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Stem Cells- A Revolution in Regeneration of the Periodontium: A Review Article

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Abstract

Stem cells are those units of the living organism that regenerate not just tissues but also organ systems. Their application is bringing about a revolution in the therapeutic world. It will eliminate the drawbacks that older reparative procedures hold. Graft rejection and complications as such are out of question with stem cell therapy. This regenerative therapy is soon to be the future of the therapeutic world. Periodontium comprises of bone, cementum and periodontal ligament making it a complex framework. Regeneration of this becomes a challenge. Stem cell therapy brings a whole new platform to the regeneration of this complex apparatus.

Keywords: Culture, Mesenchymal Stromal Stem Cells, Regeneration

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1. Introduction

Stem cells are known to be undifferentiated cells which can be stimulated to divide into specific cell. Stem cells, the natural units which are obtained from the embryonic development and tissue regeneration. They can cure disastrous diseases and this is summoned to be as one of the greatest leaps regarding therapeutic prospects in medical sciences.

The usage of cell-based therapy in treatment of destructive diseases is often referred to as *regenerative or reparative medicine.* Multicellular organisms possess these cells.

Periodontium, a complex structure, comprises the periodontal ligament, cementum and bone. Destruction of all or any of these structures leads to periodontal diseases. Research says that among the most prevalent health conditions worldwide, periodontal disease ranks sixth,[1] making periodontal health a vital issue in concern to public health. Hence, evolution of therapies to overcome this has become the utmost aim for the scientists.

2. Historical Background

1981: Evans and Kaufman gave hope to a new era by obtaining embryonic stem cells of mouse from the Inner Cell Mass (ICM) of its blastocysts[2].

1994: Human blastocysts inner cell mass was maintained in cultures and most of the cultures retained a morphology similar to stem cells[2].

1998: James Thomson and his team used the ICM of human blastocysts and suggested methods of deriving and maintaining embryonic stem cells that couples undergoing treatment for infertility donated[3].

2002: Neurons that produce dopamine from embryonic stem cells were derived by using an animal model with Parkinson's disease[4].

2003: Miura et al used human teeth and identified the multipotent stem cells.

SHED was familiarized. (Stem cells from human exfoliated deciduous teeth)[5].

2004: Seo and his team reported that human Periodontol ligament possessed multipotent stem cells[6].

2005: Saito et al developed bovine cementoblast cells[7].

3. Characteristics

Totipotent: Totipotent refers to total potential. A fertilized egg is totipotent, meaning that it has the ability to developinto various kinds of cells[8].

Pluripotent: These can form all types of cells but the ones needed to develop a fetus are exceptional[8].

Multipotent: They have the capability of maturing into multiple germ layer cells[8].

The two important characteristics of stem cells are *self-renewal* and *differentiation potential*.

Self-renewal denotes renewal of the cells through mitosis, irrespective of their span of inactivity. Differentiation of the cells into phenotypes of variable kinds is what is referred to as *differential potential*. The possession of these qualities allows for proliferation and regeneration of stem cells at sites with missing or compromised tissues. [8]

4. Types

They categorize majorly as:

- Embryonic stem cells.
- Adult stem cells (tissue stem cells).

Embryonic Stem Cells: It is defined by its origin. A realm of dividing cells is called a blastocyst. They are obtained from the embryo at a very early stage of development[8].

Human embryonic stem cells bring our imagination into reality because they are immortal and have an almost unlimited developmental potential. They are able to form every kind of cell[8].

Derivation of Embryonic stem cells was first reported in 1981[2,9].

These cells are grown by tissue culture methods.

Adult Stem Cells: These cells are discovered in every part of the body. They are undifferentiated cells. They develop and multiply by the cell division process(mitosis) and regenerate the mutilated portion. They are also referred to as the somatic stem cells[8].

The chief task of adult stem cells in a living being is maintenance and repair, whenever there is injury or disease to the tissues in which they reside[8].

Adult stem cells have the key features just as the other stem cells do. First, the property of self renewal. Secondly, they give rise to fully grown cell types having distinct morphologies with particular functions[10].

The culture and reintroduction of the patients own cells into the patient reveals the most supreme usage of stem cells. The reason for this utility to be sublime is the usage of the patients own adult stem cells would not allow for the biggest complication that is rejection by the host. Immune rejection is a vital issue for which only immune suppressive drugs help circumvent[10].

There is evidence that hematopoietic stem cells (the blood forming cells in bone marrow) could form cells originating from a completely different tissue, such as nerve cells. The term *plasticity or trans differentiation* describes this unique ability of stem cells[1].

The adult stem cells lcells exist in both juvenile animals and adults while it is not the same with the embryonic cells.

Types:

- Hematopoietic stem cells: These are obtained from the bone marrow and the umbilical cord.
- Mammary stem cells: supports mammary gland growth.
- Intestinal stem cells: they are inhabitants of the *crypts of Lieberkuhn.*
- Mesenchymal stem cells: their origin is stromal and differentiate into a various tissue kinds. These cells can be derived from, lung, adipose tissue, bone marrow and blood, Wharton's jelly from umbilical cord, teeth (dental pulp and periodontal tissue) and placenta.
- Endothelial stem cells: one of the three types of multipotent stem cells found in the bone marrow.
- Neural crest stem cells: present in hair follicles. Similar cells noticed in the GIT, sciatic nerve, cardiac outflow tract and spinal and sympathetic ganglia.
- Neural stem cells: adult neurogenesis is particularly seen only in the sub ventricular zone and the dentate gyrus of the brain. Neural stem cells and hematopoietic stem cells (HCSs) have many similar properties. Reseacrches reveal that the cells derived from the neurospheredifferentiate into many other cell types appertaining to the immune system.
- Olfactory adult stem cells: found in the lining of the nose. They participate in the olfactory sensations.
- Testicular cells:These cells are a derivative of the spermatogonial cells which belong to the testicles. The cells extracted from humans is called as human adult Germline Stem Cells (GSCs)[10].

5. Mesenchymal Stem Cells from the Oral Cavity

Mesenchymal stem cells of dental origin have been proved to be very useful in regeneration of the damaged tissue[11].

Human pulp tissue was the first location in the oral cavity from where the dental stem cell was first isolated. The term specified for these cells was *postnatal dental pulp stem cells*. Other mesenchymal stem cells-like populations of dental origin are periodontal ligament, exfoliated deciduous teeth, apical papilla of developing teeth and dental follicle precursor cells[11].

The characteristics of bone marrow and oral stem cells are comparable. Dental stem cells show more affinity towards odontogenic development than to osteogenic development. These cells manifest differentiation into neurogenic linages[11].

5.1 Dental Pulp Stem Cells

Dental pulp stem cells are obtained from pulp tissue of permanent third molars. The pulp tissue undergoes enzymatic digestion[10,11].

Dental pulp stem cells fall under the multipotent category and they can proliferate to undergo cryopreservation. Immunosuppressive properties and the express markers such as, CD13, CD29, CD44, CD59, CD73, CD90, CD105, CD146 and STRO-1 are also found in the cells[11].

Fibroblastic properties were manifested in the cells gained from explants of third molars. The prime property of dental pulp stem cells is that they are capable of differentiating into odontoblastic lineages which are signified by polarized cellular bodies and mineralized nodules[10,11].

The diversity of cell lineages that the dental pulp stem cells differentiate into are odontoblasts, osteoblasts, chondrocytes, adipocytes, myocytes, melanocytes, neurocytes, corneal epithelial cells and including induced pluripotent stem cells[10,11].

5.2 Stem Cells from Human Exfoliated Deciduous Teeth

The pulp of the human exfoliated deciduous teeth could be a tremendous source from where stem cells can be isolated. The potentials of these isolated cells include induction of dentin and bone formation and *in vitro differentiation* into non-dental mesenchymal cell derivatives. Their form, shape and structure are comparable to the dental pulp stem cells. Various cells, such as the neural cells, osteoblasts, chondrocytes, adipocytes and myocytes can be differentiated from these stem cells. They showed formation of ectopic - like tissue in vivo, but dentin-pulp nexus regeneration still remains a task[11].

5.3 Stem Cells from the Apical Papilla

Apical papilla points out to soft tissue located at the apex of the developing permanent teeth[10].

Apical papilla can otherwise be defined as the precursor of the radicular pulp. They can either be derived from explant cultures or through enzymatic digestion of the apical pulp tissue. These cells have shown to demonstrate mesenchymal markers[11].

These cells exhibit potential for osteogenic, dentinogenic, neurogenic and adipogenic differentiation. In addition, they can induce root formation[11].

5.4 Stem Cells from the Periodontal Ligament

Sandwiched between the bone and the cementum is the periodontal ligament. The cell populations present here are capable of differentiating into a variety of cells namely cells that produce cementum, cells forming bones and cells that make collagen. *In vitro* they can differentiate into adipogenic, osteogenic and chondrogenic cells. Alveolar bone regeneration can be achieved as well[11,12].

Expression levels of scleraxis was examined by Ser et al. Scleraxis is a transcription factor which is specific for tendons. This is seen in Periodontal ligament stem cells. The levels of scleraxis revealed a higher score in the periodontal ligament stem cells when in comparisonwith the levels in bone marrow stem cells[12].

5.5 Stem Cells from Human Gingiva

Differentiation into adipogenic, osteogenic and chondrogenic linages was induced[11].

Storage of Dental Stem Cells:

- Cryopreservation[13]
- Gentamicin-Saline[13]
- Controlled - rate freezing (5% DMSO)[13]

6. Stem Cells in Periodontics

Stem cells possess incredible potential to give rise to a wide range of cells in the body. Progress towards peri-

odontal regeneration has taken a phenomenal turn when stem cells were discovered and they were isolated from the periodontal ligament[14].

The highly fibrous and vascular tissue of the periodontal ligament has a very high turnover rate in the body. Populations of progenitor cells within the periodontal ligament appear to be enriched in locations adjacent to blood vessels and exhibit classical cytological features of stem cells[15].

The concept that stem cells may reside in the periodontal tissues was first proposed almost 20 years ago by Melcher[15]. The periodontal ligament stem cell cultures exhibited 30% higher rates of proliferation compared to the growth of cultured bone marrow stem cells.

Studies Using Stem Cells in Periodontal Regeneration Therapy

1. Defects of Class III furcation were created through surgery and these defects were treated using Autologous Bone marrow stem cells. The animal model used was Beagle Dog. Collagen gel carrier was the method of cell delivery. Although the test group revealed new bone, new cementum and new PDL formation, the complete regeneration of the defects was not observed[16]. The newly derived cement oblasts, osteoblasts and fibroblasts were observed in the labeled Bone Marrow Stem Cells[17].
2. Autologous Cryopreserved Bone Marrow Stem Cells were helpful in repairing surgically created fenestration defects. The animal model were Beagle dogs. The carrier was collagen sponge. New bone, cementum, and PDL fibre formation were substantially higher in both groups - Cryopreserved and non - Cryopreserved Bone marrow stem cells compared to that of the group with the carrier alone[1,18].
3. Allogenic Bone Marrow Stem Cells were used in Periodontal defects created by wire bound around teeth and by the inoculation of P. gingivalis in Sprage Dawleyrats. 0.9% NaCl solution was used to deliver the cells using local injection. Pro-inflammatory factors were inhibited, and enhancement periodontal tissue regeneration was observed[19].
4. Ex vivo Autologous Bone Marrow mesenchymal stem cells were created through replication of defective adenovirus. These stem cells were able to express the BMP 2 Gene and Pluronic F 127, which in turn was used in the regeneration of periodontal ligament attachment apparatus. This technique regenerated cementum with the insertion of their principal fibres, the Sharpey's fibres. In addition, significant amount of bone was formed, re-establishing a close to normal relationship between the components of the newly regenerated apparatus, benefiting maintenance of Periodontal health[20].

7. Conclusion

The application and outcomes of stem cells in regenerative medicine prove to be remarkable. The astounding potential of these cells, lies in their pliability and ability of differentiating into different cell strains, thereby being a cellular architect leading to the restoration of the other missing and damaged tissues.

Now that the adult human stem cells present in the periodontal ligament have been identified, their application in the clinical trails is the next step in the development of therapeutic potentials[5].

Although use of stem cells has unlimited applications, there are still significant challenges that ought to be curbed in order to gain the entire benefits of stem cell therapy. A little more research and application of this regenerative medicine would enable rejection-free transplants and bring an astounding change in the therapeutic world.

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