

## Review Article

# Stem cells-the hidden treasure:A strategic review

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### ABSTRACT

In today's scenario, medical and dental professionals face a mammoth task while treating perplexing medical situations like organ failure or tissue loss. Though, different strategies exist to replace them, but ideal one is the same natural tissue or organ. In this aspect, stem cells have emerged in a promising way to provide an ideal replacement. There are different types of stem cells starting from the embryonic stage referred to as human embryonic stem cells to adult stem cells. Though in dentistry stem cell research is lagging as compared to the medical field but still a lot progress has been achieved in recent years. The stem cells have been isolated from dental pulp, human exfoliated deciduous teeth, and apical papilla and so on. These stem cells have provided exciting results like dentin-pulp regeneration, periodontal regeneration but ambiguity still prevails. As a result, much has to be further researched before its clinical application becomes a reality. Hence, these stem cells opened a new avenue in the field of regenerative dentistry.

**Key Words:** Human embryonic stem cells, pluripotent, regenerative dentistry, stem cells, totipotent

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## INTRODUCTION

Tissue loss or organ failures are the major health care problems faced by medical and dental health care professionals all over the world. The currently used alternatives such as mechanical devices or artificial prostheses do replace the tissue or organ but don't restore the tissue or organ function and hence are unable to maintain the integrity of host tissue. Furthermore, mechanical devices or artificial prosthesis are subjected to wear upon long-term implantation, and could induce an inflammatory response in the host.<sup>[1]</sup>

It is these critical issues that have led to the question: What is the ideal replacement of lost tissues?

The gold standard to replace an individual's lost or damaged tissue is the same natural healthy tissue. This standard has led to the concept of tissue engineering that is regenerating new tissue from pre-existing tissue. The field of tissue engineering has developed over the past decade to re-create functional, healthy tissues and organs in order to replace diseased, dying, or dead tissues.

This review summarizes the latest stem cell research and development for dental, oral and craniofacial applications. Stem cell research and development will, over time, transform dental practice in magnitude far greater than did amalgam or dental implants. Metallic alloys, composites and even titanium implants are not permanent solutions. In contrast, stem cell technology will generate native tissue analogs that are compatible with the patient's own.

There are also many legal and social questions that must be addressed before stem cell-based therapies become clinically available. Legal issues that will affect stem cell applications include how to address intellectual property concerns and how to apply and enforce diverse and sometimes conflicting state and national laws. The social issues include, concerns

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about the destruction of embryos, the distribution of the benefits of research, and the protection of both physical and privacy interests of egg and sperm donors and clinical research subjects.<sup>[2]</sup>

By drawing on expert scientists, doctors, bioethicists, and others, the potential of stem cell technologies for medicine and dentistry, their ethical implications and moral dilemmas of stem cell research can be unearthed.

## STEM CELLS

The stem cells are unspecialized cells in the human body that are capable of becoming specialized cells, each with new specialized cell functions. Basically, a stem cell remains uncommitted until it receives a signal to develop into a specialized cell.

The best example of a stem cell is the bone marrow stem cell that is unspecialized and able to specialize into blood cells, such as white blood cells and red blood cells, with their pre-assigned functions. Thus, one cell type stems from the other and hence, the term “stem cell.”

The word “stem” actually originated from old botanical monographs from the same terminology as the stems of plants, where stem cells were demonstrated in the apical root and shoot meristems that were responsible for the regenerative competence of plants. Hence also the use of the word “stem” in “meristem.”<sup>[3]</sup>

The stem cells can be defined by three features, but these are not necessarily true of all stem cells<sup>[4]</sup>

1. Self-renewal = Extensive proliferation: The ability to self-renew has been linked to a stem cell’s ability to divide extensively to form vast numbers of cells. However, a stem cell is not immortal, but is endowed with a certain restricted capacity to self-renew related to how fast a tissue turns over. For example-one daughter cell remains a stem cell while the other becomes more committed to forming a particular cell type (a “committed progenitor”) by a process called “asymmetric division.”
2. Clonogenicity = Stemness: A stem cell is thought to be “clonogenic,” which means that it can proliferate to form a colony of cells. However, while clonogenicity is part of the essential assay in defining a stem cell (that is a single cell capable of proliferating and forming multiple cell types), not all cells that form colonies qualify as stem cells.

3. Stemness = Undifferentiation: In many cases, a stem cell is thought to be an undifferentiated cell type, but there are instances in which a cell with differentiated character can behave as a stem cell. For example, multipotent adult stem cells that are sometime tissue specific and at times may form one type of cell (unipotent).

### Classification and sources

Stem cells can be classified into various types:

1. Based on the ability to differentiate into various cell lineages<sup>[5]</sup> [Table 1].
  - a. Totipotent
  - b. Pluripotent
  - c. Multipotent fetal stem cells
  - d. Multipotent adult stem cells
2. Based on age at which the stem cells can be derived [Table 2].
  - a. Embryo derived stem cells<sup>[6]</sup>
  - b. Fetal stem cells<sup>[7-11]</sup>
  - c. Adult stem cells<sup>[12-14]</sup>
  - d. Dental stem cells<sup>[15-19]</sup>

Dental stem cells are further classified into:

- a. Dental pulp stem cells (DPSCs)
- b. Stem cells from human exfoliated deciduous teeth (SHED)
- c. Periodontal ligament stem cells (PDLSCs)
- d. Stem cells from apical papilla (SCAP)
- e. Side population cells (SPCs)
- f. Tooth germ progenitor cells (TGPCs)

### DPSCs

Stem cells are a matter of great interest and research activity. They have been isolated from differentiated

**Table 1: Stem cells classification based on the ability to differentiate into various cell lineages<sup>[5]</sup>**

Types of cells	Functional characteristics
Totipotent	The fertilized egg, capable of independently giving rise to all embryonic and extra embryonic tissues
Pluripotent	The inner cell mass of the blastocyst in the developing zygote and embryonic stem cells in culture, capable of giving rise to all embryonic cells and tissues
Multipotent fetal stem cells	Thought to be tissue-specific and sometimes form only one type of cell (unipotent)
Multipotent adult stem cells	Cells derived from the three embryonic germ layers (ectoderm, mesoderm and endoderm) that become more and more committed to generating particular cells as organs and tissues are formed

**Table 2: Classification depending on age at which the stem cells can be derived**

Types of cell	Characteristic features
Embryo derived stem cells	Two types: 1. ESCs. 2. EGCs 1. ESCs ESCs were first described by Martin (1981) at the University of California, San Francisco These ESCs are derived from the inner cell mass of the blastocyst which develops 5-7 days after the fertilization of an egg by a sperm and are pluripotent because they can differentiate into all of the cell types of the body. 2. EGCs: Human EGCs which are also stem cells, originate from the primordial germ cells of the gonadal ridge of 5-7 weeks old fetuses. Human EGCs have been successfully isolated and characterized. <sup>[6]</sup> These stem cells are pluripotent and are able to produce cells of all three germ layers
Fetal stem cells	These cells can be derived either from the fetus proper or the supportive extra embryonic structures that are of fetal origin. The extraembryonic structures include amniotic fluid, <sup>[7]</sup> amniotic membrane, <sup>[8]</sup> umbilical cord, <sup>[9,10]</sup> and placenta <sup>[11]</sup> from which stem cells have been successfully isolated
Adult stem cells	These stem cells are lower in the stem cell hierarchy. They are thought to have lost the pluripotent capability that ESCs have. However, throughout the organism's life, non-ESCs retain a multipotent differentiation potential. The stem cells can be derived from several sources like Adipose tissue, <sup>[12]</sup> bone marrow, <sup>[13]</sup> and skin. <sup>[14]</sup>
Dental stem cells	A variety of dental MSCs has been isolated from dental tissues. These include DPSCs, <sup>[15]</sup> SHED, <sup>[16]</sup> PDLSCs, <sup>[17]</sup> SCAP, <sup>[15]</sup> SPCs <sup>[18]</sup> and TGPCs <sup>[19]</sup>

ESCs: Embryonic stem cells; EGCs: Embryonic germ cells; DPSCs: Dental pulp stem cells; SHED: Stem cells from human exfoliated deciduous teeth; PDLSCs: Periodontal ligament stem cells; SCAP: Stem cells from apical papilla; SPCs: Side population cells; TGPCs: Tooth germ progenitor cells; MSCs: Mesenchymal stem cells

sources in the body, but none has attempted to isolate stem cells from dental tissues. Therefore, the identification and isolation of an odontogenic progenitor population from adult dental pulp tissue for dental repair has never been done.

However, it is known that under certain conditions, cultures of pulp cells derived from early developing dental root tissue and pulp tissue can develop an odontoblast-like appearance with the capacity to form mineralized nodules *in vitro*,<sup>[20]</sup> a trait normally attributed to cultures of bone or bone marrow cells.<sup>[21,22]</sup>

Gronthos *et al.*<sup>[15]</sup> for the first time in the history of dental stem cells successfully isolated them from human impacted third molars. Based upon analogy they compared bone marrow stromal stem cells (BMSSCs) with DPSCs and found out that

- DPSCs exhibited a higher proliferation rate compared with bone marrow stromal stem cells (BMSCs) *in vitro*
- Both DPSCs and BMSSCs express smooth muscle and endothelial markers
- Demonstrates the potential of DPSCs to form calcified deposits *in vitro*, as do BMSSCs.<sup>[21,22]</sup> However, DPSCs formed sparse and dense calcified nodules, and failed to develop lipid-laden adipocytes, whereas BMSSCs developed extensive sheets of calcified deposits and abundant lipid-laden adipocytic clusters

- They found out that DPSCs express dentin sialophosphoprotein (DSPP), a gene that encodes for dentin sialoprotein<sup>[23]</sup> and dentin phosphoprotein,<sup>[24]</sup> which is important for dentinogenesis.<sup>[25]</sup>
- They are also able to generate a dentin pulp-like complex by *in vivo* transplantation.

Hence, the postnatal dental pulp contains cells that are clonogenic, highly proliferative, and capable of regenerating a tissue, properties that effectively define them as stem cells and are therefore, termed as DPSCs.

#### SHED

SHED were identified to be a population of highly proliferative, clonogenic cells capable of differentiating into a variety of cell types including neural cells, adipocytes, and odontoblasts.<sup>[16]</sup>

Miura *et al.*<sup>[16]</sup> demonstrated that SHED has the ability to induce recipient cell-mediated bone formation *in vivo*. They also concluded that SHED could not differentiate directly into osteoblasts but did induce new bone formation by forming an osteoinductive template to recruit murine host osteogenic cells implying that deciduous teeth may not only provide guidance for the eruption of permanent teeth as generally assumed, but may also be involved in inducing bone formation during the eruption of permanent teeth.

SHED, just like DPSCs<sup>[26]</sup> and BMSSCs<sup>[27]</sup> were also capable of differentiating into neural-like cells after *in vivo* transplantation.

SHED is distinct from DPSCs with respect to their higher proliferation rate, increased cell-population doublings, sphere-like cell-cluster formation, osteoinductive capacity *in vivo*, and failure to reconstitute a dentin–pulp-like complex.<sup>[16]</sup>

Hence, SHED represents a population of postnatal stem cells capable of extensive proliferation and multipotent differentiation. Deciduous teeth therefore, may be an ideal resource of stem cells to repair damaged tooth structures, induce bone regeneration, and possibly to treat neural tissue injury or degenerative diseases.

#### PDLSCs

These cells were first of all isolated from the periodontal ligament (PDL) tissue obtained from surgically extracted human third molars by Seo *et al.*<sup>[17]</sup>

Following conclusions can be drawn from their studies:

- They assessed the expression level of scleraxis, a tendon specific transcription factor, in PDLSCs since PDL is similar to tendon with respect to its dense collagen fiber structure and its ability to absorb mechanical stress during normal physiological activity. PDLSCs expressed a higher level of scleraxis than did BMSSCs and DPSCs, suggesting that PDLSCs might belong to a unique population of postnatal mesenchymal stem cells (MSCs).
- They also found out that although PDLSCs were found to express an array of cementoblastic/osteoblastic markers, they did not form dentin or bone and its associated hematopoietic components *in vivo*.
- To validate the PDLSCs to differentiate into functional cementoblast-like cells, *ex-vivo*-expanded PDLSCs were transplanted into immunocompromised mice. A typical cementum/PDL-like structure was regenerated, in which a thin layer of cementum-like tissue formed on the surface of the carrier, along with condensed collagen fibers with sparse cells that resembled PDL structures.
- PDLSCs, like DPSCs, had the potential to differentiate into other cell lineages such as adipocytes.

Hence, postnatal PDLSCs are clonogenic, highly proliferative cells and capable of regenerating cementum/PDL-like tissues, properties that effectively define them as stem cells. Consequently, PDLSCs have potential for use in periodontal tissue regeneration.

Many new approaches have been developed for treating periodontal defects, including guided tissue regeneration, growth factors, and enamel matrix proteins,<sup>[28-33]</sup> but so far, none of these treatments have provided consistently predictable outcomes.

Still, further studies are required to unleash the therapeutic capacity of these cells to repair periodontal defects induced by periodontal disease.

#### SCAP

The discovery and isolation of a new population of MSCs residing in the apical papilla of incompletely developed teeth promoted immense interest.<sup>[34]</sup> These cells are termed as SCAP.

The tissue is loosely attached to the apex of the developing root and can be easily detached with a pair of tweezers. Apical papilla is apical to the epithelial diaphragm, and there is an apical cell-rich zone lying between the apical papilla and the pulp. Importantly, there are stem/progenitor cells located in both dental pulp and the apical papilla, but they have somewhat different characteristics.<sup>[34]</sup> Because of the apical location of the apical papilla, this tissue may be benefited by its collateral circulation, which enables it to survive during the process of pulp necrosis.

#### SPCs

SPCs were detected in adult pulp tissue from several species, including, human, bovine, canine, and porcine species. SPCs from dental pulp have been isolated and characterized as a new alternative source by Iohara *et al.*<sup>[18]</sup> They were purified by flow cytometry on the basis of efficient efflux of vital fluorescent dye Hoechst 33342.<sup>[35]</sup>

The three key characteristic features under which SPCs is studied were self-renewal capacity, expression of stem cell surface markers, and multi-lineage differentiation.<sup>[18]</sup>

#### TGPCs

They were first isolated by Ikeda *et al.*<sup>[19]</sup> in 2007 from discarded third molar.

These TGPCs were negative for hematopoietic markers (CD [CD is not an abbreviation, instead

CD itself is a name of a hematopoietic marker] 14, CD34, and CD45) but strongly positive for markers present in mesenchymal cells (CD29, CD44, CD90, CD105, and CD166) and weakly positive for STRO-1 [STRO-1 is not an abbreviation, instead STRO-1 itself is a name of a hematopoietic marker], indicating that TGPCs have a mesenchymal phenotype. TGPCs showed high proliferation activity and capability to differentiate *in vitro* into cells of three germ layers including osteoblasts, neural cells, and hepatocytes.<sup>[19]</sup>

### Potential applications of stem cells in dentistry

1. Regeneration of dentin
2. Pulp regeneration
3. Regeneration of periodontium
4. Regeneration of the whole tooth.

#### *Regeneration of dentin*

Regeneration of dentin could have a marked effect in dentistry

1. As an enhanced pulp capping agent,
2. As perforation repair material
3. As a potential means of reducing tooth sensitivity often associated with the placement of tooth fillings.

Successful attempts have been made by several investigators leading to regeneration of dentin. These studies demonstrated that recombinant human bone morphogenic protein-7 (BMP-7) complexed with an insoluble type I collagen matrix delivery vehicle predictably and reliably induced reparative dentinogenesis when placed on the freshly cut healthy pulp tissues in non-human primates<sup>[36]</sup> although dentin failed to regenerate in infected pulps.<sup>[37]</sup>

Therefore, further investigations are needed to make dentin regeneration practical.

#### *Pulp regeneration*

The various techniques have been suggested,<sup>[38]</sup> which will aid in regeneration of pulp and restoring pulp vitality such as root canal revascularization, postnatal stem cell therapy, pulp implant, scaffold implant, 3-D cell printing, injectable scaffold, and gene therapy. The main objective is to restore tooth vitality. However, much of the research is still needed to bring this to reality as a much awaited restorative procedure.

#### *Regeneration of periodontium*

Periodontitis is a disease of the periodontium that is characterized by the irreversible loss of connective tissue attachment and supporting alveolar bone.<sup>[39]</sup>

Ultimately, this chronic inflammatory disease can lead to loss of the affected teeth.

The main rationale behind periodontal therapy is to regenerate periodontium that is lost by the progression of periodontitis and periodontal regeneration has come to the forefront as much awaited procedure to restore periodontium. Successful regeneration requires the coordination of many events at both cellular and molecular levels.

Though, local application of human recombinant cytokines accelerates the regeneration of periodontal tissues, but the main aim is regenerate periodontium as a whole. In a recent study utilizing recombinant human fibroblast growth factor-2 (FGF-2) with 3% hydroxypropylcellulose as scaffold, demonstrated gains in clinical attachment level and alveolar bone gain at 36 weeks suggesting that some efficacy could be expected from FGF-2 in stimulating regeneration of periodontal tissue in patients with periodontitis.<sup>[40]</sup>

Therefore, further research is still needed to make its application practical along with search of other biomolecules and scaffolds.

#### *Regeneration of the whole tooth*

Loss of tooth occurs due to a variety of oral diseases and physiological causes, such as dental caries, periodontal disease, trauma, genetic disorders and aging, and can lead to physical and mental suffering that markedly lower an individual's quality of life (QOL).<sup>[41,42]</sup> Keeping one's own teeth throughout life is not only beneficial for enjoying food but also helps in maintaining QOL.

Current treatment modalities for replacing a tooth include bridges, artificial dentures and implants. However, these non-biological "teeth" have several disadvantages as compared with a biological one, including uncomfortable sensation, insufficient biocompatibility, damage to the surrounding tissues, and unpredictable long-term therapeutic efficacy.

Therefore, it's highly imperative to develop a technique that allows the regeneration of teeth in the individual mouth.

Thus, the public interest in tooth regeneration is high, and it is of particular relevance to the field of regenerative medicine.

### **Ethical issues**

The main bioethical issues associated with human stem cells involve their derivation and use of research. Although there are interesting ethical

issues surrounding the collection and use of somatic (adult) stem cells from aborted fetuses and umbilical cord blood, the most intense controversy to date has focused on the source of human embryonic stem (hES) cells. At present, new ethical issues are beginning to emerge around the derivation and use of other hES cell-like stem cells that have the capacity to differentiate into all types of human tissue. In the near future, as the stem cell field progresses closer to the clinic, additional ethical issues are likely to arise concerning the clinical translation of basic stem cell knowledge into reasonably safe, effective, and accessible patient therapies.<sup>[43]</sup>

## CONCLUSION

Stem cell research is lagging in dentistry as compared to the medical field but still, *in vitro* studies and trials on animals have yielded interesting results with possible clinical applications. Various types of stem cells have been isolated from human dentition that includes, DPSCs, SHED, PDLSCs, SCAP, and SP cells. The best cells being the SCAP that show both CD 24, marker of pluripotency as well as DSPP expression either of which may be expressed or absent in the remaining stem cells. Recently, new type of stem cells have been explored which are referred to as TGPCs which has shown to give promising results but further studies are required to exploit their full potential.

The ambiguity about the application of stem cells is still persisting, whilst a new avenue has been opened in the field of regenerative dentistry with the exploration of these stem cells.

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