Journal of Applied Dental and Medical Sciences
NLM ID: 101671413 ISSN:2454-2288
Volume 3 Issue3 July-Sept 2017

Review Article

DENTAL STEM CELLS- ORIGIN, BANKING, ENGINEERING AND APPLICATIONS

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ARTICLE INFO

Keywords:
Odontogenic stem cells, application in dentistry and medicine, tooth banking, tissue regeneration

ABSTRACT

Stem cells are group of undifferentiated cells that can renew on its own. During the process of proliferation, the newly formed cell can remain as a stem cell or as a cell with special function. The two chief groups of stem cells are embryonic stem cells and adult stem cells. Dental stem cells are type of adult stem cells and includes stem cells obtained from Dental pulp,deciduous teeth that are exfoliated, apical papilla, periodontal ligament and dental follicle. The most important attribute of the stem cell is its ability to generate and transform into a particular type of a cell when cultured in a specific medium. Stem cells of odontogenic origin are employed in various therapeutic purpose and in tissue regeneration. Tooth banking aims at preserving the stem cells of odontogenic origin and has gained momentum in the recent past across the world. The fundamental objective of the article is to review the scientific literature on the stem cells of odontogenic origin, its clinical applications, preservation of stem cells of odontogenic origin and tissue regeneration from stem cells.

Introduction

"Stem cell" - the terminology was put forth by Alexander Maksimov in 1908. [1] Stem cells can regenerate and produce different tissues that are specialized in function. Stem cells can be totipotent or pluripotent or multipotent in nature.

- Totipotent stem cells can give rise to cells of embryonic and extra embryonic origin. Ex: fertilized egg and the Morula cells. [2]
- Pleuripotent stem cells can procreate cells of three embryonic layers – the ectoderm, endoderm and mesoderm which are derivatives of totipotent cells. [2] Ex: The cells that can form foetus arising from the inner cell mass in a blastocyst. [3]
- Multipotent stem cells can generate different group of cells that are associated to a particular tissue. Adult hematopoietic stem cells form multiple blood cells. (Red Blood cells, White blood cells and platelets). [4]

Stem cell types: There are two main groupings of stem cells that are classified based on their development

- Embryonic stem cells
- Post natal stem cells.

Embryonic stem cells (ESC): Embryonic stem cells arise from the blastula and are pluripotent. [5] The cells undergo unrestricted, symmetrical multiplications in cultures. The character of the cells derived after division resemble the original cell. Mere presence of the ESC in the inner cell mass region of the blastocyst characterizes them. [6] The pleuripotent nature of the

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embryonic stem cells are maintained by molecules like Oct 4 protein and Nanog protein. [2].

Post natal stem cells:Post natal stem cells are multipotent and are also called adult stem cells or tissue specific or organ specific stem cells. [5]These cells are present in all the body tissues. [2] Adult stem cells lack indefinite multiplication .The cells require stem cell markers and studies under experimental conditions to identify and categorize them. [6] The origin of adult stem cells include bone marrow, brain, skin, skeletal muscle etc. Studies have established the presence of stem cells even in tissues of dental origin. [7]

The main source of dental stem cells are:

1. Dental pulp (DPSC - Dental pulp stem cells)
2. Exfoliated deciduous teeth (SHED – stem cells from human exfoliated deciduous teeth)
3. Apical papilla (SCAP – Stem cells from apical papilla)
4. Periodontal ligament (PDLSC – Periodontal ligament stem cells)
5. Dental Follicle (DFSC - Dental follicle precursor cells) [8]

The dental stem cells are basically the ecto mesenchymal stem cells (EMSC) that are derived from the neural crest cells after their epithelial mesenchymal transition. The EMSC generate various craniofacial structures after their formation but some are retained in the pulp and periodontal tissues as stem cells. [9]

DPSC:

These stem cells can generate many cells like odontoblasts, muscle cells, adipocyte, chondroblast and neurons under in vitro conditions .[9] In a study with immunocompromised mice, when ex vivo expanded DPSC in combination with hydroxy apatite/TCP (Tri calcium phosphate) were transplanted it resulted in ectopic pulp – dentin like tissues.[10]

The stem cells obtained from the pulp of third molar tooth are called Dental Pulp Pleuripotent Stem cells. (DPPSCs) .The cells have exhibited positivity for various pleuripotent markers Oct 4, Lin 28, SOX 2 and Nanog. [9] The pulp of 3rd molar tooth constitutes approximately 2,00,000 to 3,00,000 stem cells are and the studies done before emphasize that stem cells can be isolated from extracted tooth until 5 days from day of extraction. [11] DPSC are isolated from pulp by size sieved isolation, stem cell colony cultivation, magnetic activated cell sorting and fluorescence activated cell sorting.[12] In a study done by Wei Wu, dental pulp stem cells obtained from teeth of diverse age group were compared and studied. The derivation efficacy and the expression of CD29 was more positive with stem cell lines obtained from teeth of younger age group. Stem cells obtained from the aged teeth groups showed increased doubling time and apoptotic cells. [13]

SHED:

Refers to stem cells obtained from the pulp of exfoliated deciduous teeth. These stem cells possess higher rate of division than the DPSCs. [14] The various mesenchymal markers that are used to identify the cells are CD44, CD90, STRO- 1, Vimentin, alpha SMA and CD 105. [15] Nerve cell, adipocyte and odontoblasts can develop from the stem cells of deciduous teeth. In tissue regeneration alveolar and orofacial bones have been produced from these cells. [14] In a study done by Werle et al, the stem cells obtained from the pulp of carious deciduous teeth were compared with the stem cells from sound deciduous

teeth. Though the amount of stem cells isolated from the carious deciduous teeth were less when compared to the sound teeth, the proliferation rate with the expression of the markers (CD 29, CD 73 and CD90) and the cells capacity to regenerate were similar in both the groups.[16]

SCAPs:

This refers to the stem cells obtained from apical papilla of immature permanent teeth. Wataru Sonoyama et al, in their study with organ cultures determined that the cells obtained from apical papilla had greater multiplication rate than the cells obtained from the pulp. [17]According to the literature, the apexogenesis process that occurs in infected immature permanent tooth could be due to the presence of the SCAP cells that escaped the infection in the apical region. [8] Various neural markers like beta III tubulin, GAD, Nestin, NeuN, NSE, GFAP, and Neurofilament M are positive in SCAPs [17]

Vanacker et al in their study illustrated that under hypoxic condition though the SCAP cells do not multiply they undergo osteogenic and neurogenic differentiation .This proves that pulp – dentin complex can be produced from these stem cells.[18]

PDLSCs:

Periodontal ligament stem cells were first obtained from impacted third molar by Seo et al. [19]The PDLSCs give rise to structures like bone, cementum and periodontal ligament.[10] The cells are known to exhibit pericyte like characters and positivity for mesenchymal markers like CD 105, CD 90 and CD73. [19]

Study by Ng TK et al compared the periodontal ligament stem cells of smokers and non-smokers and identified that the delayed periodontal tissue healing in smokers could be due to the effect of tobacco on stem cells, inhibiting its proliferation. [20]

Study on PDLSC s by Wang et al, revealed the fact that the property of PLSC depends upon the location from which it is extracted. In their study, when a-PDLSCs (PDLSC derived from alveolar socket)were compared with r-PDLSC (PDLSCs from root surface), a-PDLSC exhibited high regenerating and differentiating capacity with greater expression of mineralisation and mesenchymal stem cell markers.[21]

Stem cells from dental follicle:

The stem cells derived from dental follicle are called Dental Follicle Precursor cells and was isolated by Morsczeck et al. [22] .Under experimental conditions, the stem cells from the dental follicle are known to give rise to osteoblasts, cementoblasts, adipocytes and neuronal cells. [23] In, in vitro condition, the cells are known to form calcified nodules. [8] In a comparative study, between DFPC, SCAP and DPSC in, in vitro conditions, DFPC were noticed to form more mineralized nodules than DPSC and SCAP. Unlike DPSC and SCAP, DFPC s expressed all the three markers - aggrecan, type I and type III collagen markers in chondrocyte generating conditions. [24]

Tooth banking:

Dental stem cells have diverse clinical applications. For the same reason steps are being taken to save the tooth which is the main source of dental stem cells.

In the reviewed literature, the main steps involved in tooth banking are tooth selection, transportation, disinfection, pulp extirpation, enzymatic treatment of pulp tissue, deriving single cell suspensions, cell line

formation in mesenchymal cell medium. Cell lines formed depend upon the constituents added to it. [25]

Stem cells that are collected should be preserved well so that they can be used when required. . The 2 common methods of preservation are cryopreservation and Magnetic freezing.

Cryopreservation:

It is a method of preserving and protecting the cells in which the cells are freezed at sub-zero temperature. When liquid Nitrogen is used for cryopreservation, the temperature is maintained at less than -150 Celsius. [26] The main disadvantages associated with cryopreservation are it allows ice nucleation and crystal growth. The expansion of the crystals damages the cell wall. This is overcome with vitrification process in which the tissue is converted to glass like substance that is amorphous .Cooling and thawing rates, concentration of the substance, the sample size and the carrier system are the vital factors that influence vitrification. [27]

Magnetic freezing method:

In this method, magnetic field is used. When the tissue gets cooled uniformly, the magnetic field is removed. This snap freezes the tissue. This produces 83% increase in the survival rate of cells. [25] The basic advantage in this method is, though the tissue's freezing point is reduced by 6 to 7 degree Celsius, freezing does not occur in the tissue. [25,28] This prevents the cells from cell wall damage and the nutrient damage due to ice expansion and capillary action that normally occurs in regular freezing methods .[28]

The advantages associated to Dental stem cells are, they can be preserved for a longer duration. The cells have good plasticity and workableness with growth factors. [29] The main benefits associated with SHED banking are, the stem cells can serve as autologous transplant and can be used amidst relatives. The procedures associated with it are also simple and harmless. [30]

Tissue regeneration:

Dental stem cells are used in tissue regeneration. The stem cells obtained from pulp are appropriate for dentin and pulp regeneration. Scaffold is biodegradable polymer material that is used in tissue engineering to provide a 3D environment for the cells to grow [31] Scaffolds are in injectable and castable forms. Injectable forms are the low viscosity gels that can be shaped well and castable forms are the rigid and custom made. In pulp tissue regeneration the former scaffolds are used as the canal space is less and confined presenting variegated structure in the apex .[32]According to the literature, experiments on regeneration of pulp like tissue in immunocompromised mice have been done. In the study, the pulp tissue obtained via synthetic scaffolds like PLLA (poly-L-lactic acid) was advantageous in terms of quality than the pulp tissue obtained from collagen matrix scaffold. It was observed that Collagen matrix had the property of undergoing contraction when filled with dental pulp cells. [31] Saline is used to carry the growth factors like BMP 2, 4, 7, BSP. Cbfa1, DMP1, DSPP, DSP, DPP, FGF2, Wnt/BETA Catenin, TGF –BETA 1, TWIST 1 and VEGF. Alginates are used as carriers and mechanical barriers that prevent the diffusion of chemicals and proteins. [32]

Stem cells in dental tissue regeneration:

In a study done by Cordeiro, dental pulp tissue was regenerated in immunodeficient mice using SHED and human tooth slices. The resultant cells resembled pulp and odontoblast and endothelial like cells were also formed. [33]

According to the literature, stem cells obtained from the pulp are reputed for tissue engineering as it involves easy approach to the collection site, safe cryopreservation and less generation time for typical dentin tissue when compared to the generation time obtained from non odontogenic origin stem cell. [12]

Use of dental stem cells in medicine:

1. DPSCs in corneal regeneration: In a study by Gomes et al, on animals, when human (hIDPSCs) undifferentiated immature DPSC was transplanted to the corneal bed in rabbits' eyes, it resulted in healthy corneal epithelium with improved transparency. The study highlighted the beneficials of making use of hIDPSCs in corneal regeneration. [34]

2. Therapeutic role of DPSCs in Ischemia: Studies were done on mouse with ischaemia in hind limb, to determine the efficiency of dental pulp stem cells. The use of DPSC in the study showed increased blood supply with intense capillary formation proving their vasculogenic ability. [30]

3. Stem cells for muscular dystrophy:

Stem cells obtained from the human dental pulp stem cells were observed to create significant number of muscle cells that produce Dystrophin in Gold Retriever muscular dystrophy dogs.[35] .This proves the myogenic ability of the stem cells and inferred the hope that these stem cells can be used in the treatment of muscular dystrophy in patients.[36]

4. DPSCs considerations for Type 1 diabetes:

Insulin producing cells, are used in the treatment of the chronic degenerative disease – Diabetes. In a study by Chen et al. Insulin producing cells (IPCs) were obtained from DPSCs. [30, 36]

Study by Masaki et al has also proved that DPSC could be efficiently used in the treatment of Diabetic polyneuropathy .Freshly obtained DPSC and the cryopreserved DPSC were known to provide similar results in the studies done. [37]

5. D 'Aquino R stated that the human dental pulp stem cells can be used in tissue engineering to regenerate bone with sound vascularisation. [38] Study by D'Aquino evidenced bone regeneration from DPSC s. clinically and radiographically. Bone formation was evident radiographically within a duration of three months of colonisation of scaffold. [36] Studies done by Mendonca Costa et al and Chadipiralla et al have also confirmed the use of DPSC and PDLSC as efficient source of stem cell for bone formation respectively. [36]

Limitations associated with stem cells' use: Though its alluring to know that various structures in specific can be obtained from stem cells, there are certain shortcomings associated with its use.

The prime difficulty is in selecting and isolating the stem cells that is required for the study. Also, since the stem cells have the property to propagate and renew themselves, it is very important to study and know its oncogenic potential. Extensive research activity is still required for proper practical handling of stem cells in patients which are now used primarily in animal studies.[12]

Conclusion:

Dental tissues have established the fact that they are rich source of stem cells. They have proved their

ability to regenerate various tissues that can be used to treat diseases. Research activities are continuous in discovering the stem cells' potential in regenerating tissues. Dental Stem cells are a source of great fortune and extensive research on these stem cells focusing on overcoming the limitations will enable its use beneficial.

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