Stem Cells in Regenerative Dentistry: An Overview

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Abstract

The study of stem cells in regenerative dentistry is the most precious in-progress research. Stem cells are the cells that have the self-renewal capacity and can differentiate to mature cells. Stemcells also have the prospective to form dentin matrix, bone and neuronal cellsrapidly. Stem cell-based therapeutic approaches provide a better and attractive alternative that the classical dental treatments because of their questionable efficacy and durability. The most promising alternative for tooth loss is the utilization of stem cells and induced pluripotent for the regeneration of the whole tooth. Therefore helping with the progress in inducing bone rejuvenation, treating damaged teeth, stem cell-based therapy plays a vital role. So, this article will highlight the role and importance of stem cells in regeneration in Dentistry.

Keywords: *Stem Cells; Regenerative Dentistry; Therapeutics; Future Prospects.*

Introduction

Stem cells are defined as clonogenic cells capable of both self-renewal and multi-lineage differentiation since they are thought to be undifferentiated cells with varying degrees of potency and plasticity.[1] In all multi-cellular organisms, these primitive types of cells i.e. presence of stem cellsalong with the properties of self-renewal in addition to the potential to change into mature cell types. They show an impressive capacity for regeneration and perhaps could be utilized for the treatment of diseases like cancer, Parkinson's, Alzheimer and many more, with its ability to replace or repair of the damaged cells.[2] The stem cells can be classified as,[3]

Classification of stem cells:

The classification of stem cells are the following:

1. Embryonic stem cells (ESCs)
2. Adult stem cells (ASCs)
    a. Hematopoietic stem cells (HSCs)
    b. Mesenchymal stem cells (MSCs)
3. Induced pluripotent stem cells (IPSCs)

The identification of orofacial tissues as a foundation and therapeutic objective with clinical curiosity in dentistry for stem cells. The main properties of stem cells were first defined by Ernest McCulloh and James till in the 1960s.[4] The capabilities of the stem cells are mainly; produce cells having the same characteristics (daughter cells) and produce cells that have different properties. Mesenchymal stem cells are interpreted as multipotent because they tended to display the capacity for segregation into cells of a different variety, even as the mesenchymal stem cells are clonally isolated cells. They have the skill to differentiate along the other particular mesenchymal ancestry, and also can stay in an inactive undifferentiated state until offered the indication to segregate asymmetrically.[5]

Dental stem cells, which are derived from postnatal stem cells, are one of the most recent types of stem cells found in the mesenchymal stem cells (MSC) list. It shows capabilities based on development, differentiation, regeneration, and immunoregulatory/ immunomodulatoryproperties.[6]Afterthediscovery,study and progress towards medicalapplications of stem cells had made so much progress. For bone and dental regeneration, cell sources from dental pulp stem cells (DPSCs), periodontal ligament stem cells (PLSCs), stem cells from human exfoliated deciduous teeth (SHED), stem cells from apical papilla (SCAP)and dental follicle cells are taken due to their accessibility and abundance.[7]

Dental stem cells in India are still at the budding

stage, and there seems to be limited awareness regarding dental stem cells. SHED is obtained from baby teeth, the multipotent stem cells population are easily collected as the characteristics are either shed naturally or are removed physically for the suitable growth of permanent teeth, of the deciduous teeth.

The different diseases and trauma causes bone and dental loss and defects which has become a worldwide distress of elevated frequency. This affects the physical condition and wellbeing of a very big population and also put down a grave economic load on the public.[1,2] The present therapies done for dental diseases can only provide an improvement based on parameters of clinical diagnosis and arrest development of disease, although regeneration of missing tissue is not able to be done. Therefore, there is a high demand for new technologies that can help to accomplish the regeneration of bone and dental tissues.[8,9]

Table 1. History of Stem Cell[10]

1868	German biologist, Haeckel mentioned the term "Stem Cells" in his research works.
1908	Russian histologist, Alexander Maksimov hypothesized the subsistence of Hematopoietic stem cells
1932	G. L. Feldman demonstrated proof of regeneration of pulp in favorable conditions.
1985	Yamamura reports that pulp tissues contain stem cells.
2000	Gronthos et al separate dental pulp stem cells from human dental pulp of an adult thatcan regenerate complexes like dentin pulp.
2003	Miura et al reports the isolation of population of stem cells from the living pulp remnants of exfoliated tooth.
2004	Seo et al discovered the periodontal ligament stem cells from human periodontal ligament.
2005	Morsczeck et al and kemoun et al each of them discovered exclusive lineage-committed cells that cant be differentiated with the possession of features of progenitor mesenchymal in dental follicles of human.
2006	Sonoyama et al identified and characterized stem cells from dental apical papilla of human permanent immature teeth.
2009	Zhang et al informed the separation of a stem cell from the human gingiva's spinous layer.

Applications in dentistry:

The isolation and characterization of human dental stem cells are:[7]

1. Stem cells from human exfoliated deciduous teeth
2. Dental Pulp Stem Cells
3. Periodontal ligament stem cells
4. Stem cells from apical papilla

The different separation, culturing and differentiation procedures have highly developed over the decade for the various MSCs. The first isolation of mesenchymal stem cells was done from bone marrow, they appeared like cells similar to fibroblast and were capable of sticking to plastic dishes, and the single cells form colonies which divide to form mature cells of the mesenchymal pedigree which are osteoblasts and chondrocytes. The most familiar resource of Dental mesenchymal stem cells (DMSCs) is dental pulp stem cells (DPSCs), which were first isolated from human teeth in the year 2000.[4] These organs are the vital pool of adult stem cell populations as they have a parallel purpose to mesenchymal stem cells. Hence, DMSCs can be utilized in favor of rejuvenation of teeth or other organs that have essential restore possibility. The dental pulp stem cells are considered a rich source of mesenchymal stem cells due to the number of potential stem cells isolated from the human tissue samples, adding to its advantages apart from the cell number, is that lesser time consumption in the process of enzymaticabsorption from the dental tissues by extracting stem cells when compared with the other mesenchymal stem cell sources. These features make the dental stem cells less vulnerable to potential enzymatic stress and help to expand rapidly than other cells. Hence, even if from a tiny amount of dental tissue, they are extracted, yet latently adequate quantity of cells for a different type of clinical applications can be generated.[5]

The dental pulp stem cells are an amazing source of stem cells believing their multipotent differentiation potential. Under in vitro culture conditions, they are differentiated into odontogenic cell types, but apart from that, it has been also reported to distinguish into osteoblasts, chondrocytes, myocytes, neurons, melanocytes, hepatocyte-like cells and adipocytes.[5] The DMSCs in the dental pulp are situated normally in two slots, they are

1. Apical niche
2. Perivascular niche

These two types of niche hasa separate role for themselves, but in a way, their role is exchangeable at times.[4]

Mesenchymal stem cells have the perspective in support of the revival of dental tissues. Deciduous teeth contain residents of added undeveloped multipotent stem cells, that are competent in forming dentin like structures although not an entire dentin-pulp complex. Teeth contain well-defined pulp chambers, odontoblasts, pre dentin and dentin, and also enamel organ consisting of dental enamel, ameloblasts, stratum reticulum, stratum intermedium. The DPSCs are skilled in forming a reparative dentine like structure which is present straight on the surface of dentin.[11]

The lost regenerative ability within the PDL space to be domesticated is the foremost goal of the gene-enhanced regeneration of periodontal ligament. This technique has the maximum capability if it can be tailored for use with entirely adult cells, despite gene enhanced tissue engineering exercised within concurrence with stem cells.[9]

The different ways on how the regenerative procedures can take place are:

1. **Pulpal regeneration:** Pulpal tissue regeneration is done mainly by postnatal stem cells. To reduce the chances of immune response allogeneicstem cells can be used. Gene therapy and 3d printing are the newer modalities for perfectly placing the cells in their proper place which may also lead to the formation of new dentin.[8,12]
2. **Periodontium Regeneration:** Periodontal tissue surgeries are quite complex as it requires various factors to facilitate the production of a sufficient amount of tissues. Alveolar bone, periodontal ligament and cementum can be derived from bone marrow stem cells. Periodontal stem cells are started with biocompatible scaffolding helps to generate a 3D matrix which incorporated with various growth factors that are reported to the area which necessitates regeneration.[8,13]
3. **Facial tissue Regeneration:** After the treatment of a large oral lesion involving facial tissues, reconstruction will play an important role. Collagen along with myoblasts can be engineered along with various growth factors for reconstruction. For the correction of large defects, bone marrow-derived stem cells can be used.[8,14]
4. **Tooth Regeneration**- Epithelial and mesenchymal cells and the cells capable to differentiate to from tooth buds. The use of prenatal stem cells is more popular for regeneration because of their propensity. After tooth loss, the most ideal therapeutic approach would be the rejuvenation of the whole tooth. The different kinds of approaches that can be taken is, the formation of tooth germs which is prepared by the union of DMSCs, and DESCs in the alveolar bone is transplanted where the process of development, eruption and finally becoming functional tooth of germs is seen. An additional approach is implantation into the jaw of tooth-shaped polymeric biodegradable scaffolds packed with DESCs and DMSCs to rejuvenate a new tooth. Well, the experiments have been done only in mice, as the results have not been obtained in human cells.[4,15-17]
5. **Bone Regeneration:** Periosteal stem cells can be used for this. For closure of various bony defects, inorganic bone along with plasma rich platelets can be used. Mesenchymal stem cells along with autogenic stem cells can be used for TMJ reconstruction. The production of bioengineered TMJ is done by the adult mesenchymal cell in a biomimetic scaffold. The scaffolds which are strengthened with the mi-RNA showed improved osteoinductive properties and functionality.[8,18]

Tooth Stem Cell Banking: It is an unpopular trend around the world currently, but most of the developed countries have started the acceptance of stem cell banking. The different types of stem cell banking companies around the world are Stem Save (Stemsave Inc, New York) and Store-A-Tooth (Provia Laboratories, Littleton, Massachusetts, USA). The first tooth bank in Japan was instituted in Hiroshima University and was

named 'Three Brackets' company in 2005. Recently the thought of dental stem cell deposition was launched in Delhi and Mumbai in our country.[7]

The dentists would have immense prospect to make their patients attentive of the potential of the regenerative uses of stem cells, only if the stem cell banking system is matured and confirmed to be effective and safe, and can encourage the patients to store their dental mesenchymal stem cells for further medical usage during any kind of treatment. The different boons of dental stem cell deposition are that it can be stored in second chance if the first chance is failed to spot, unlike blood stem cells from the umbilical cord. The isolation procedure is painless and simple; also banking of stem cells can provide an ideal source of iPS banking. It also provides for future therapeutic uses, an autologous cell source. Adding to its numerous advantages, it is also not focused on any ethical concerns like the embryonic stem cells.[5]

Future Research and Prospects: The MSC-based regeneration researches have shown tremendous results in theremedy bone and dental loss and defects, both by exogenous transplantation and endogenous restoration. But as mentioned by Chengxi Zhang et al[1], the MSC-mediated regeneration is under tight charge of the micro environment based on its remedial efficiency, with the capability of controlling inhabitant MSCs under pathological and physical conditions and also adapt MSCs that are transplanted in tissue engineering and cytotherapy. As a result, the biggest challenge remains the accomplishment of MSC based dental and bone regeneration in an unhealthy microenvironment.[16]

T. C. Srijaya et al[5] mentioned about the huge amount of curiosity of dental stem cells in medical research because of their budding function in regenerative medicine. They have elevated capability of regenerating which has given higher expectations for therapeutics in the future. However, to achieve the complete therapeutic capability of dental stem cells much more work and research is to be done. In the future, for the research of dental stem cells, the biomaterials used and the diseases associated with teeth many more efforts and advances are very essential.

The environment in addition to conditions under which the stem cell research takes place and how it would effectively help in dental procedures are still a bigger problem to solve. The different clinical trials and researches have been going on stem cells and have not been fully studied. Moreover, in tooth regeneration the greater challenge is time; it acquires 7 years in humans for the whole process of odontogenesis. The individuals with missing teeth may find this long term physiological process discouraging and will look forward to instantaneous treatment outcomes.[18]

Bringing light to the topic of regeneration of periodontal ligament, Electron microscope radio-autography was utilized in an attempt to recognize if there is any connection among the site and degree of differentiation of cells in PDL. The existence of an undifferentiated perivascular population of progenitor cells was concluded and also that cytodifferentiation was seen in the progenitor cells, which is present in PDL. Narang et al. demonstrated that from solid-frozen human PDL, the postnatal stem cells can be recovered.[9]

Conclusion

While much progress has been achieved in the department of regenerative procedures through stem cells in dentistry, we still have a long way to go. The basic and pre-clinical stem research is very slow in the dental clinics, as the very obvious safety, regulatory, technical and ethical concerns exist. The depth of scope present in stem cells is enormous which would take the dental regeneration procedure to another level, bringing more success in the field of Dentistry. The various approaches started now are just the beginning, but it is very well known how much potential it carries in the future to help patients all over the world. The various new promising technologies such as imaging systems, mathematical modeling and nanotechnology would help to speed the stem cell researches all over the world to provide more qualitative and dependable results in the dental clinics.

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