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RESEARCH ARTICLE

STEM CELLS IN DENTISTRY

*,[1]Dr. Satyendra Kumar Jha, [2]Dr. Imit Pal Saluja, [3]Dr. Samiksha Acharya, [4]Dr. Manish B Sarode and [5]Dr. Pranjan Mitra

[1,3]Department of Oral Medicine, Diagnosis and Radiology, Guru Gobind Singh College of Dental Sciences and Research Centre, Burhanpur, Madhya Pradesh – 450331
[2]Dental Dept, R.D Gardi Medical College, Ujjain, M.P.
[4]Department of Oral Pathology, Guru Gobind Singh College of Dental Sciences and Research Center, Burhanpur, M.P.
[5]Department of public health dentistry, Institute of Dental Education and Advance Studies, Gwalior, M.P.

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ABSTRACT

The capacity to replace missing parts of the body lost due to disease process, trauma or other reasons have been fascinating scientist since decades. Regeneration of lost part of skin intestinal and buccal epithelium, blood etc by the body paved the way for search of basic parent cell from which all other cells are derived. This led to the discovery of stem cells in1960 and since then stem cell-based treatments are being used and investigated in medicine for neural, cardiovascular and autoimmune diseases. In recent history, stem cells from teeth have been researched and is said to be able to cure various tooth-related and maxillofacial defects. This article presents a brief introduction on stem cell and its futuristic application in the field of dentistry.

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INTRODUCTION

In routine dental practice we have been utilizing the potential of dental pulp in repair and regeneration of dentin through indirect and direct pulp capping treatment. Now researches prove presence of stem cells in dental pulp, periodontal ligament and at tips of growing roots. In medicine stem cells treatments have been investigated for neural, cardiovascular and autoimmune diseases (Understanding stem cells) and this led to the first successful bone marrow transplantations in 1968. (Gatti *et al*., 1968) In the field of dentistry stem cells can be used to regenerate periodontium and even entire tooth, thus taking care of two highly prevalent dental diseases as caries and periodontal diseases. (Mao, 2008) The term 'stem cell' was coined by Russian histologist Alexande Maksimov in 1908 and research on stem cells grew out of findings by Canadian scientists in the 1960s. (Becker *et al*., 1963)

Corresponding author: Dr. Satyendra Kumar Jha,
Department of Oral Medicine, Diagnosis and Radiology, Guru Gobind Singh College of Dental Sciences and Research Centre, Burhanpur, Madhya Pradesh – 450331

Definition

Stem cells are defined as primal cells common to all multi-cellular organisms that retain the ability to renew them-selves through mitotic cell division and can differentiate into a wide range of specialized cell types. (Mao, 2008)

Classification

Classification of stem cell is based mainly on its potential and the type of tissue from which it is isolated. Based on their potential, stem cells are divided into four types: Totipotent cells, Pluripotent cells, Multipotent cells, Unipotent cells and based on the type of tissue from which they are isolated, stem cells can be classified into embryonic stem cells and adult stem cells. (Gatti *et al*., 1968; Cherian, 1st edition) Embryonic stem cells (ESCs: These are derived from the cells of the inner cell mass of the blastocyst during embryonic development. (Understanding stem cells; Mao, 2008; Cherian, 1st edition)

Adult Stem Cells: An adult stem cell is an undifferentiated cell found among differentiated cells in a tissue or organ. Different adult stem cell lines are hematopoietic stem cells, neural stem cells, skeletal muscle stem cells, skin stem cells, intestinal epithelium, pancreas, lung, liver, testis and umbilical cord blood stem cells. (Cherian, 1st edition; Astori *et al*., 2010; Kaderait; Xu *et al*., 2010)

Properties of Stem Cells: These are unspecialized, can divide and renew themselves and can give rise to specialized cells. (Cherian, 1st edition) The capability of stem cells to proliferate without changing its phenotypes indefinitely, and to differentiate into one or more new kind of cells depending on the culture conditions make them capable of treating diseases that involves cell loss. (Chung *et al*., 2011)

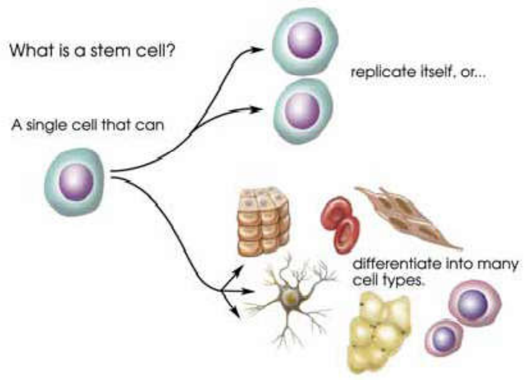

Figure 1. Properties of Stem Cells

Rationale for the application of stem cells

- Having the capacity to differentiate into any cell type, they can directly replace the affected cell.
- Exert Paracrine effects by secreting VGEF and FGF-1 thus stimulating local cell growth.
- Release signalling factors that recruit stem cells from other regions by modulating the immune system (Jayakrishna *et al*., 2011).

Stem cell and dental tissue

In routine dental practice we have been utilizing the potential of dental pulp in repair and regeneration of dentin through indirect and direct pulp capping treatment. Now researches prove presence of stem cells in dental pulp, periodontal ligament and at tips of growing roots. Dental tissue and other craniofacial structures are formed by neural crest-derived mesenchymal cells. Tooth-derived stem cells belong to subfamilies of mesenchymal stem cells. (Mao, 2008) The DPSCs and BMSCs have similar genetic expressions for around 4,000 genes and in general, DPSCs can differentiate into odontoblasts, osteoblasts, chondrocytes, fibroblasts, adipocytes, myocytes, melanocytes and neurons. (Daniela *et al*., 2011) Moreover stem cell recovery from teeth are easily accessible, affordable, is less invasive procedure and convenient, thus making teeth ideal for testing new cell-based treatments. (Cherian, 1st edition; Daniela *et al*., 2011) Postnatal root formation is a developmental process, and thus offer more embryonic-like cell than other sources of dental stem cells. Thus tooth can play a major role in future developments in regenerative medicine.

Sources of tooth stem cells

Stem cells can be recovered from deciduous tooth or permanent tooth. The ideal deciduous tooth for stem cell recovery is a canine or incisor that has just started to loosen, has more than a third of the root structure left intact, and is not extracted for reasons such as infection or associations with pathology. As the wisdom tooth undergoes root development till the age of 18-25 years, it can be a good source of dental stem cells as Dental Pulp Stem Cells (DPSC), Periodontal Ligament Stem Cells (PDL) and Stem Cells from Apical Papilla (SCAP). (Cherian, 1st edition; Jones and Yang, 2011)

Dental Stem Cell Banking

Stem cell banking has existed for years, and preserving stem cells by banking umbilical cord blood is already in use. With the discovery of stem cells in deciduous teeth and wisdom teeth, it provides another source of stem cell banking. (Cherian, 1st edition) DPSCs are isolated and cultivated in a special media composed of alpha-MEM, 2% FCS, EGF, PDGF, dexamethasone and finally treated with trypsin-Ethylenediaminetetraacetic acid (EDTA) and divided into laboratory dishes with standard surfaces. (Daniela *et al*., 2011)

Figure 2. Stem cell banking

Types of tooth stem cells: (Cherian, 1st edition)

1. Adipocytes
2. Chondrocytes and osteoblasts
3. Mesenchymal stem cells

Dental stem niche

Dental stem niche is the special microenvironment which house adult stem cells and transient amplifying cells. For tooth formation to occur two different populations of stem cells have to be taken into account, epithelial stem cells giving rise to ameloblasts and mesenchymal stem cells which form the odontoblasts, cementoblasts, osteoblasts and fibroblasts.

Epithelial stem cells

Ameloblasts and its precursors are lost after tooth eruption so formation of enamel in-vivo is not possible. (Volpini *et al*., 2012) Epithelial stem cells isolated from juvenile animals and further dissociated enzymatically, amplified and associated with MSC in-vitro have been tried with synthetic polymers for new tooth formation. (Cherian, 1st edition; Volpini *et al*., 2012)

Mesenchymal stem cells

Friedenstein *et al* in 1970 was the first to describe MSCs in bone marrow. Now it is been extensively characterized in-vitro by the expression of STRO-1, CD146 or CD44. Mesenchymal stem cells have high renewal capacity and ability to differentiate into muscle, cartilage, bone and adipose tissue. (Mao, 2008; Cherian, 1st edition; Xu *et al*., 2010; Jones and Yang, 2011; Huang *et al*., 2009; Shi *et al*., 2005)

Mesenchymal progenitors for tooth engineering purposes are

Dental pulp stem cells (DPSC)

These are the first stem cells isolated from adult human dental pulp. (Volpini *et al*., 2012) Studies have shown that DPSCs can differentiate into dentine/pulp-like complexes, odontoblasts, adipoctyes, chondrocytes and osteoblasts. (Cherian, 1st edition; Volpini *et al*., 2012; Koyama *et al*., 2009; Yu *et al*., 2010; Graziano *et al*., 2008)

Stem cells from human exfoliated deciduous teeth (SHED)

Research on SHED have shown that it can generate dentine and can induce new bone formation. (Volpini *et al*., 2012; Sakai *et al*., 2010; Nakamura *et al*., 2009)

Periodontal ligament stem cells (PDLSC)

PDLSC have been shown to give rise to cementoblast like cells and adipocytes. (Gault *et al*., 2010; Lin *et al*., 2008)

Stem cells from Root apical papilla (SCAP)

Tip of growing tooth roots possess SCAP which can differentiate into odontoblasts and adipocytes. In a study conducted in mini pigs, it showed that co-transplantation of SCAP and PDLSC can form dentine and periodontal ligament, thus making the possibility of creating a biological root. (Volpini *et al*., 2012)

Dental follicle stem cells (DFSC)

DFSC have been shown to express 'Nestin and Notch-1'. Transplantation of DFSC into SCID mice showed formation of cementum and bone. (Volpini *et al*., 2012)

Areas of research for dental stem cells

Regeneration of periodontium

Implantation of periodontal ligament cell in athymic rat with periodontium and cementum removed showed fibril anchoring resembling native periodontal ligament fibres. (Volpini *et al*., 2012; Hasegawa *et al*., 2005)

Regeneration of dental pulp

DPSC and SCAP seeded on poly-D, L lactide/glycolide scaffold and transplanted into SCID mice showed pulp-like tissue with well-established vascularization on histological analysis after a period of 3-4months. (Volpini *et al*., 2012)

Regeneration of entire tooth: Entire tooth regeneration requires interaction of mesenchyme-originated odontoblast and epithelium-derived ameloblast. (Volpini *et al*., 2012) Tooth formation can be induced by pre-bud stage dental epithelium when combined with mesenchymal cells. (Ohazama *et al*., 2004) Depending on which cell type is responsible for induction of tooth formation there are two approaches for tooth regeneration. (Volpini *et al*., 2012)

Odontogenic responsive epithelial cells: Epithelial rests of Malassez when isolated and cultured and maintained in vitro on feeder layers, have been shown to induce enamel-like tissues. (Kat *et al*., 2003; Shinmura *et al*., 2008) Oral mucosal epithelial cells grown as cell sheets and re-associated with dental mesenchyme have been shown to give rise to tooth like structures. (Bruder *et al*., 1998) Signalling proteins, Growth Factor and Bone Morphogenic Protein are some exogenous factors that have been shown to induce epithelial cells. (Volpini *et al*., 2012)

Odontogenic inductive mesenchymal cells: Non-dental mesenchymal cell sources such as bone marrow stromal cells when combined with inductive embryonic oral epithelium have been shown to form tooth in-vitro. (Ohazama *et al*., 2004) In-vivo tooth can be formed by the early embryonic neural crest-derived ectomesenchyme cells which have already received the first inductive signals from the dental epithelium.

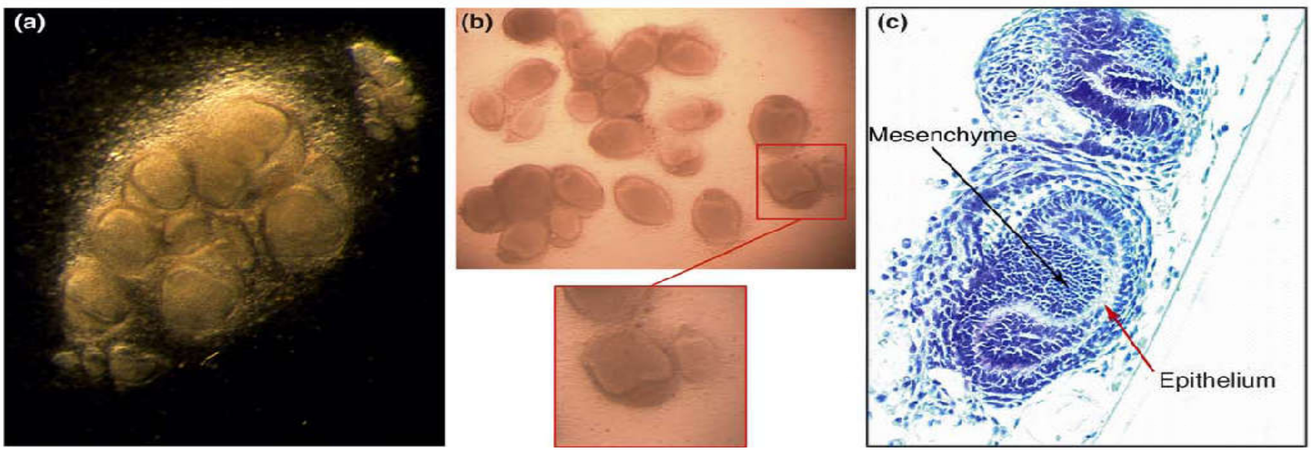

Figure 3. Tooth formation in-vitro from combinations of mouse epithelial and mesenchymal cells. Red arrow denotes epithelium and black arrow denotes (mesenchyme). (a) The cells at 6 days. (b) Gross appearance of tooth premordium after 9 days in culture. (c) Bell stage (Volpini *et al*., 2012)

Clinical trials related to stem cell application in Oro-facial complex

1. Human mesenchymal stem cell-loaded hydroxy-apatite/p-tricalcium phosphate cubes implanted in the subcutaneous space of athymic rats displayed evidence of osteogenesis by 4 weeks. (Bruder *et al*., 1998)
2. Stem cells isolated from miniature pig deciduous teeth and engrafted in the critical-size bone defects generated in swine mandible models indicated that stem cells from miniature pig deciduous teeth, were able to engraft and regenerate bone to repair mandibular defects at 6 months post-surgical reconstruction. (Zheng *et al*., 2009)
3. Following in vivo implantation of MSC derived chondrogenic and osteogenic cells in immunodeficient mice for up to 12 weeks, the retrieved mandibular joint condyles retained the shape and dimensions of the native condyle. (Mao, 2008)

Conclusion

A durable and biological-based treatment approach for repair and regeneration of lost tissue in dentistry is the need of hour. As researched, dental stem cells are present in dental pulp, periodontal ligament and growing root tip and have the potential for regenerating dentin, pulp, periodontal ligament and orofacial bone. Although there is enormous progress in this field, still many hurdles needs to be taken care of so that simple, safe and reproducible cell-based treatment approaches for tooth repair and regeneration can be formulated. Further research in this field will pave the way for a new era in the field of dentistry.

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