Stem Cell Therapy – "The Edge of a New Frontier for Dentistry": A Review

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ABSTRACT

It's a fantasy of every dentist's to achieve complete regeneration and repair with predictability and naivety, and this is being attempted to transform into reality by using stem cell science. Stem cell science is a fascinating tool which promise futuristic complete regeneration. Stem cells can be obtained from embryonic and adult tissues, and mostly they are multipotent mesenchymal stem cells (MSCs) which brought new fervor among the researchers because of their qualitative and quantitative features. This review article brief us about basics of stem cells, where it stands in the human dental stem cell research and what are its future scopes. It is still in an infancy stage, but a paradigm shift can take place if the complete potential of stem cells can be utilized in clinical applications.

KEYWORDS: Adult Stem Cells, Dental Stem Cells, Mesenchymal Stem Cells

INTRODUCTION

It's not enough for a dentist to be acquainted with stem cell therapy but should have appropriate knowledge of its basics to be capable enough to explain it to their patients. Even though stem cell therapy is measured as a fiction today, in near future it will become the part of the dentist's clinical practice. The veracity of the periodontium and the activity of the pulp are responsible for supplying nutrition to teeth, plumps the health of teeth. Proliferation and condensation of the ectomesenchymal cells will lead to a formation of dental papilla which in turn produces mature pulp. So it can be considered that the mature pulp bears a strong resemblance to the embryonic connective tissue, and it has a layer of highly specialized cells, the odontoblasts, along its periphery. The physical confinement of the dental pulp, its high incidence of sensory nerve innervation and the rich microcirculatory components make the dental pulp a unique tissue.[1,2]

The pulp is formed of odontoblast and undifferentiated mesenchymal cells which are specialized cells that can form dentine throughout the human's life. This specialized cells can compensate for the loss of enamel or dentine by forming hard tissue barrier which isolates the irritants from the remaining pulp tissue.[3]

So the current curiosity is concerning for the development of substitution for dental tissues which has led to numerous dental research to be acknowledged to the application of dental tissue engineering as a clinical method, which can regenerate the dental tissues and also the generation of whole tooth, which will expand the horizon of endodontic treatment.[4]

Regenerative Endodontics is an emerging concept which is defined as "biologically based procedures designed to replace damaged tooth structures, including dentine and root structures as well as cells of the pulp-dentine complex." One novel approach to restore the tooth structure is based on tissue engineering.5

The eventual goal of endodontic treatment is to completely restore physiologic, structural and mechanical integrity of the pulp-dentine complex. Every regenerative techniques have advantages and disadvantages while some techniques are hypothetical or at a premature stage of development. Briefly tissue engineering procedures will direct the Endodontist towards framing sound clinical judgments to be applied successfully regarding the regeneration of endodontically involved teeth and increase their longevity, as the French would say: "Viva la Dente"(Long live the teeth)

DENTAL STEM CELLS

Stem cells are undifferentiated cells in the human body that are proficient of becoming specialized cells, each with new specialized cell functions (for example, liver cells, kidney cells, brain cells). All specialized cells arise originally from stem cells, which are eventually formed from and embryonic cells. Stem cells differ from other kinds of cells in the body.[4, 6, 7]

The Dental stem cells have been classified according to

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various ways. These have been highlighted as under:

CLASSIFICATION ACCORDING TO POTENCY OF STEM CELLS [6]

Embryonic stem cells from inner cell mass of 3-5 days embryo(blastocyst)	Totipotent	Can give rise to all cells of the body, including those cells making the extra embryonic tissues. Unconstrained ability to divide
Embryonic stem cells Induced pluripotent stem cells	Pluripotent	Can give rise to all embryonic germ layers Can give rise to all of various cell types of the body
Adult stem cells(postnatal)	Multipotent	Can form more than one cell type of the body
Linage stem cells	Oligopotent	Cell lines have the ability to transform into quite a limited number of several other types of cells
Tissue determined stem cells	Unipotent	Can give rise to only one cell type

CLASSIFICATION ACCORDING TO THEIR ORIGIN

- Embryonic stem cells,
- Somatic or adult stem cells, and
- Induced pluripotent stem cells

DSCS (Dental stem cells):

DEFPCs	Dental Follicle Precursor Cells
DPPSCs	Dental Pulp Pluripotent like Stem Cells
DPSCs	Dental Pulp Stem Cells
DSCs	Dental Stem Cells
PDLSCs	Periodontal Ligament Stem Cells
PDLPs	Periodontal Ligament Progenitor Cells
SCAP Cells	Stem Cells From Apical Papilla
SHED Cells	Stem Cells From Human Exfoliated Deciduous Teeth

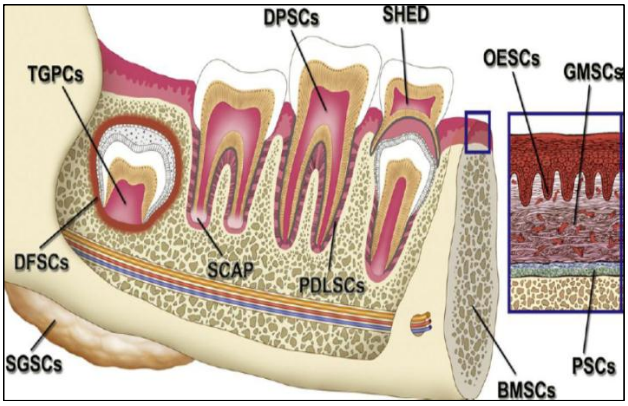

FIG- 1 Sources of adult stem cells in the oral and maxillofacial region. BMSCs: bone marrow-derived MSCs from orofacial bone ; DPSCs: dental pulp stem cells; SHED: stem cells from human exfoliated deciduous teeth; PDLSCs: periodontal ligament stem cells; DFSCs: dental follicle stem cells; TGPCs: tooth germ progenitor cells; SCAP: stem cells from the apical papilla ; OESCs: oral epithelial progenitor/stem cells; GMSCs: gingiva-derived MSCs , PSCs: periosteum-derived stem cells ; SGSCs: salivary gland-derived stem cells. [7]

DPSCs (Dental pulp stem cells) [8]: DPSCs were first isolated from human permanent third molars in 2000. The cells have more colony formation frequency as they have increase clone forming property. They were highly proliferative and can produce densely calcified, albeit sporadic, nodules. Dentin and pulp like tissues were generated following the transplantation of DPSCs in hydroxyapatite/tricalcium phosphate (HA/TCP) scaffolds into immunodeficient mice.

Various studies have been done which have proved that DPSCs satisfied all the norms needed to be stem cells i.e multipotency which is the capability cells to differentiate into adipocytes and neural cells and odontoblasts and self-renewal capabilities. Additional studies have confirmed that DPSCs can also differentiate into osteoblast, chondrocyte, and myoblast like cells and demonstrate axon guidance.

SHED CELLS (Stem cells from human exfoliated deciduous teeth) [9]: Exfoliated deciduous teeth have capability to differentiate into variety of cell types and SHED cells are one of them. Stem cells from the deciduous teeth can proliferate into various type of cells like osteoblasts, neural cells, adipocytes, and odontoblasts which are capable to form dentine and bone. Like DPSCs, SHED cells can engender dentin-pulp like tissues with separate odontoblast like cells which lined the mineralized dentin-matrix generated in HA/TCP scaffolds implanted in immunodeficient mice.

SHED cells are more proliferative than DPSCs and BMMSCs, suggestive of more immature population of multipotent stem cells.

SHED cells are genetically diverse from DPSCs and BMMSCs; genes related to cell proliferation and extracellular matrix formation. Transforming growth factor (TGF)-b, fibroblast growth factor (FGF)2, TGF-b2, collagen (Col) I, and Col III are the genes which can impart the property of being highly proliferative and it more expressed in SHED cells compared with DPSCs.

Studies have been done for tissue engineering by incorporating odontoblastic and endothelial differentiation occurred when SHED cells were seeded in tooth slices/scaffold and implanted subcutaneously into immunodeficient mice. The resultant tissues closely resembled those of human dental pulp, and tubular dentin mediated by dentin-derived BMP-2 protein was secreted. The result of these study and various other studies have shown that stem cells from exfoliated deciduous teeth are excellent for tissue engineering and autologous stem cell transplantation.

SCAP CELLS (stem cells from apical papilla) [10]: SCAP cells can be procured from the apical papilla located at the apices of developing teeth.

The apical papilla is essential for root development. SCAP cells were first isolated in human root apical papilla collected from extracted human third molars. The cells are clonogenic and can undergo odontoblastic/osteogenic, adipogenic, or neurogenic differentiation.

SCAP cells have higher proliferation rates and greater expression of CD24 when compared to DPSCs. SCAP cells differentiation decreases with increase alkaline phosphate expression.

PDLSCS (Periodontal ligament stem cells)[11]: Multipotent MSCs in human periodontal ligaments were identified and first reported in 2004.

Seo and colleagues demonstrated the presence of clonogenic stem cells in enzymatically digested PDL and further showed that human PDLSCs transplanted into immunodeficient rodents generated a cementum/PDL-like structure that contributed to periodontal tissue repair. Advanced research showed that PDLSCs differentiation was promoted by Hertwig's epithelial root sheath cells in vitro.

PDLSCs have the capability to differentiate into cementoblastlike cells, adipocytes, and fibroblasts that secrete collagen type I. As with BMMSCs, PDLSCs can undergo osteogenic, adipogenic, and chondrogenic differentiation. PDLSCs have also been shown to differentiate into neuronal precursors.

DFPCs(Dental follicle progenitor cells)[12] : DFPCs were first isolated from the dental follicle of human third molars and further research showed that it forms at the cap stage by ectomesenchymal progenitor cells. It is a loose vascular connective tissue that contains the developing tooth germ, and progenitors for periodontal ligament cells, cementoblasts, and osteoblasts.

Because DFPCs come from developing tissue, it is considered that they might exhibit a greater potency than other DSCs. Indeed, heterogeneity was found between the different cloned DFPC lines. In addition, after transplantation in immunodeficient rodents, DFPCs differentiated into cementoblastlike and osteogeniclike cells, and surface markers compatible with those of fibroblasts were identified in human dental follicle tissues, suggesting the presence of immature PDL fibroblasts.

DFPCs can be differentiated into odontoblasts, and four weeks after combining rat DFPCs with treated dentin matrix the root-like tissues stained positive for markers of dental pulp.

STORAGE OF STEM CELLS

Adult stem cells can be easily procured and readily available from individuals at any stage in life which can provide a source of cells for autologous transplants. Such procedures invariably require stem cell storage, which is achieved by cryopreservation in liquid nitrogen. As long as they are dispersed in cryoprotectants stem cells can survive these low temperatures. Human periodontal ligament stem cells (PDLSCs), after cryopreservation for 6 months, are successfully recovered; although the number of colonies was less than for fresh PDLSCs, the proliferation rate was similar. Cryopreservation of intact teeth provides another potential storage method that can allow later extraction of stem cells demonstrating similar behavior as stem cells extracted from fresh teeth. [13,14]

TISSUE ENGINEERING OF STEM CELLS

Tissue engineering approach requires the three main key elements that is termed as tissue engineering triad

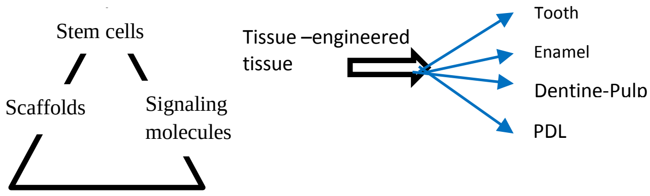

Fig 1: Triad of Tissue engineering

But a conductive environment is equally important for successful engineering of any tissue and/or organs.[4, 5]

Promising result have been shown by Dental tissue engineering using dental stem cells which can be considered as a novel approach to treat diseases like periodontitis, dental caries or to improve dental pulp healing and the regeneration of teeth.[15]

FUTURE SCOPE IN DENTISTRY

It is imperative for the researchers to have proper knowledge about differentiation of stem cells and how to control the differentiation .The main goal of endodontic treatment is to regenerate the pulp which can possibly be achieved by use of stem cells. In addition to it there are scope to regenerate the whole tooth with stem cells which could mark a revolutionary achievement in the dentistry. There is substantial evidence that dental ectomesenchymal stem cells are more promising for dentistry in future.[16]

Development in stem cell therapy is stirring up in a way that they are beyond our imaginations. Consuming stem cells and developing cell-based regenerative therapies for the repair of the tooth (enamel, dentin, and cementum) and tooth supporting, periodontal ligament is a novel striking approach. Stem cell therapy can be delivered internally in recruited area to regenerate craniofacial structures in temporary scaffolding biomaterials which would change the current clinical practice by replacing durable materials such as amalgam, composites, and metallic alloys. Dentistry can touch its new heights if craniofacial tissue engineering becomes a part of clinical practice.[17,18]

Dental pulp tissue is thought to be derived from migrating neural crest cells during development. Dental ectomesenchymal stem cells, DPSCs were found to be useful in cell based therapies to treat neurological diseases and injury.[19]

CONCLUSION

As the dental pulp stem cells can be easily procured and are readily available it is considered to be the most feasible source of adult mesenchymal stem cells which can be used for regenerative medicine. DPSCs, SHED cells, SCAP cells, PDLSCs, and DFPCs are the human dental stem/progenitor cells which are being highly studied for regenerative dental procedures.

But still the research is in the infancy stage i.e it is done for animal models and it will take time to come into clinical practice. If this dream becomes reality than there will be increased possibility of regenerating pulp cells in root canal treatment as well as possibility to regenerate whole tooth with DPSCs. Stem cell regeneration therapy can become the part of our clinical practice if different faculties of science like clinicians, engineers, scientists, and technicians work together by contributing his own area of expertise to expand research. There is an extensive need to translate preclinical research in to clinical realities

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