STEM CELLS: A PROMISING TOOL IN DENTISTRY

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Abstract
Stem cell research is aimed towards using one's own cells for repairing that part of the body which has become affected due to a particular disease. Advances in tissue engineering have been used for periodontal treatments and dental implant applying stem cell research. Dental field has a revolutionary achievement marked by the use of dental stem cells to generate a physiological anchorage of dental implants to the adjoining alveolar bone. For periodontal disease guided tissue regeneration is a recent advancement in stem cells therapy.
Keywords: Regeneration, Replacement, Stem Cells.

Introduction

A major health care problems faced all over the world by medical and dental health care professionals is tissue loss or organ failures. Mechanical devices or artificial prostheses are currently used as alternatives, which replace the tissue or organ but the original function is not restored and hence causes the loss of integrity of host tissue. Moreover, these artificial prosthesis or mechanical devices may perhaps bring an inflammatory response in the host when worn for long-term implantation.[1]

Stem cells are the cells with an ability to self-replicate and differentiate into at least two different types of cells. Both these conditions are mandatory, for a cell to be called as stem cell.[2] These cells also have a capability to regenerate and repair tissues like bone, dentin, tooth, skin, cartilages, adipose tissues, and glands. Scientists reported that the temporary teeth that children starts losing near their fifth - sixth birthday i.e. "baby" teeth have a rich supply of stem cells in the dental pulp.[3]

Stem Cells

These are unspecialized cells present in the human body with a capability of becoming specialized cells, carrying new specialized cell functions.[4]

A cell that can continuously generate unaltered daughters and also have a capability to produce daughter cells with different, more restricted properties.[5] (Figure 1)

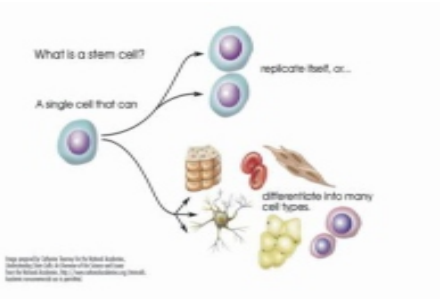

Figure 1: Characteristics of stem cells

Unique Properties of Stem Cells

1. They are unspecialized cells.
2. They have ability to divide and renew themselves for long periods.
3. They can produce specialized cells.
4. They can divide either symmetrically or asymmetrically.
5. Adult stem cells inhabit in a specific area called stem cell niches.[6, 7]

Classification of Stem Cells

Based on their source [8]
Based on their potency [9]
Based on their growth stage [10]
Based on their origin [4]

I. Based on their Source

- **Autologous stem cells**: Cells obtained from and implanted in same individual.
- **Allogenic stem cells**: Cells that originate from a donor of same species.
- **Xenogenic stem cells:** Cells obtained from donor of other species.[8]

II. Based on their Potency

Potency means the capability of the stem cell to differentiate into several different types of cells.

- **Totipotent stem cells** (toti means whole, potent means able to):
  These cells have a capability to construct a complete and viable organism.
- **Pluripotent stem cells** (pluri means several, potent means able to):
  These are true stem cells. They have a potential to make any differentiated cell of the body.
- **Multipotent stem cells** (multi means many, potent means able to):
  They can differentiate into a number of cells, but only to the family of cells which are closely related.

- **Oligopotent stem cells:**
  They have a differentiation potential to differentiate into only a few cells, such as lymphoid or myeloid stem cells.
- **Unipotent cells**:
  They have capability to produce only one cell type i.e. their own, but carry the property of self-renewal. This property distinguishes them from non-stem cells.[9, 11, and 12]

III. Based on their Growth Stages
Stem cells can be broadly categorized as
1. Embryonic stem cell
2. Adult stem cell
   - Mesenchymal stem cell
   - Hematopoietic stem cell
3. Induced pluripotent stem cell.[10]

IV. Based on t heir Origin
Based on their source of origin, stem cells can be classified in to four different types:
- Stem cells from Embryos
- Stem cells from the Fetus
- Stem cells from the Umbilical cord
- Stem cells from the Adult. [4]

The embryonic stem cell has its origin from blastocyst, one of the earliest stages of the development of the embryo. They are derived from the inner cell mass of the blastocyst, before its implantation in the uterine wall.[13]

Fetal Stem Cells can be obtained from two distinct sources; one is the fetus proper and second is the supportive extra embryonic structures. Wharton's jelly, Amniotic fluid (AF), placenta and amnion have all generated putative stem cells.[14]

An adult stem cell is considered to be an undifferentiated cell, which is found among differentiated cells within a tissue or organ that can renew it and can differentiate to produce some or all of the most important specialized cell types of the tissue or organ. In the 1950s, it was discovered that at least two kinds of stem cells are found in the bone marrow.
- One population, which forms all the types of blood cells in the body called hematopoietic stem cells.
- Second population was discovered a few years later called bone marrow stromal stem cells (also called skeletal stem cells, or mesenchymal stem cells by some).

Adult stem cells have been isolated from many tissues and organs, including skeletal muscle, brain, bone marrow, skin, heart, liver, gut, teeth, blood vessels, ovarian epithelium, and testis.[15]

Induced Pluripotent Stem Cells

The iPSCs resembles to embryonic stem cells in terms of their morphology, gene expression, cell behavior, differentiation potential and epigenetic status both in culture and in vivo.[16] iPSCs are adult cells that have been genetically reprogrammed to an embryonic stem cell state by being enforced to express factors and genes essential to maintain the defining properties of embryonic stem cells. iPSCs seems to be a useful tools for modeling of diseases and drug development, and scientists are planning to use them as transplantation medicine.[15]

Stem Cells of Dental Origin
Stem cells can be derived from various oral tissues (Figure 2):

1. Stem cells for pulp of human exfoliated deciduous teeth (SHED)
2. Dental pulp stem cells (DPSCs)
3. Dental follicle derived stem cells (DFSCs)
4. Periodontal ligament derived stem cells (PDLSCs)
5. Stem cells of apical papilla (SCAP)
6. Salivary gland derived stem cells (SGSCs)
7. Gingiva derived mesenchymal stem cells (GMSCs)
8. Periosteum derived stem cells (PSCs)
9. Oral epithelium derived stem cells (OESCs)
10. Tooth germ progenitor cells (TGPCs)
11. Bone marrow derived stem cells (BMSCs).[17]

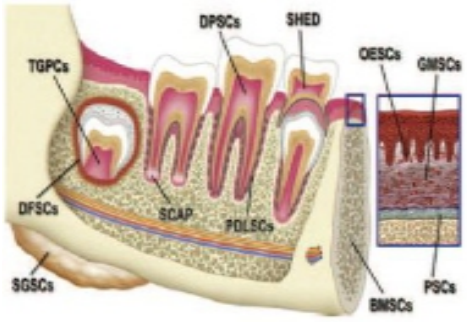

Figure 2: Stem Cells of Dental Origin

Dental Pulp Stem Cells (DPSC)
DPSC are mesenchymal stem cells isolated from the dental pulp of permanent teeth. They are generally isolated from permanent third molars and show signs of high proliferation and colony formation producing calcified nodules.[18] DPSCs have a potential to differentiate into endothelial cells leading to generation of functional blood carrying blood vessels.[19]

Stem cells from Human Exfoliated Deciduous teeth (SHED)
These are the mesenchymal stem cells which are principally derived from the dental pulp of exfoliated deciduous teeth so they are termed as Stem cells from Human Exfoliated Deciduous teeth (SHED)[18]. These cells did not grow as individual cells, but grow as clustered into colonies and on separation, grow as individual

fibroblast-like cells.[20] SHED cells can arouse dentin or bone formation *in vivo*.[21]

Dental follicle derived stem cells (DFSCs)

The Dental Follicle is a loose connective tissue sac which is derivative of ectomesenchymal tissues. It is found surrounding the developing tooth and plays different roles during the life of a tooth. DFSCs can be easily isolated from impacted teeth. Human DFSCs have a feature to adhere to plastic and forming colonies *in vitro*. DFSCs carry osteogenic differentiation capacity. DFSCs also have the potential to differentiate into neural cells.[22]

Periodontal ligament derived stem cells (PDLSCs)

Mesenchymal stem cells isolated from the periodontal ligament are termed as Periodontal ligament derived stem cell (PDLSC).[18] These are multi- potent cells with features resembling to BMSCs and DPSCs, competent in developing different types of tissues like bone and tooth associated- tissues.[23] PDLSCs have the capacity to generate cementum and periodontal ligament like structure thus contributing in repair of periodontal tissue. PDLSC can differentiate into cementoblasts like cells, collagen forming cells and adipocytes.[24]

Stem cells from the Apical Papilla (SCAP)

Mesenchymal stem cells isolated from the apical part of roots of developing tooth are termed Stem cells from the Apical Papilla (SCAP).[18] SCAP are easy to get as they can be taken from human third molars.[25]

Current and Future Scope in Dentistry

The regenerative ability of stem cells isolated from different sources including oral tissues has been of great interest for the clinicians. Research is mainly directed towards achieving:

- Regeneration of damaged coronal dentin and pulp
- Regeneration of resorbed root, cervical and apical dentin and repair perforations.
- Regeneration of periodontium
- Replacement and Repair of bone in craniofacial defects and
- Whole tooth regeneration.[26]

Regeneration of enamel

Neural crest cells (NCCs) are a multipotent embryonic cell population which contribute developing enamel organ and enamel formation. It was found that NCC-derived cells add to the four cell types present in the enamel organ i.e. stellate reticulum, inner enamel epithelium, outer enamel epithelium, and stratum intermedium, during histo-differentiation of tooth development.[27]

Regeneration of dentine

DPSCs were implanted into immune-compromised mice along with hydroxyapatite-tricalcium phosphate, they produced a dentin-like structure with collagen fibres running perpendicular to the mineralizing surface as is found *in vivo*, and contained dentin sialo-phosphoprotein, a dentin-enriched protein. This newly formed dentin was also lined with human odontoblast like cells.[28]

Regeneration of pulp

The pulp tissue is vascularised, innervated and serves as a source of stem cells. These characteristics enable the pulp to play a significant role in formation of reparative dentin and homeostasis. Dental pulp tissue regeneration has been explored using some biomaterials, where pulp cells grown on poly-glycolic acid (PGA) formed pulp-like tissue in both *in vitro* and *in vivo* models .[29,30]

To regenerate pulp tissue in an empty root canal space, pulp stem cells were implanted into a scaffold and inserted into the canal space. The canal content was totally removed and the cnal was enlarged to 1–3 mm in diameter and one end of the canal opening was sealed with MTA cement. Three-four months later, it was observed that the emptied canal space was filled with a good quality of vascularised pulp-like tissue. Moreover, canal dentin wall was lined by a newly generated dentin-like layer having uniformed thickness as well as onto the MTA cement.[31,32]

Whole tooth regeneration

The ultimate goal in dentistry is to replace the naturally lost teeth biologically; in essence, a cell-based implant rather than a metal one. To sum up the entire process of tooth regeneration via stem cells, currently under experimentation follows the triad of tissue engineering that includes:

STEP I: Stem cell isolation and identification

STEP II: Culturing stem cells along with scaffold materials either *in vitro* or *ex vivo*

STEP III: Delivery of growth factors and transplantation into anatomical site.[33]

Regeneration and Repair of Temporomandibular Joint Defects

Temporomandibular joint disorders (TMD) can be described as myalgia, pain, headaches, and structural destruction, collectively termed as degenerative joint disease. The recent advances in stem cell technology assure the construction of a bioengineered TMJ replacement. It is a biocompatible model and is capable of withstanding the physiological loads required for this joint. Cells from various sources, including human umbilical cord matrix cells, fibroblasts, articular cartilage cells, and mesenchymal stem cells, are effectvely used in efforts to reconstruct the TMJ.[34]

Regenration of Peridontium

In dentistry, the first tissue-engineering technology was invented by in 1982 Nyman and colleagues by doing the regeneration of periodontium now called as guided tissue regeneration (GTR), which is carried out by placing a

barrier membrane under the periodontal tissue flap to stop the in development of gingival epithelium and connective tissue, which created a space on the root surface from the periodontal ligament for progenitor cells including fibroblasts, cementoblasts, and osteoblasts to move around in and budding the new periodontal structures together with periodontal ligament, cementum, and alveolar bone.[35]

Afshin K. et al conducted a study which aimed to investigate effects of dental pulp stem cells (DPSCs) on regeneration of a defect in the periodontium of a canine model. Surgically mesial 3-walled periodontal defects were created, bilaterally in the first lower premolar teeth of 10 mongrel dogs with ligature induced periodontitis. Four weeks after creation of this model, Bio-Oss combined with autologous passaged-3 DPSCs were implanted on one side as the test group and simply Bio-Oss was implanted on other side as a control. Regeneration of the periodontal defects was evaluated after eight weeks of surgery and was found that the biocomplex consisting of DPSCs and Bio-Oss would be promising tool in the regeneration of periodontal tissues.[36]

Legal Issues

There are two general basic issues related to bioethics that should be looked forward with care and separately are:

1. Therapeutic and Scientific relevance
2. Overtime cost of cryopreservation .[37]

Embryonic Stem Cells are always morally objectionable as a young human is destroyed in order to harvest the stem cells. Embryonic Germ Cells are morally objectionable while making use of cells derived from elective abortions, but can be acceptable while utilizing cells from spontaneous abortions after taking informed consent from parents. Adult Germ Cells like pluripotent stem cells derived during testicular biopsy are acceptable, going along with the informed consent from the adult donor. Umbilical Cord Stem Cells, Placentally-derived Stem Cells are morally acceptable as they have no importance after baby is delivered. Post-Natally Derived Stem Cells/ Adult Stem Cells are morally acceptable, after taking informed consent from the adult donor. Reprogramming Strategies are widely acceptable as long as the reprogramming generates a distinctly non-embryonic entity.[38]

Cell therapy is one of the advanced therapy products (ATPs), collectively with tissue engineering and gene therapy. Aspects to be keeping pace including control of development, manufacturing, and stability and discharge tests quality; some non-clinical aspects like the need for studies on cell viability and proliferation, differentiation levels and rates, bio-distribution, and time of in vivo function; and clinical aspects such as stratification risk, dose special character, and specific pharma-cyovigilance and issues associated to traceability.[37]

Conclusion

Stem cell research seems to be a very promising field with a lot of potential to generate new therapies. Mesenchymal stem cell collection and storage can be better done from a young and healthy patient. Most individuals are free from chronic diseases at a younger age so, their stem cells have undergone less cell divisions and lesser somatic mutations. Tooth-derived stem cells are readily accessible, provide an simple and minimally invasive method to obtain and preserve stem cells for future use. Banking teeth and tooth-derived stem cells is a simple, quick, cost effective and easy option for harvesting stem cells as compare to other tissues as they require invasive surgical procedures, and these does not enclose any kind of ethical problems as related to embryonic stem cell harvesting.

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