REVIEW ARTICLE

Stem Cells : A Review

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ABSTRACT

Stem cells have the remarkable potential to develop into many different cell types in the body. Serving as a sort of repair system for the body, they can theoretically divide without limit to replenish other cells as long as person or animal is still alive. There are 2 major classes of stem cells a) Pluripotent cells which can become any cell in the adult body b) Multipotent cells which are restricted to become a more limited population of cells. Presently dental treatment for missing teeth largely utilize partial or complete dentures and titanium implants which are not equivalent, neither in function nor esthetics, to natural teeth. However, progress in stem cell biology and tissue engineering may present new options for replacing heavily damaged or lost teeth, or even individual tooth structures.

KEYWORDS: Odontogenic Epithelium, Regeneration, Stem cells, Tissue engineering

INTRODUCTION

For centuries, scientists have known that certain animals can regenerate missing parts of their bodies for example starfish which can constantly regenerate blood, skin, and other tissues.[1] The identity of the powerful cells that allow us to regenerate some tissues was first revealed when experiments with bone marrow in the 1950s established the existence of stem cells.[2] Stem cells are called stem cells because of the way the word 'stem' is used, 'stem' means the main ascending (going up) stalk of a plant. Similarly, in humans, there are main cells which grow through time, a main stem from which other stems/cells can branch out from in our bodies and led to the development of bone marrow transplantation, a therapy now widely used in medicine.[1,3] Stem cells have the ability to build every tissue hence they can be used for future therapeutic uses in tissue regeneration and repair.[3]

How to cite this article:
Alok A, Singh ID, Singh S, Kishore M. Stem Cells: A Review. Int J Dent Med Res 2014;1(2):92-97.

There are two kinds of stem cells from animals and humans: embryonic stem cells and non-embryonic "somatic" or "adult" stem cells. Nowadays these are described as pluripotent stem cells and multipotent stem cells.[4] Pluripotent stem cells are so named because they have the ability to differentiate into different cells. During development, pluripotent stem cells are only present for a very short period of time in the embryo before differentiating into the more specialized multipotent stem cells that eventually give rise to the specialized tissues of the body.[5] These more limited multipotent stem cells come in several subtypes: some can become only cells of a particular germ line (endoderm, mesoderm, ectoderm), and others can become only cells of a particular tissue.[6] However, progress in stem cell biology and tissue engineering may present new options for replacing heavily damaged or lost teeth.

STEM CELLS AND DENTISTRY

As tooth formation results from epithelial-mesenchymal interactions, two different populations of stem cells have to be considered: epithelial stem cells (EpSC), which will give rise to ameloblasts, and mesenchymal stem cells (MSC) that will form the odontoblasts, cementoblasts, osteoblasts and fibroblasts of the periodontal ligament.[7] Various approaches for tissue regeneration could be used according to the origin of stem cells.[8]

Fundamentally, two means of tissue regenerating teeth are described. The first is conventional tissue engineering and second is much more innovative process of tooth regeneration using dental epithelium and mesenchymal cells in vivo. Regeneration of teeth can be broadly divided into: [9]

1. Regeneration or de novo formation of entire, anatomically correct teeth.
2. Regeneration of dental pulp.
3. Regeneration of dentin based on biological approaches and potentially as biological fillers.
4. Regeneration of cementum as a part of periodontium regeneration or for loss of cementum/ dentin resulting from trauma.
5. Regeneration of the periodontium including cementum, periodontal ligament and alveolar bone
6. Regeneration or synthesis of enamel like structures that may be used as biological substitutes for the lost enamel.

INDICATIONS AND CONTRAINDICATIONS

Stem Cells have the following indications and contraindications:

INDICATIONS

- Primary kidney disease, Primary Nephrotic Syndrome, Acute Glomerulonephritis,
- Renal injury caused by Autoimmune Diseases and connective tissue disease:
- Renal injury caused by Metabolic Diseases: Diabetic Nephropathy, Hyperuricemic
- Renal injury caused by infectious diseases: hepatitis B Virus associated glomerulonephritis, hepatitis C Virus
- associated glomerulonephritis
- Cardiorenal Syndrome and Hepatorenal Syndrome
- Renal Injury caused by hypertension.
- Leukaemia and lymphoma
- Baldness, Missing teeth

CONTRAINDICATIONS

- The patient who is allergic to stem cell or patient with serious allergy
- Pregnant women (woman in lactation period is allowed)
- Infected patients who is still out of control
- Serious mental illness patient, including patient with tristimania
- Severe Hypertension (BP is higher than 160/100mmHg)
- Patient with coronary disease, unstable angina, myocardial ischemia
- Patients with obvious renal atrophy
- Patients with severe bleeding tendency
- Polycystic Kidney Disease

DENTAL PULP STEM CELLS (DPSCs)

The identification and isolation of an odontogenic progenitor population in adult dental pulp were first reported by Gronthos and co-workers in 2000 by virtue of their clonogenic abilities, rapid proliferative rates, and capacity to form mineralized tissues both in vivo and in vitro.[10]

The most striking feature of DPSCs is their ability to regenerate a dentin-pulp-like complex that is composed of mineralized matrix with tubules lined with odontoblasts, and fibrous tissue containing blood vessels in an arrangement similar to the dentin pulp complex found in normal human teeth.

DPSCs are isolated from dental pulp, can either regenerate new stem cells or undergo a differentiation process. Dental pulp can be acquired from third molars or pulpectomized teeth left in situ. In vitro, DPSCs can differentiate to odontoblasts, osteoblasts, adipocytes, chondrocytes, smooth muscle cells. DPSCs were able to produce a pulp-like tissue.

DPSCs express several markers including the mesenchymal and bone marrow stem cell markers, STRO-1 and CD146 as well as the embryonic stem cell marker. The characteristic features and multi-lineage differentiation potential of DPSCs have established their stem cell nature and indicated their promising role in regenerative therapy.[11]

Following their transplantation, DPSCs were able to form pulp-like tissue, odontoblast- like cells, ectopic dentin as well as reparative dentin-like and bone-like tissues.

STEM CELLS FROM HUMAN EXFOLIATED DECIDUOUS TEETH (SHEDs)

In 2003, Miura *et al*. isolated cells from the dental pulp which were highly proliferative and clonogenic. The technique used for isolation of SHEDs was similar to those used in the DPSCs.[12] However, there were two differences: i) the source of cells was the pulp tissue of the crown of exfoliated deciduous teeth and ii) the isolated SHEDs did not grow as individual cells, but isolated SHEDs clustered into several colonies which, after separation, grew as individual fibroblast-like cells.

SHEDs were found to express early mesenchymal stem cell markers (STRO-1 and CD146).[12] In addition, embryonic stem cell markers such as stage-specific embryonic antigens (SSEA-3, SSEA-4), and tumor recognition antigens (TRA-1-60 and TRA-1-81) were also found to be expressed by SHEDs.

The multi-lineage differentiation potential of SHEDs was demonstrated under different inductive conditions. SHEDs showed the

capacity to undergo osteogenic and adipogenic differentiation. When SHEDs were cultured with neurogenic media, they formed clusters and changed their fibroblastic morphology into cells with multiple cytoplasmic processes. Under the same neurogenic culturing condition, SHEDs expressed different neuronal and glial cell markers such as nestin.[12] The expression of these markers may suggest a neural crest origin of these cells. When SHEDs were transplanted into immune-compromised mice, dentin-like structure was formed, and was immune-reactive to dentin specific sialophosphoprotein antibody.

However, unlike DPSCs, SHEDs did not form a dentin-pulp complex after *in vivo* transplantation. This indicates that SHEDs have different odontogenic differentiation potential than DPSCs. Unlike DPSCs, SHEDs were not able to differentiate into osteoblast or osteocyte, but were able to induce the host cells to undergo osteogenic differentiation. This is another difference in the differentiation potential of SHEDs and DPSCs which demonstrates that SHEDs, unlike DPSCs, have an osteoinductive potential rather than a differentiation potential.[12]

PERIODONTAL LIGAMENT STEM CELLS (PDLSCs)

The periodontal ligament (PDL) contains stem cells which have the potential to form periodontal structures, such as cementum and ligament. Heterogeneity and continuous remodelling of PDL is an indication for the presence of progenitor cells which can give rise to specialized cell. In 2004, this speculation led to the discovery of the third type of dental stem cells which was referred to as PDLSCs. It can be harvested from the roots of extracted teeth. In vitro, PDLSCs differentiate into cementoblasts and osteoblasts. PDLSCs have a multi-lineage differentiation potential when cultured with the appropriate inductive medium.[13] When PDLSCs were transplanted into immune compromised mice, a typical cementum-PDL structure was formed, which was not produced in the case of DPSCs or bone marrow MSCs. The newly formed PDL-like tissue was composed of type I collagen and interestingly it was connected to the cementum in the same way Sharpey's fibres of the PDL attach to the cementum of the tooth.

DENTAL FOLLICLE PRECURSOR CELLS (DFPCs)

The dental follicle (DF) is a loose connective tissue of an ectomesenchymal origin and it is present as a sac surrounding the unerupted tooth. It plays a major role in the genesis of cementum, PDL and alveolar bone.

In 2005, Morsczeck *et al*. were successfully able to isolate stem cells from the dental follicle of the human impacted third molar. The cells were fibroblast-like and expressed various markers, such as nestin and Notch-1.[14] The potential of DFPCs to undergo differentiation (osteogenic, adipogenic and neurogenic) was demonstrated using *in vitro* studies.[14] DFPCs were also able to differentiate and express cementoblast markers (cementum attachment protein and cementum protein-23) after being induced with enamel matrix derivatives, or BMP-1 and BMP-7.[15]

STEM CELLS OF APICAL PAPILLA (SCAPS)

SCAPs were isolated from dental papilla and are located in tip of growing tooth roots. SCAPs, similarly to DPSC and SHEDs, comprise a heterogeneous population capable of osteoblastic and odontoblastic differentiation and to a lesser extent adipogenic differentiation.[16] Since the dental papilla is the

precursor tissue for radicular pulp, it is possible that SCAPs convert into DPSCs and therefore SCAPs may constitute a population of earlier stem cells. SCAPs express the early mesenchymal surface markers, STRO-1 and CD146. However, SCAPs also express CD24, which could be a unique marker.[17] SCAPs have the capacity to undergo differentiation, when they are cultured in the appropriate inductive media. As in the case of DPSCs, when SCAPs were transplanted into immune-compromised mice in an appropriate carrier matrix, a typical dentin-pulp like structure with odontoblast-like cells was formed.[17] Recent studies have shown that SCAPs have the capacity to produce vascularised pulp-like tissues in vivo into 5-6 mm long root canals.

ROLE OF DENTAL STEM CELLS IN REGENERATIVE MEDICINE

The dynamic features of isolated dental stem cells revealed much potential for their use in regenerative medicine and tissue engineering. (Table No.2)

- *Dental pulp regeneration*
- *Bio-Root Engineering*
- *Neural Regeneration*
- *Cardiac Repair*

Table No 2: Role of dental stem cells in regenerative medicine

STEM CELL BANKING

In 2005, the National Academies issued a report, Cord Blood: Establishing a National Hematopoietic Stem Cell Bank Program, which recommended that a national cord blood "bank" should be established to utilise the medical potential of stem cells.

LICENSED CORD BLOOD BANKS IN INDIA

There are number of Licenced Cord Blood Banks in India such as :[1]

1. Reliance Life Sciences, Delhi, Life cell, Chennai.
2. Cordlife Sciences and Cryobanks International plan to establish cord blood banks in Kolkata and New Delhi, respectively.
3. Histostem, a South Korean biotech company plans to establish the world's largest cord blood bank in Mumbai.

CONCLUSION

Dental tissue regeneration provides an attractive alternative to traditional, synthetic tooth restoration therapies. The vision of natural dental restorations generated from stem cell, or the stem cell based autologous regeneration of tissues is what makes stem cell research interesting for dentistry. The development of such “test tube teeth” requires precise regulation of regenerative events in order to achieve proper tooth size and shape, as well as development of new technologies to facilitate these processes. It may prove to be a milestone in the regenerative medicine and dentistry. The minimal intervention required to obtain dental soft tissues within the oral cavity provides an advantage and may help avoid rejection by recipients. Although many studies have to be conducted before applying stem cells, stem cells represent a powerful tool which holds a significant potential for advancement in the field of regenerative dentistry and medicine.

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Source of Support: Nil
Conflict of Interest: Nil