**STEM CELLS IN DENTISTRY**

Kaushitaki Bhaumik1,Praveen Rai2 ,Amrita Upadhyay3 ,Barkha Bhoneja4

134Senior lecturer, Dept of Prosthodontics and crown & bridge, Babu Banarasi Das College of Dental Sciences, Lucknow

2Readerr, Dept of Prosthodontics and crown & bridge, Babu Banarasi Das College of Dental Sciences, Lucknow

INTRODUCTION

Tooth loss or absence may be due to numerous pathologies such as periodontal diseases, dental caries, fractures, injuries or even genetic alterations. The treatment modalities available are patient’s own tissues, allogenic grafts, metallic alloys or synthetic implants. But they carry disadvantages like risk of failure and limited service time. Even success of implants greatly depends on osseointegration, quantity and quality of bone. In autologous tissue grafting, the drawback is donor site trauma and morbidity. Thus a major question arises, if there is any material that will restore the missing part and simultaneously have acceptable durability. The answer to this question is stem cells. Researches on stem cells has got significant importance in dentistry. It has been seen that stem cells may play an mentionable role in future medical and dental treatment as they can be readily grown and induced to differentiate into any cell type in culture.[1]

BACKGROUND

Because of the broad spectrum of opportunity for autologous cell based therapies stem cell therapy has gained much attention in the dental community. Limitations of prevalent procedures have made researchers to explore the possible use of stem cells for the regeneration and restoration of lost dental structures. Any effort to advance stem cell therapy into the therapeutic genre will require advances in directed differentiation protocols that can efficiently epitomize the embryological developmental processes of dental tissue.

WHAT ARE STEM CELLS

Stem cells (SCs) are undifferentiated cells capable of self-renewal and differentiation into more specialized cells. SCs can be classified as totipotent, pluripotent, or multipotent [2]. based on their differentiation potential:

a) Totipotent SCs can differentiate into both embryonic and extraembryonic tissues [3].

b) Pluripotent SCs (PSCs) can differentiate into the three embryonic germ layers – endoderm, mesoderm, and ectoderm [4].

c) Multipotent SCs, including the still debated mesenchymal SCs (MSCs), can differentiate into a limited number of specialized cells [5].

HISTORY

In 1868, the term “stem cell” appeared in the works of German biologist Haeckel for the first time.[6] Wilson coined the term stem cell.[7] Russian histologist, Alexander Maksimov, in 1908, postulated existence of hematopoietic stem cells at congress of hematologic society in Berlin,[8] where term “stem cell” was proposed for scientific use.

TYPES OF STEM CELLS

Stem cells can be broadly classified as embryonic stem cells (ESCs) and adult stem cells (ASCs). ESCs are cells derived from the inner cell mass of the blastocyst - an early stage of an embryo. Whereas ASCs are present in adult tissues, have limited ability to proliferate and are further classified into hemopoietic stem cells (HSC) and mesenchymal stem cells (MSC).

Dental stem cells shows characteristics of mesenchymal stem cells. They have the capacity to generate dentin‑producing odontoblasts, adipocytes, osteoblasts, bone, cartilage, and smooth and skeletal muscle. According to studies dental stem cells can change lineage to form ectodermal tissues (neurons or epithelial‑like stem cells) and endodermal lineage (endothelial cells, hepatocytes, and insulin‑producing cells).[1]

Dental stem cells isolated from different parts of teeth are:

1. Adult dental pulp stem cells (DPSC)

2. SHED

3. Stem cells from the apical part of the

papilla (SCAP)

4. Periodontal ligament stem cells (PDLSC)

5. Stem cells from the dental follicle (DFSC)

6. Bone marrow derived mesenchymal stem

cells (BMSC).

1. DPSCs are mesenchymal type of stem cells found inside dental pulp. DPSCs have osteogenic and chondrogenic capacity *in vitro.* Theycan differentiate into dentin, *in vivo* and also differentiate into dentin-pulp-like complex. Immature dental pulp stem cells were also identified which are a pluripotent sub-population of DPSC generated using dental pulp organ culture.

DPSCs have presumptive potential for dental tissue engineering due to:

a. Easy access to surgical site for collection and low morbidity after extraction of the dental pulp.

b. DPSCs are able to generate much more typical dentin tissues in a short period of time than nondental stem cells.

c. Recombined with many scaffolds and can be safely cryopreserved.

d. Have immuno-privilege and anti-infl ammatory capabilities helpful for the allotransplantation experiments.[9]

2. SHED: In 2003, Dr. Songtao Shi discovered SHED. Studies showed SHED were able to differentiate into a variety of cell types to a greater extent than DPSCs, including osteoblast-like, odontoblast-like cells, adipocytes, and neural cells, Miura *et al*.[10]. Abbas *et al*. [11] investigated the neural crest origin of SHED. The formation of mineralized tissue, which can be utilised to enhance orofacial bone regeneration seems to be the main task of these cells.

Types of stem cells present in human exfoliated deciduous teeth are:

a. Adipocytes: used to treat various spine and orthopedic conditions, Crohn’s disease, cardiovascular diseases and may also be useful in plastic surgery.

b. Chondrocytes and osteoblasts: used to grow intact teeth in animals.[10]

c. Mesenchymal stem cells (MSCs): used to repair spinal cord injury and to restore feeling and movement in paralyzed human patients. They can also be used to treat neuronal degenerative disorders such as Parkinson’s disease, cerebral palsy, Alzheimer’s disease, and other such disorders. MSCs have better curative potential than other type of adult stem cells.[10]

3. SCAP: MSCs can be seen in the apical papilla of permanent teeth with immature roots. They are known as SCAP, discovered by Sonoyama *et al*.[9] SCAP are able to form odontoblast-like cells, producing dentin *in vivo*, and are likely cell source of primary odontoblasts for the formation of root dentin. SCAP supports apexogenesis. SCAP can generate primary odontoblasts even after endodontic infection, which complete root formation under the influence of the surviving epithelial root sheath of Hertwig. [12]

4. PDLSCs: Seo *et al*. [13] reported the presence of multipotent postnatal stem cells in the human periodontal ligament (PDLSCs). PDLSCs had the capacity to generate a cementum/periodontal ligament-like structure and contributed to periodontal tissue repair in rodents. While retaining their stem cell characteristics these cells can also be isolated from cryopreserved periodontal ligaments , including single-colony strain generation, cementum/periodontal ligament-like tissue regeneration, expression of MSC surface markers, multipotential differentiation and hence providing a ready source of MSCs.

5. DFSC: Based on its ability to generate cementum, bone and periodontal ligament dental follicle surrounding the developing tooth germ has long been considered a multipotent tissue. Dental follicle precursor cells (DFPC) differentiate into osteoblasts/cementoblasts, adipocytes, and neurons. DFPCs have widened their prospective for use in tissue engineering applications, including periodontal and bone regeneration.[1]

6. BMSC: BMSCs are cells that originate from bone marrow. They have capacity to differente along multiple mesenchymal lineages. Studies now a days focus on their ability to form cementum, PDL and alveolar bone after planting into defective periodontal tissues. Another study showed the probability that BMSCs can give rise to different types of epithelial cells and their possibilities to aid as a source for ameloblasts. Thus, for tooth‑tissue engineering BMSCs have become a futuristic prospective and could be induced into mesenchymal and epithelium cells in tooth tissue engineering.[1]

Aplications in oral diseases

Clinical applications of dental stem cells has a broad spectrum for emergence scope in near future. Currently researches on dental stem cells focuses on regeneration of dentine, pulp and teeth; alveolar bone; regeneration of periodontal ligament after periodontal disease; salivary gland regeneration; repair of craniofacial defects; and even in the treatment of lichen planus.

1.Regeneration of teeth

Dental tissue stem/progenitor cells can differentiate into dental cell lineages, and are used to regenerate some dental tissues in the treatment of tooth defects and tooth loss. Studies now focus on whole tooth regeneration using a approach of transplanting artificial tooth germ and allowing it to develop in the adult oral environment. Two different means of regenerating teeth are conventional tissue engineering, in which the application of cells in a carrier material *in vitro* under the influence of a stimulus leads to tissue regeneration. The second one is using dental epithelium and mesenchymal cells *in vivo* after direct implantation, which is based on knowledge of general embryogenesis and physiological tooth development during childhood.[1]

2.Use of the dental stem cells for the treatment of periodontitis

At present, there is no periodontal treatments that help regenerate the affected region and the lost periodontal tissue into a normal and functional structure. *In vivo* studies transplanted PDLSCs associated with scaffolds in immunocompromised animal models and had showed regeneration of periodontal tissue, as they can differentiate into osteoblasts and cementoblasts, and induce tissue formation around the surface of dental implants.[14,15] In three humans Feng *et al*.[16] obtained significant improvement in the injured area after the use of PDLSCs. In recent study, Chen *et al*.[17] performed autologous transplant of PDLSCs and DPSCs in 30 patients and showed that the use of these cells in areas of periodontal disease is safe and the does not produce significant adverse effects. Thus, the use of DPSCs for the regeneration of bone loss from periodontal disease may be clinically relevant.

3.Use of the dental stem cells for bone regeneration

DPSCs have been studied also for reconstruction of maxillofacial bones. D’Aquino *et al*.[18] transplanted autologous DPSCs associated with a collagen scaffold to repair the defects in alveolar bone secondary to extraction of impacted third molars in seven patients and, after three months, Scithere were bone regeneration areas. Three years after the transplant, Giuliani *et al*.45 showed that the transplanted area was comprised of uniformly vascularized compact bone, with bone matrix histologically different from the normal alveolar bone. Inspite the histological difference, dental function and chewing pattern were not altered.

4.Use of the dental stem cells for pulp regeneration

Studies have been conducted seeking an effective technique for pulp regeneration after endodontic treatment. Currently, two strategies have been investigated: DPSCs autologous transplantation associated with scaffolds and pulp canal revascularization, which invite MSCs to the site of injury. However, after the root canal and pulp chamber revascularization histological analysis shows that there is no tissue formation similar to pulp. The majority of the cases present non-pulp-like tissues, comprising cementum, periodontal and bone-like-tissues.[19] In a study in an animal model (dogs), after transplantation of a subset of DPSCs (CD105+) with stromal cell-derived factor-1 (SDF-1) [20] pulp-like tissue with nerves and vasculature was regenerated in the tooth root.

5.Salivary gland regeneration after radiation therapy

The capability of salivary gland tissue to regenerate after atrophy has enlightened about location and isolation of cell populations that contain salivary gland stem cells. Stem cells isolated from mouse salivary glands have revealed to rescue saliva production in irradiated salivary glands. Based on the major advances in the field of stem cell research, stem cell‑based therapy has wide potential for the treatment of xerostomic conditions in humans.

6.Lichen planus

Conventional treatment modalities of lichen planus are usually challenging and unsatisfactory. In the past several years, studies have focussed on immunosuppressive properties of mesenchymal stem cells on various immune cell types. Based on these studies it is proposed that mesenchymal stem cells can be utilized to treat oral lichen planus patients via systemic infusion or local application.[1]

7.Mandible condyle regeneration

Injury to the temporomandibular joint disc or condyle (condylar osteochondral defect) arising from trauma or arthritis can cause pain and disturbed masticatory function for patients. Human-shaped mandibular condyle was successfully engineered from chondrogenically and osteogenically induced rat BMSCs encapsulated in a biocompatible polymer. BMSCs that were induced to differentiate into chondrogenic and osteogenic cells regenerated rabbit mandibular condyle that was enhanced by low-intensity pulsed ultrasound. These studies provide an initial pathway of concept for the ultimate stem-cell-based tissue engineering of degenerated articular condyles in the conditions of diseases such as rheumatic arthritis.[21]

STEM CELL BANKING

Dental stem cell banking is the process of storing stem cells obtained from patients’ deciduous teeth and wisdom teeth. This can be a significant strategy to study the potential of dental-stem-cell-based regenerative therapy. The trend is attaining acceptance mainly in the developed countries.

-Stem cell banking companies like Store –A- Tooth (Provia Laboratories, Littleton, Massachusetts, USA) and StemSave (Stemsave Inc, New York, USA) are expanding their horizon internationally.

- In Japan, the first tooth bank was named as “Three Brackets” (Suri Buraketto) in 2005. Nagoya University (Kyodo, Japan) also came up with a tooth bank in 2007.

- Taipei Medical University in collaboration with Hiroshima University opened the nation’s fi rst tooth bank in September, 2008.

- The Norwegian Tooth Bank (a collaborative project between the Norwegian Institute of Public Health and the University of Bergen) set up in 2008 is collecting exfoliated primary teeth from 1,00,000 children in Norway.[9]

- In Brazil, The National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária* – ANVISA) authorizes the storage of SCs originated from umbilical cord blood and placenta, as well as SHEDs in private establishments with proper operating license.

- Stemade introduced the concept of dental stem cells banking in India recently by launching its operations in Mumbai and Delhi.

CONCLUSION

Stem cell research in dentistry has given opportunity for dentists to assume a leading role not only in the treatment chain of dental pathosis, but also in medical disease. Stem cells of dental origin have multiple applications nevertheless there are certain limitations as well. Currently, the use of DSCs has been only applied in scientific research, but it is believed that, in a near future, this practice becomes a reality, which will represent a great advance in Dentistry.50 More studies on the DSCs differentiation mechanisms and applications are needed to use these cells in routine dental practice.

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