

Stem Cells: Introduction and Role in Regenerative Dental Medicine

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ABSTRACT

Stem cells have been effectively segregated from an assortment of human and animal tissues, including dental pulp. This accomplishment marks advance in regenerative dentistry. The leap forward of stem cells has created new yet abnormal potential outcomes in the recovery of various organs and tissues. At present, studies and research work to know inert and capacities of stem cells and their usage in dentistry are getting to be energizing themes. In couple of years a lot's of studies and disclosures have been surrendered which demonstrates that stem cells and tissue designing are offering ascend to a different branch named "Regenerative Dentistry" that will have its own particular position in future dental practice. Stem cells will be cells with one of a kind limit with regards to self-restoration and strength. With suitable biochemical signs stem cells can be changed into attractive cells. The tooth is nature's "sheltered" for these valuable stem cells, and there is a heap of these cells in wisdom teeth, changeless teeth and deciduous teeth. The stem cells contained inside teeth are fit for recreating themselves and can be intentionally recuperated at the season of a proposed dental technique. Aside from being the most appropriate stem cells to get to, dental stem cells have extensive medical advantages in the advance of new medical therapies.

1. Introduction

Stem cells are biological cells that have two properties: self-restoration, i.e. the capacity to experience boundless cycles of cell division to replenish the cell pool, and intensity, i.e. the ability to separate into other cell types. Inferable from the cells' proliferative limit, the accessible pool of stem cells isn't lessened when cells are changed into different tissues and take an interest in the reestablishment of indispensable structures, for example, the bone marrow. A zygote is the underlying, perfect stem cell. A zygote is a totipotent cell which can form into any develop cell. Vast quantities of stem cells are seen amid fetal advancement. As the embryo develops, stem cells are continuously denied of their ability to change into different cells, and separation may happen just in a given germ layer. The embryo's ability for boundless division is safeguarded until stem cells separate into three germ layers [1].

Cells that are changed exclusively into endoderm, ectoderm and mesoderm layer cells are known as multipotent stem cells. Unipotent stem cells have the ability to form into just a single kind of cell. Stem cells found in an embryo amid fetal advancement and also placental stem cells are known as embryonic stem cells (ESC). Stem cells in the blood of adult people are known as somatic stem cells (SSC). The quantity of undifferentiated somatic stem cells stays steady in the circulation system of adult mammals, including humans [2]. This cell pool is required for the recharging of biological structures, and it must be routinely renewed all through life. To guarantee cell restoration, stem cells experience asymmetric division. One of the subsequent cells holds the properties of the mother stem cell and experiences asymmetric division, while the other cell is changed into a specific cell. The cell's self-restoration potential winds up constrained upon specialization. Asymmetric division produces tremendous

quantities of stem cells that frame tissues and organs all through a living being's life and assurance its self-reestablishment limit. In adult humans, stem cells are available in tissues, for example, bone marrow, dental pulp, nervous tissue and skin, and organs, including the liver, heart, pancreas, bones, kidneys and retina. Endeavors are made to utilize stem cells in the repair of damaged heart muscle and pancreatic islets, in the treatment of Alzheimer's infection, Parkinson's ailment etc. Stem cells are likewise a promising instrument for dental reconstruction and regeneration [3].

Characteristics of Stem Cells

1. Totipotency: Property of a cell to differentiate into both embryonic and extra embryonic tissues. For example Zygote is a totipotent cell.
2. Pluripotency: Property of a cell to differentiate into embryonic tissue only (Somatic cells and germline cells). They cannot form extra embryonic tissue. e.g.- Embryonic stem cell.
3. Multipotency: These cells differentiate into cells of their lineage. e.g.- hematopoietic stem cells.
4. Unipotency: (committed begetters): These cells deliver one specific cell type.

Stem Cell Properties

A great stem cell ought to have two properties to be specific self renewal and potency.

➤ Self-renewal is the capacity of the cell to experience various cycles of cell division keeping up the undifferentiated state [4]. A perfect stem cell ought to have the capacity to multiply to around 40-60 populace doublings before it accomplishes senescence.

➤ Potency implies the differentiation capacity of the stem cell.

Types of Stem Cells

Stem cells are of following types:

1. Embryonic stem cell
2. Adult stem cell
- ✓ Hematopoietic stem cell
- ✓ Mesenchymal stem cell
3. Induced pluripotent stem cell

Embryonic stem cell: Embryonic stem cells are fit for multipotential differentiation yet clinical practicality is restricted because of moral issues. The internal cell mass (the part that would shape baby) of the embryo is utilized to frame embryonic cell lines. Embryonic stem cells can possibly separate into germ layers specifically ectoderm, endoderm and mesoderm. Tumorigenesis is normal with embryonic stem cells [5].

Adult stem cell: Adult stem cells are multipotent stem cells. They have been gathered from various sort of tissues like bone marrow, umbilical cord, amniotic fluid, brain tissue, liver, pancreas, cornea, dental pulp, and adipose tissue. Adult stem cells are relatively less demanding to confine and don't have any moral issues. Insusceptible dismissal and teratoma arrangement is likewise uncommon with adult stem cells. Adult stem cells are regularly utilized as a part of current day rehearses.

Induced pluripotent stem cell: Induced pluripotent stem cells (IPS) is a developing idea in which 3– 4 qualities found in the stem cells are transfected into the contributor cells utilizing proper vectors. The stem cells along these lines will have properties relatively like embryonic stem cells. This way breaking revelation may have a noteworthy part in future stem cell therapy [6].

Sources of Stem Cells

There are numerous potential sources for stem cells

1. Embryonic stem (ES) cells received from the inner cell mass of a blastocyst from a 4 or 5 days old embryo.
2. Embryonic germ (EG) cells received from fetal tissues at a somelater phase of advancement (from an area called the gonadal edge) [7].
3. Adult stem cells received from develop tissues and are found in adult tissues. They act as a repair system for the body, renewing specific cells, yet in addition keep up the typical turnover of regenerative organs, for example, blood, skin, or intestinal tissues

The advancement of mouse ES cells in 1981 gave the world a view that it can be a significant part of the innovation, for the improvement of human ES cells; however the idea of a pluripotent embryonic cell is far more seasoned than that. As human ES cells can create most, if not all, the separated cell types in a human body, they may give boundless cell resources to cell therapy. Be that as it may require detailed examinations for better understanding of human ES cell properties before they could be utilized as a part of the clinical applications. In 1992, Brigid Hogan and her partners detailed the immediate inference of EG cells from mouse primordial germ cells. These EG cells have a formative capacity,

fundamentally the same as that of ES cells, however they vary in their appearance of some engraved qualities. The mouse ES cell gives a benchmark to the non specific prerequisites for ES cells. Its key highlights are these: It is isolated from a pluripotent cell populace; it is steadily diploid and karyotypically ordinary in vitro; it can be proliferated uncertainly in the crude embryonic state; it can separate immediately into various cell types illustrative of each of the 3 embryonic germ layers, both in teratomas or in vitro under suitable conditions; and it can offer differentiation to any cell type in the body, including germ cells, when permitted to colonize a host blastocyst [8].

2. Different Types Of Tooth Stem Cells

Dental Stem Cells:

Dental epithelial cells:

Ameloblasts are the dental epithelial cells and derive from the stem cells of epithelial origin. These cells form enamel and lost immediately after the tooth eruption. Thus these do not exist in the permanent tooth and cannot compensate for the tooth wear and tear.

Dental mesenchymal stem cells:

These cells are multipotent and can proliferate & differentiate into variety of cells depending upon the requirement. Dental mesenchymal stem cells were first identified by Dr. Friedenstein and his associates in the bone marrow [9]. Specific properties of these cells include their osteogenic potential, their ability to adhere to tissue culture surface and similarity in morphology with fibroblasts. These cells can further be subdivided into various groups. Such as:

- a) Stem cells from Human Exfoliated Deciduous tooth (SHEDs) [10]
- b) Dental Pulp Stem Cells (DPSCs) [11]
- c) Periodontal Ligament Stem Cells (PDLSCs) [12]
- d) Dental Follicle Stem Cells (DFSCs) [13]
- e) Stem cells from the dental Apical Papilla (SCAPs) [14]

3. Use Of Stem Cells In Dental Tissue Engineering And Regenerative Medicine:

Stem cells from Human Exfoliated Deciduous tooth (SHEDs)

SHEDs were first isolated by the Miura M et al. in 2003. They collected these cells from the deciduous incisors of 7 year old kids and came up with the conclusion that SHEDs can differentiate into various cells such as: odontoblasts, osteoblasts, adipocytes and few neuro like cells too. In contrary to those cells which are received from the permanent teeth (DPSCs) SHEDs transplantation in mice successfully produced dentin and bony tissues. Reason behind the utility of SHEDs in comparison to DPSCs is that they have different developmental processes, function and structure of tissues than the adult mesenchymal stem cells which allows them to be utilized for various functions.

Several studies in the literature suggests the use of SHEDs in the dental engineering regenerative techniques. Cordeiro et al conducted a study and concluded that these cells are potent source for the repair of damaged teeth and for the bone tissue formation [15].

Dental Pulp Stem Cells (DPSCs)

The entire reconstruction of lost crowns brings the most astounding expectations up in regenerative dentistry. Endeavors are made to utilize DPSCs to incite the reaction of mesenchymal stem cells. The dental epithelium first structures a tooth bud (germ) which instigates tooth development. Next, the dental epithelium multiplies strongly to shape a structure with a top like appearance. The enamel tie, which involves the external and internal enamel epithelium, stratum intermedium and stellate reticulum cells of the enamel organ, does not multiply amid the above procedure. Tooth buds are clusters of thick, multiplying tissue in the oral epithelium. Ectomesenchymal cells of the dental papilla total beneath the enamel organ [16]. The dental follicle is framed outside the enamel organ and the dental papilla, and it is in the end changed into periodontal tissue.

In physiologically created teeth, the enamel shaped by the epithelium is the main completely mineralized tissue. Epithelial tissues don't have regenerative capacities. Tooth areas framed from the mesenchyma have a specific capacity for self-renewal, most likely because of the nearness of stem cells.

Societies of pulp cells got from early creating dental root tissue and pulp tissue can separate into odontoblasts. The above perception negates the past conviction that dentin-framing cells create from osteoblasts. Dental pulp cells have stem cell properties, and they can offer ascent to, for instance, new pulp-like tissues. Dental pulp stem cells add to the advancement of connective tissue required for tooth recuperation. Dental pulp is the source of mesenchymal stem cells. In 2011, dental pulp stem cells were detached from transgenic mice to improve our understanding of these cells' biological properties. Cell societies uncovered the nearness of assorted cell populaces with mesenchymal cell markers normal for embryos. Following two weeks of in vitro culture, the cells started to separate towards adipocytes, chondrocytes and bone cells. The most recent research discoveries (2011) recommend that adipose tissue-determined stem cells (ADSCs) are a more productive source of stem cells for dentin regeneration. Rabbit ADSCs are likewise described by more exceptional development and higher opposition than DPSCs.

Periodontal Ligament Stem Cells (PDLSCs)

Periodontal ligament is a connecting fibrous element between the tooth and alveolar bone and it keeps the tooth firm in the alveolar socket. Stem cells from the periodontal ligament can be isolated from the extracted tooth or accidentally avulsed teeth. These cells have the capacity to differentiate into tissues such as cementum, and alveolar bone [17]. In vitro these can also be differentiated into osteoblasts, adipocytes, chondrocytes [18].

When stem cells from PDL were transplanted in mice they induced formation of structures such as bone, cartilage, periodontal ligament and cementum. Where as in pigs, these cells differentiated and cured various periodontal lesions. In one study these cells were combined with stem cells from the dental apical papilla and they regenerated the whole root and periodontal ligament complex and helped in restoring the normal function of a tooth [19]. Another study was conducted

by Orciani et al and they demonstrated that transplantation of these cells along with nitric oxide can also be used to cure different periodontal lesions [20].

Dental Follicle Stem Cells (DFSCs)

For the regenerative therapies and reconstructive treatments mesenchymal stem cells from the dental follicle are mainstay. Dental follicle surrounds the developing tooth and gives rise to cementum, alveolar bone and periodontal ligament.

These cells have capabilities to differentiate into multiple other cells such as adipocytes, osteoblasts, cementoblasts etc [20,21] According to a study when DFSCs transplanted into mice they regenerated the whole periodontal ligament in the duration of 4 weeks [22].

Stem cells from the dental Apical Papilla (SCAPs)

SCAPs are isolated from the dental papilla. Dental papilla differentiates and gives rise to dental pulp. Important source for SCAPs isolation is maxillary third molar. These cells can be differentiated into various other cells such as osteoblasts and odontoblasts [23, 24]

In regenerative therapies SCAPs are particularly useful in revascularization. Transplantation of these cells and stem cells from the periodontal ligament along with hydroxyapatite differentiates into cementum, dentin and Sharpey's fibers. This experiment proves that utilization of various stem cells in different combinations can differentiate into complete attachment apparatus and support tooth structure [19].

4. Clinical Trial Of Stem Cells

Over decades several attempts have been made to do the whole tooth reconstruction by using stem cells. Some of these were performed on various animals such as mice and few were done in humans.

In 2007, Nakao et al successfully achieved the tooth formation in the mouse mandible. They used both epithelial and mesenchymal stem cells and then put these on the collagen bed and implanted in the mouse's mandibular tooth socket. This biologically engineered arrangement of the epithelial and mesenchymal cells differentiated into structurally correct sequence of all the various tooth layers and formed enamel, dentin, pulp, periodontal ligament, alveolar bone [25].

In 2009, another study was conducted and it achieved the similar results as in Nakao study. Here successful functional tooth transplantation was done in the mouse oral cavity. One tooth was extracted and then bioengineered tooth was transplanted after a healing period of 3 weeks in the tooth socket. This bioengineered tooth responded favorably to the hardness required for chewing and to the orthodontic forces too. It responded to the thermal stimuli in the similar ranges to the natural tooth [26].

5. First Dental Tissues Clinical Trial In Humans

First dental tissues engineering model was presented by d'Aquino et al in 2009. They conducted their research on the human subjects with third molar extraction and then restoration of bone loss in the mandibular bone with the implantation of

Dental Pulp Mesenchymal Stem Cells with the carrier of collagen bed. Researchers used panoramic radiographs to determine the extent of bone loss after third molar extraction and found that at least 1.5 mm of bone loss is evident distal to the second molar after third molar extraction. This happens because of slow bone repair after extraction which eventually causes the loss of adjacent second molar.

They isolated the DPSCs from the extracted maxillary third molars and cultured for 21 days. To detect the protein markers on the surface of DPSC's flow cytometry was used and finally they placed these isolated cells on the collagen bed and transplanted on the extraction site of the mandibular molars.

Periodic evaluation of the extraction site revealed higher rate of mineralization and cortical bone formation. There was no inflammation and functionality was also restored. Histological and immunofluorescence analysis revealed well vascularized bony structure with developed haversian system. Bone morphogenic protein and endothelial growth factors were also present in abundance[27].

This study successfully provides evidence of first dental tissue engineering clinical trial in humans with satisfactory level of bone regeneration in the extracted molars site and restoration of periodontal tissues.

6. Pros Of The Stem Cell Therapy

- ✓ It offers a great deal of medical advantages in the therapeutic divisions of regenerative medicine and cloning.
- ✓ It demonstrates extraordinary potential in the treatment of various conditions like Parkinson's disease, spinal cord injuries, Alzheimer's disease, schizophrenia, cancer, diabetes and numerous others.
- ✓ It enables the specialists to find out about the development of human cells and their advancement.
- ✓ In future, the stem cell research can enable the researchers to test various potential medicines and medications without completing any test on animals and humans. The medication can be tried on a populace of cells specifically.
- ✓ The stem cell therapy additionally enables specialists to contemplate the formative stages that can't be known straightforwardly through the human embryo and can be utilized as a part of the treatment of various birth defects, and pregnancy misfortunes. A

higher understanding will permit the treatment of the irregular improvement in the human body.

- ✓ The stem cell therapy puts into utilization the cells of the patient's own particular body and henceforth the danger of dismissal can be decreased on the grounds that the cells have a place with a *similar* human body.

7. Cons Of The Stem Cell Therapy

- ✓ The long haul symptoms of the therapy are as yet obscure.
- ✓ The disservice of adult stem cells is that the cells of a specific type would produce cells just of that compose, similar to brain cells would create just brain cells and so on.
- ✓ If the cells utilized as a part of the therapy are embryonic then the disservice is that the cells won't be from a similar human body and there are odds of dismissal.
- ✓ The stem cell therapy is still under the procedure of research and there are various things that should be set up before it is utilized as a treatment line.

8. Conclusion

Amid late decades, a few stem cell lines with critical changeability in potency have been secluded from human adult teeth. Impressive heterogeneity exists between singular cells confined from a similar dental stem cell pool that may influence the clinical results. Hence, the ID and refinement of stem cell subpopulations with enhanced potency is an important advance before utilization of cell-based treatment in dental centers. Notwithstanding the decision of dental stem cell populaces, an assortment of variables, for example, the injury size and profundity, wellbeing status of the encompassing tissues, and in addition the delivery techniques are likewise prone to affect on the accomplishment of therapy. The future dentistry will be a greater amount of regenerative based, where patients claim cells can be utilized to treat diseases. Stem cell therapy has a fundamental part as a future treatment modality in dentistry. Regenerative dentistry should run in pace with regenerative medicine. Then again, stem cells ought to be separated to the fitting cell types before they can be utilized clinically, else it may prompt pernicious impacts. Deciding the part of nearby conditions, for example, the kind of framework and the nearness of the microorganisms ought to be deliberately investigated. Longer patient follow up is expected to think about the existence time of recovered tissue.

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