem cells have the capability to influence the millions of lives by offering unparalleled possibilities for emerging new medical therapies for crippling and terminal diseases and a new way to explore essentials of biology, making a template for cell-based therapies. These unique cells have remarkable potential of endless self-renewal and differentiation into numerous cell types. Every new cell in turn can either remain as a stem cell or get differentiated to emerge into a new cell with more specialized function e.g a muscle cell, brain cell or red blood cell. Recent literature has targeted the use of several stem cells extracted extraoral and intra orally that can be applied in regenerative dentistry; posing numerous potential therapeutic applications. This leads us to the cutting edge of stem cell research as it has numerous applications in dentistry. An innovative perspective for the application of stem cells in multifaceted dentistry requires detailed planning and comprehensive research work. It is the need of the hour to shift from corrective dentistry to preventive and regenerative dentistry. Thus, this review emphasizes on characteristic properties, challenges and current research, along with new avenues and prospects of stem cells in dentistry and in management of oral mucosal lesions.*

Keywords-- *Regenerative dentistry, Adult stem cells, Mesenchymal stem cells, stem cell banks*

I. INTRODUCTION

Regeneration of tissues is no longer a newer concept to humankind due to several discoveries during the past 25 years, which have lead to progress and developments in the field of cellular and molecular biology. The increasing basic understanding of biological concepts in the regeneration of oral tissues coupled with stem cells and by translating extensive laboratory research work to successful clinical applications resulted in a paradigm shift from therapeutic management to the reconstruction of the biological substitutes, thus removing all possible barriers and offer biological solutions in promoting health, assessing risks, diagnosing, treating, and evaluating prognosis of the disease. All these conclusive research work ushered in a new era for regeneration and transplantation medicine and its applications in dentistry will radically change our lives in the near future[1,2].

[1] *Senior Lecturer, Department of Oral Medicine and Radiology. I.T.S Dental College, Muradnagar, Ghaziabad, Uttar Pradesh, India

[2] Associate Professor, Department of Oral Medicine and Radiology. I.T.S Dental College, Muradnagar, Ghaziabad, Uttar Pradesh, India

[3] Head of Department and Professor, Department of Oral Medicine and Radiology. I.T.S Dental College, Muradnagar, Ghaziabad, Uttar Pradesh, India

[4] Professor, Department of Oral Medicine and Radiology. I.T.S Dental College, Muradnagar, Ghaziabad, Uttar Pradesh, India

[5] Reader, Professor, Department of Oral Medicine and Radiology. I.T.S Dental College, Muradnagar, Ghaziabad, Uttar Pradesh, India

[6] Senior Lecturer, Department of Oral Medicine and Radiology. I.T.S Dental College, Muradnagar, Ghaziabad, Uttar Pradesh, India

[7] Associate Professor, Department of Oral Medicine and Radiology, I.T.S Dental College, Muradnagar, Ghaziabad, UP.

Received: 12 Mar 2020 | Revised: 22 Apr 2020 | Accepted: 09 May 2020

Stem cells are unspecialized, undifferentiated cell present in almost every multicellular organism; havingaunique capacity to differentiate ad evolve into numerous cell lines and renew themselves throughout their entire life (Fig 1). Essentially, stem cells are progenitor cells which have the capacity to regenerate and differentiate into diverse group of specialized cell types and the inflammatory signals are received and followed by these cells when they are administered and hence, help them to in repairing process. Due to recent advancements in better understanding of biology of stem cells provide an opportunity to investigate the underlying procedure that regulates the formation of embryo, cell differentiation, and maintenance of an organ[3]. Stem cell therapy, a preface to an era of breakthrough in medical advancements based on cell-based therapies, has probable targeted therapeutic uses such as spinal cord injuries, myocardial infarction, Parkinson's disease, and diabetes[4].

With clinical aspects in dentistry, Oral tissues have been recognized as an important source and therapeutic target for stem cells. Various reviews in literature have targeted on the several extraorally and intraorally extracted stem cells that can be implemented in regenerative dentistry; posing numerous potential therapeutic applications. Tooth is the most common, essential and noninvasive source of Dental stem cells that can be conveniently collected. In dentistry, novel innovations in management and treatment of a number of oral diseases, have attained dental stem cells from the pulp of primary and permanent dentition and from periodontal ligament. The objective of the current review is to evaluate the applications of stem cells in various fields of dentistry and to understand the procedure by which dental stem cells can be used for regeneration of oral tissues. This comprehensive review, deals with the origin of the stem cells, its classification, the characteristics, properties, challenges and current research, along with highlighting its potential applications in dentistry and oral mucosal lesions. In addition, "dental stem cell banking" is also available for regenerative therapies in the future. The important highlighting properties of stem cells should be understood by the dental clinicians in the betterment of dentistry. A futuristic approach for the implementation of stem cells in multifaceted dentistry requires detailed planning and comprehensive research work. It is the need of the hour to shift from corrective dentistry to preventive and regenerative dentistry.

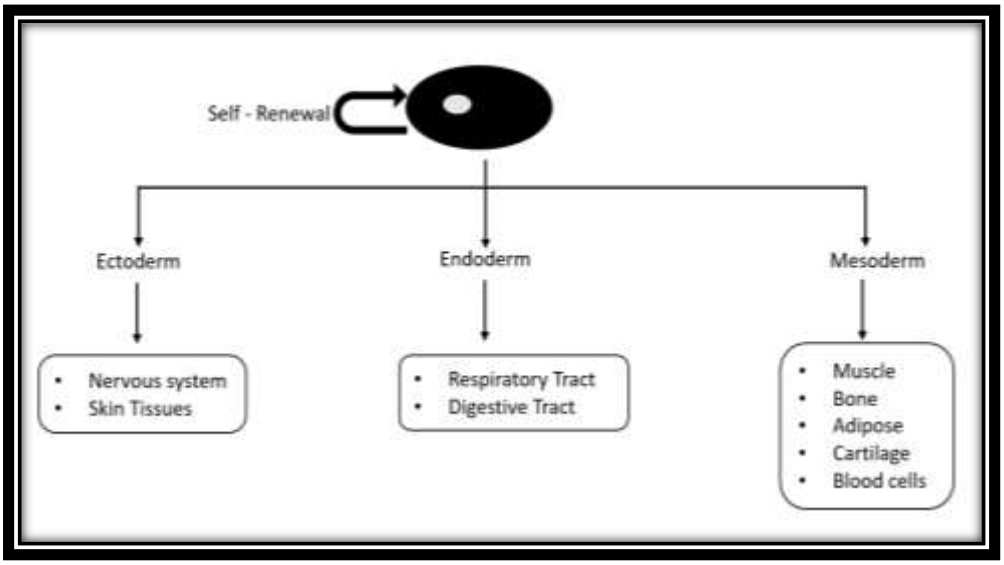
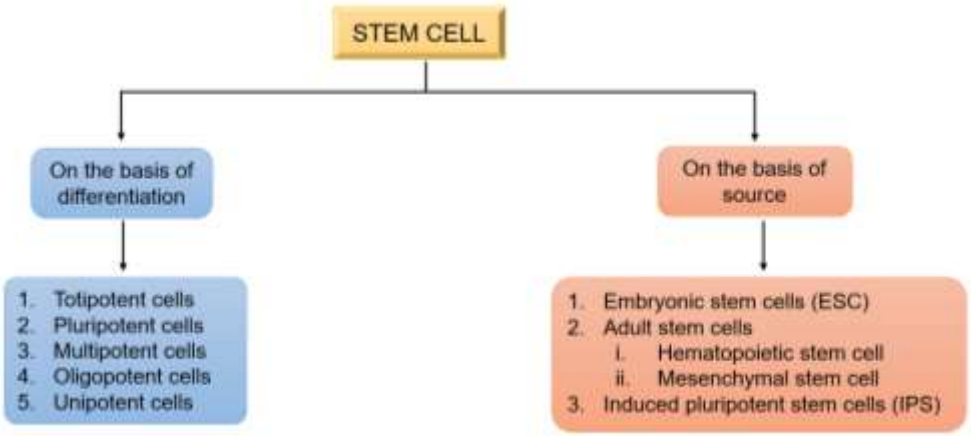


Figure 1: .bIllustrating self-renewal through replication, and differentiationinto tissue-specific cell lineages.

CLASSIFICATION OF STEM CELLS; Stem cells can be categorized as:[5,6]



II. HOW STEM CELLS WORK-

By the capacity of performing three important functions[7]:

1. **Plasticity – or trans-differentiation ability –** Potential to change into other cell types by breaking the unipotent restriction. (Fig. 2)
2. **Homing –** These cells migrate to site of tissue damage. (preference for specific tissues).
3. Engraftment– To unite with other tissues; ability to invade and be incorporated in the other tissues.

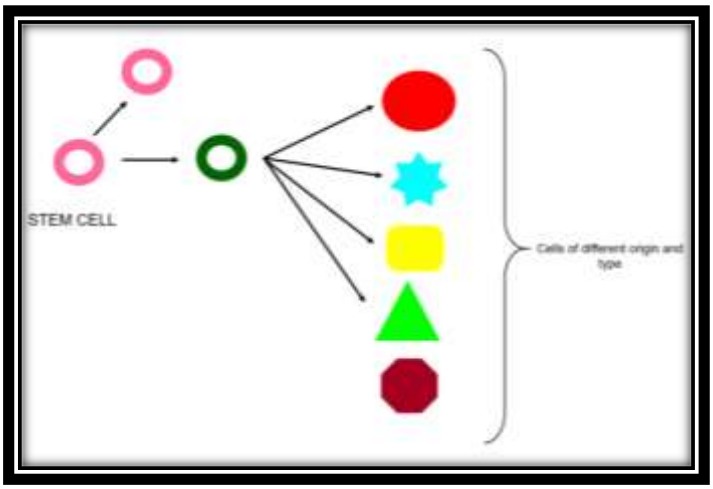


Figure 2: Diagram illustrating stem cell plasticity.

III. CHARACTERISTICS OF STEM CELLS

1) Stem cells can differentiate and renew themselves throughout life.
2) Stem cells are unique unspecialized cells and lacks specific structure to achieve specialized task.

Received: 12 Mar 2020 | Revised: 22 Apr 2020 | Accepted: 09 May 2020

3) Stem cells has the ability to adventinto specialised differentiated cell.

IV. STEM CELLS FROM OROMAXILLOFACIAL REGION

Adult stem cells that have been till date distinguished in dental tissues are epithelial and MSC-like stem cells.[8]In1999, adult epithelial stem cell was first demonstrated having capability to differentiate into enamel producing ameloblast from apex of the tooth Dental stem cell predominantly contains mesenchymal stem cell and includes:

- Dental pulp stem cell (DPSCs)
- Stem cells from exfoliated deciduous teeth (SHED)
- Periodontal ligament stem cells (PDLSCs)
- Stem cells from apical papilla (SCAP)
- Dental follicle progenitor cells (DFPCs)
- Oral mucosa derived stem cell
- Periosteum derived stem cell
- Salivary gland derived stem cell

Postnatal dental pulp stem cell (DPSCs) was first to be extracted from pulp tissue by Gronthos and colleagues via enzymatic treatment of pulp tissue and are phenotypically analogous toMSCs (BMSCs) derived from bone marrow.

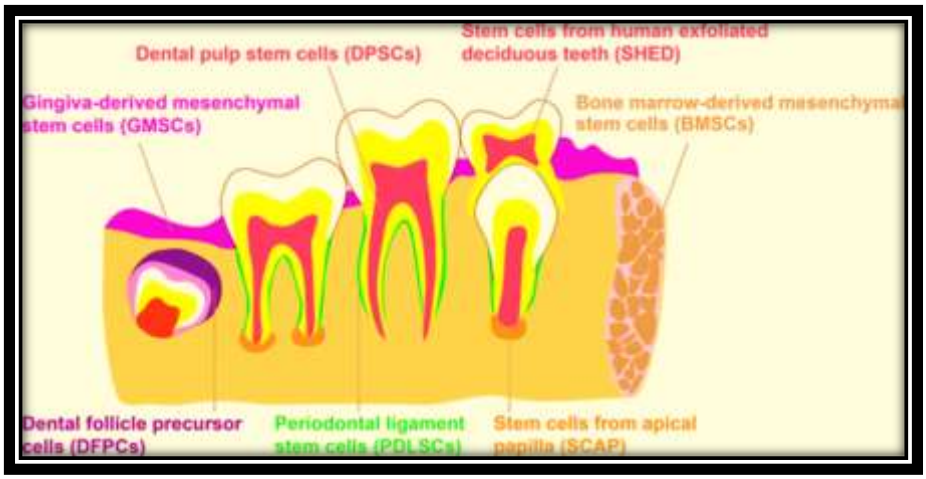


Figure 3: Dental stem cells sources(Image source: Stem Cells Transl Med. 2020;9(4):445-464)

V. ADVANTAGES OF DENTAL STEM CELLS

1. High transdifferntiation.
2. Extendedduration of Cryopreservation ; an ideal requisite for stem cell banking
3. Interactions with the various growth factors are highly appreciable.

VI. DENTAL STEM CELLS ISOLATION, STORAGE AND TRANSPORT

Isolation and preservation of stem cell is essential for clinical application, administration and research based on stem cell therapy in regenerative medicine[9]. Subsequently following the extraction; the tooth is carefully washed by immersing it in 70% ethanol and then cleansed by dipping it five to seven times in Dulbecco'sphosphatebuffered saline containing antibiotics (100 IU/ml penicillin and 100 μg/ml streptomycin) without calcium and magnesium ions to remove ethanol in two separate tubes. For further processing, the tooth is thencautiously carriedinto third tube containing 2ml of tooth preservation cocktail (TPC). After 5 min; 1 ml of nutrient medium is added over the TPC in this tube and is secured with paraffin film and at room temperature; within 48hrs it is transported to the cell processing lab.[9]

Pulp is retrieved either by using sterile barbed broach or by cutting the tooth using diamond disc accompanied with coolant to prevent anyinjury to the underlying pulp. The colonies of stem cells are obtained by the trypsinization and cultureof the isolated pulp. The cell sorting is thendone by using fluorescence activated cell sorting system and passing the cells through relevant and suitable stem cell markers. Isolated and sortedcells storage are then stored either by cryopreservation or magnetic freezing.[10]

VII. STEM CELL THERAPY IN REGENERATIVE DENTISTRY

The main aim of stem cell research in dentistry is to regenerate missing oral tissues and this can be achieved by the properties exhibited by stem cells such as self - regeneration and differentiation. Thus, the implications of stem cell therapy in dentistry are

1. Renewal of oral hard tissues
    a. Renewalof Dentine
    b. Renewal of Cementum
    c. Enamel formation
    d. Regenerative endodontics
2. Bone regeneration
    a. Regenerating of bone from autologous stem cells
    b. Implant associated bone regeneration
    c. Condyle regeneration
    3. Periodontal tissue regeneration
    4. Stem cells in sinus augmentation
    5. Repair of cleft lip & palate defects
    6. Regeneration of irradiated salivary glands:
    7. Peripheral nerve regeneration
    8. Management of oral cancer

VIII. REGENERATION OF HARD TISSUES

Received: 12 Mar 2020 | Revised: 22 Apr 2020 | Accepted: 09 May 2020

Aesthetic and functional rehabilitationof structure of the toothis the aim of present day restorative dental treatment. Till recently, diverse syntheticmaterials have beeninstituted and implemented to restore the structure of damaged tooth. Although these processedmaterials have been proved to be efficacious, they lackthe same characteristic features of naturally developed dentine andenamel. Natural dental hard tissues, i.e. dentin,enamel and cementum displaynegligibleregenerative capability. Hence, substitution of dental tissuesis required and is the ultimate need of the hour for regeneration of tooth. Tissueengineering technique is aninventive discipline and highly exciting sector of research which canmakerestoration ofdamaged tissues practically achievable.

In attempts at tooth regeneration, when epithelial and mesenchymal stem cells were co –cultured together with collagen scaffold (hydroxyapatite/tricalcium phosphate) and introduced into the cavity of an adult immunodeficient mice, the formation of all dental structures such as odontoblasts, periodontal ligament, dental pulp etc was observed. In pulp exposed teeth, reparative dentin bridge formation have been found to be stimulated by the dentinal chips as theymay have the ability tocontribute a matrix for attachment of pulp stem cell and may function as an accumulationfor growth factors while in response the pulp stem cells will exhibit natural reparative activity tofurnish some support for the use of scaffolds in order to regenerate the dentin – pulp complex[11] (Fig.4)

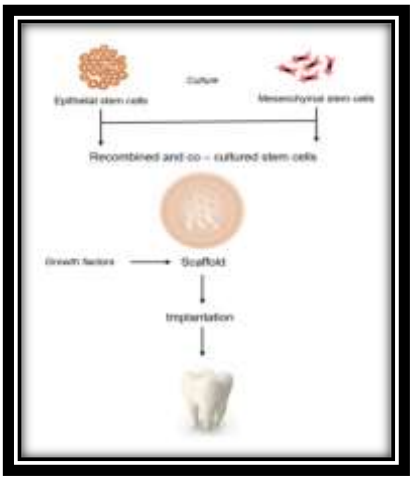


Figure 4: In vitro and in vivo culture of tooth

IX. Bone Regeneration

Adult mesenchymal stem cells (hMSC) can effectively and efficiently differentiate into osteoblasts and helps in bony regeneration in the maxillofacial bony defects. Bone marrow mesenchymal cells can differentiate into bone, cartilage, muscle, blood vessels and nerves in culture or by transplantation into the tissues. Dental pulp stem cells can be utilised as areliable source for bone formation as they have a capability to differentiate into osteoblasts. They may be useful for treatment of craniofacial defects, periodontal diseases, osteoporosis, bone fractures, enhancement of the alveolar ridge, sinus lifting, correction of large surgical bone defects such as cancer and repair of inborn bone defects[12].

Stem Cells in Periodontal Regeneration

Stem cells therapy provides aninnovative way for rejuvenation of the periodontal structures like periodontal ligament, alveolar bone and other supporting components.

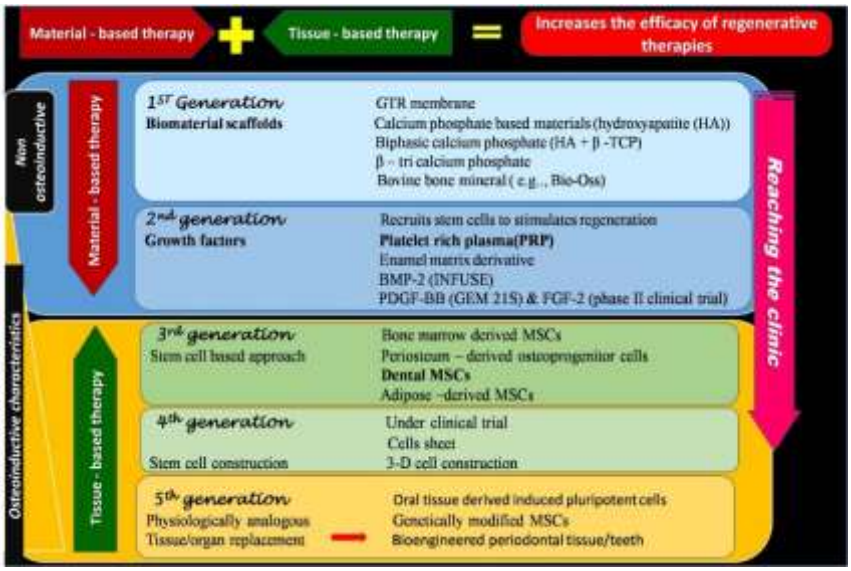


Figure5: Progress in regenerative periodontal/bone therapies.

Short while agomultipotentcell known as PDLSCs have been segregated from the PDL of extracted human third molar which give rise to adhering clusters of clonogenic cellssimulating fibroblasts and have the capability to formadipocytes, osteoblast and cementoblastlike cells in vitro, and validate the extent to produce tissues mimicing cementum and periodontal ligament in vivo[12].

Stem Cell Therapy in Oral Lesions

Mesenchymal cells extracted from bone marrow differentiate in various cell types like osteoblasts, adipose cells, cartilage, neural cells, and endothelial cells.Mesenchymal cells have unique immunemodulatory and anti-inflammatory effects through their propensity to relocate themselves to the inflammatory sites and gets engaged in regeneration of impaired cells and tissues by stimulating amplification, alteration and differentiation of resident progenitor and stem cells[13] (Fig 6).

Ding G et al (2011) had hypothesized that MSCs can be used a treatment for oral lichen planus as these cells have immunosuppressive properties. MSCs inhibits the extensiveand diverse functions of immunecells, including T cells and B cellsby suppressing T cell activation and accumulationin vitro. Hence, MSC therapy can be a promising therapeuticmodality for oral ulcers and wounds[14].The future could be seen promising in the lesions with inflammatory component where stem cell therapy can provide long term benefits. The action of stem cells in oral lesions is summarized in figure 6.

Received: 12 Mar 2020 | Revised: 22 Apr 2020 | Accepted: 09 May 2020

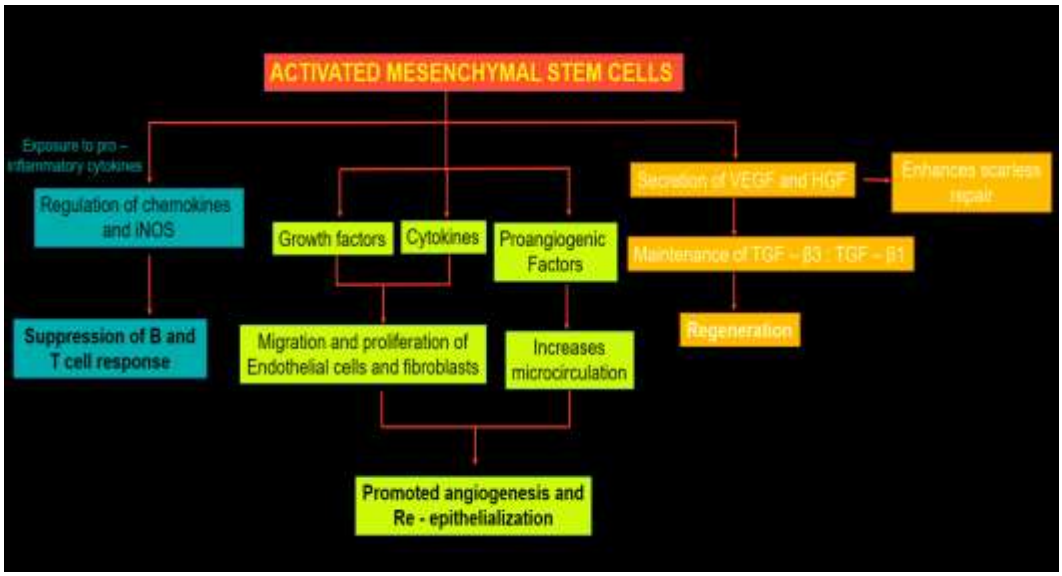


Figure 6 : Immunomodulatory and anti-inflammatory action of Stem cells

Stem Cell Therapy in Oral Cancer

Majority of the anti-cancer treatment modalities used are based on the traditional and long – established view that the tumor cell is produced by a population of cells having equivalent proliferative potentials[15].However hierarchical model of organization of OSCC demonstrates that for the successful treatment procedures of cancer eradication unusual properties of the Cancer stem cell (CSC) subpopulation should be taken into account. CSCs, mostly slowly dividing, has not yet been determined for OSCCs, but these appear to be slowly cycling in leukaemias and in some epithelial cancers.[16,17]The beneficial effects of cytotoxic drugs may also be decreased by the high CSC expression of drug transporters which enable swift transmission of noxious substances from the cytosol[18].

Reversible procedures that results into the augmentation of epithelial stem cell populations appears to occur during normal growth and healing and pharmacological handling of CSC self – regeneration ability appears feasible at least in vitro.[19]Thesekinds of mechanisms could be utilized to avoid self-renewal of malignant stem cells which could be followed by tumor atrophy effectively.

X. DENTAL STEM BANKING

Literature evidence reveals that dental tissues are arich source of MSCs. Dental stem cells banking is the procedure to store dental stem cells from patient's deciduous dentition and third molar teeth that may be useful for future regenerative and immune therapies[12]. Nowadays, labs like Tooth Bank, Ree labs and Stemadehave been established which facilitates dental stem cell banking in India.

XI. CONCLUSION

Stem cells are a category of precursor cells having potency for proliferation, regeneration, and differentiate into distinct cell types. The regenerative capacity of these stem cells acts as base for the new field of regenerative medicine and dentistry. **Regenerative dentistry** comprises of biomedical clinical research on elaborating and

exploring the potential of stem cells for regeneration of pathological tissues in the Oro-maxillofacial region. Stem cell research and biology is in its primitive stages; thus analyzing the exact potential of these cells is yet difficult to access at this stage. But it is the need of the hour to shift from corrective dentistry to preventive and regenerative dentistry. An innovative perspective for the application of stem cells in multifaceted dentistry requires detailed planning and further comprehensive research work to utilize the advantages of stem cells; as this has possibility to change the future of dentistry towards healing and regeneration.

REFERENCES

1. Nadig RR. Stem cell therapy – Hype or hope? A review. J Conserv Dent. 2009; 12(4): 131–138
2. Wobus AM, Boheler KR. Embryonic Stem Cells: Prospects for Developmental Biology and Cell Therapy. Physiol Rev. 2005;85(2):635-78.
3. Ramalho-Santos M, Willenbring H. On the origin of the term 'stem cell'. Cell Stem Cell 2007; 1: 35–38.
4. Fortier LA. Stem cells: classifications, controversies, and clinical applications. Vet Surg. 2005;34(5):415-23.
5. Ann A. Kiessling& Scott C. Anderson. Human embryonic stem cells - 2nd edn. New York:Elsievier;2010.p.26-8.
6. PM Sunil, R Manikandhan, MS Muthu, and S Abraham. Stem cell therapy in oral and maxillofacial region: An overview. J Oral MaxillofacPathol. 2012; 16(1): 58–63.
7. Loebinger MR, Aguilar S, Janes SM. Therapeutic potential of stem cells in lung disease: progress and pitfalls. ClinSci (Lond). 2008 ;114(2):99-108.
8. Egusa H, Sonoyama W, Nishimura M, Atsuta I, Akiyama K. Stem cells in dentistry – Part I: Stem cell sources. J Prosthodont Res. 2012;56(3):151-65.
9. Hanna J, Hubel A. Preservation of stem cells. Organogenesis. 2009;5(3):134-7.
10. Sunil PM, Manikandan R, Muthumurugan, Yoithapprabhunath TR, Sivakumar M. Harvesting dental stem cells - Overview. J Pharm Bioallied Sci. 2015;7(Suppl 2): S384-6
11. Bluteau G, Luder HU, De Bari C, Mitsiadis TA. Stem cells for tooth engineering. European Cells and Materials 2008;16: 1-9
12. Egusa H, Sonoyama W, Nishimura M, Atsuta I, Akiyama K. Stem cells in dentistry--Part II: Clinical applications. J Prosthodont Res. 2012 ;56(4):229-48.
13. Hu MS, Borrelli MR, Lorenz HP, Longaker MT, Wan DC. Mesenchymal Stromal Cells and Cutaneous Wound Healing: A Comprehensive Review of the Background, Role, and Therapeutic Potential. Stem Cells Int. 2018; 2018:6901983.
14. Ding G, Wang W, Liu Y, Zhang C, Wang S. Mesenchymal stem cell transplantation: a potential therapy for oral lichen planus. Med Hypotheses. 2011;76(3):322-4.
15. SarrafC.Emerging themes of cancer stem cells : Editorial –overview. Cell Profile 2005;38:343-5.
16. Holyoake TL et al. Premetive quiescent leukemia spontaneously initiate factor dependent growth in vitro in association with up- regulation of expression of interleukin-3.Blood 2001;97:720-8.
17. XinL,LawsonDA,WitteON.The Sca-1cell surface marker enriches for a prostate –regenerating cell subpopulation that can initiate prostate tumorigenesis. ProcNatlAcadSci USA 2005;102:6942-7.

Received: 12 Mar 2020 | Revised: 22 Apr 2020 | Accepted: 09 May 2020

18. Hirschmann-Jax C et al. A distinct side population of cells with high drug efflux capacity in human tumor cells. ProcNatlAcadSci USA 2005;01:14228-33.
19. Sherley JL. Asymmetric cell kinetics genes: the key to expansion of adult stem cells in culture.Stem cells 2002;20:516-72.
20. Gonçalves GAR, PaivaRMA.Gene therapy: advances, challenges and perspectives.Einstein (Sao Paulo). 2017 ;15(3):369-375.