

## REVIEW ARTICLE

# Dental Stem Cells: Part of Regenerative Medicine

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## ABSTRACT

Stem cells are undifferentiated cells that can give rise to an indefinite number of more cells of the same type, and some specific kinds of cells by differentiation. These cells can be differentiated into odontogenic, osteogenic, adipogenic, myogenic, neurogenic, and melanocytic cells and even to corneal cells and islet cells of pancreas. Stem cell therapy is emerging as a promising treatment modality to treat certain diseases and injury with a wide range of medical benefits. The combined advantages of multipotency/pleuropotency and the ease with which stem cells can be extracted from teeth have made dental pulp stem cell/stem cells from exfoliated deciduous teeth attractive options in regenerative dentistry and medicine. The aim of this review, therefore, is to give an overview of the papers that have described the use of dental stem cells in cell therapy or bioengineering. The search was done using “dental pulp stem cell” and “human exfoliated teeth stem cell” as the keywords.

**Keywords:** Dental pulp stem cell, Regenerative medicine, Stem cells from exfoliated deciduous teeth.

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## INTRODUCTION

Stem cells have a major role in regenerative medicine. These unspecialized, undifferentiated cells are different from other cells in the body, as they are capable of dividing and renewing themselves for long periods, and can give rise to specialized cell types. There are two main types of stem cells—embryonic stem cells and adult stem cells, according to their origin and differentiation potential.

Mesenchymal stem cells (MSCs), a type of the adult stem cells, can be isolated from bone marrow, umbilical cord, placenta, amniotic fluid, liver, adipose tissue,

synovial membrane, and teeth. Stem cells are found in the dental pulp of permanent<sup>1</sup> and deciduous teeth.<sup>2</sup> Inside the tooth, there are two types of stem cells, Dental pulp is the soft live tissue inside a tooth containing stem cells, known as dental pulp stem cells (DPSCs) and stem cells from exfoliated deciduous teeth (SHED). However, other sources of dental stem cells have been identified, such as apical papilla, periodontal ligament (PDL), and the dental follicle.<sup>3-5</sup> These cells can differentiate into various cell types like chondrocytes, osteoblasts, and adipocytes. A large number of studies have evaluated these cells for dental<sup>6</sup> as well as nondental<sup>7,8</sup> biomedical applications. Dental stem cells can also generate solid structures of the body, such as bone, new dental tissue (cementum, dentin, PDL, and dental pulp), cartilage, muscle, and can also regenerate nerves. Thus, they can be used to replace or repair damaged cells, and can change the treatment of conditions like cancer, diabetes mellitus, corneal defects, Alzheimer’s and Parkinson’s disease, and even paralysis, and even have promising use in patient-specific gene therapy.

## ISOLATION AND CRYOPRESERVATION OF DENTAL STEM CELLS

Stem cells can be recovered from a healthy viable dental pulp, diffusely spread throughout the cellular zone adjacent to the nerve and blood vessels within the pulp. For a healthy pulp, the tooth must be free of infection, deep caries, and other pathologies, and should have an intact blood supply. Stem cells can be collected from baby teeth as they naturally loosen, from wisdom teeth, or supernumerary teeth being extracted, or from teeth extracted for orthodontic reasons. It is best to recover stem cell, when a patient is young and healthy, and the stem cells are most proliferative. Stem cells can also be recovered from the permanent teeth of middle-aged individuals. If the pulp of deciduous teeth that have fallen out on their own is necrotic, stem cells cannot be collected from these teeth.

After collection of stem cells, cryopreservation is done. Cryopreservation is the process of preserving cells or tissues at subzero temperatures, at which biological activity or any cellular process that leads to cell death is stopped. These cells can be cryopreserved for a long time and, when needed, can be used.<sup>9-11</sup>

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## USAGE AND APPLICATIONS OF DENTAL STEM CELLS

### Muscular Dystrophy

The DPSCs can be used in patients of muscular dystrophy. In a research done by Kerkis et al,<sup>12</sup> these cells were transplanted into four littermate dogs (aged 28–40 days) by either arterial or muscular injections. Two noninjected dogs were kept in the control group. Then immune reactions were analyzed by blood investigations. Migration, engraftment, and myogenic potential of these stem cells were recorded, and the expression of human dystrophin in affected muscles was also noticed. No signs of immune rejection were observed, and these results suggested that DPSC cell transplantation may be done in cases of muscular dystrophy without immunosuppression.

### Pulp and Tooth Regeneration

Regenerative endodontics is done in immature permanent teeth (teeth in which roots are not fully developed). When regenerative endodontic procedures are followed in non-vital teeth with incomplete root apex formation, stem and progenitor cells from the pulp and/or periodontium can contribute to continued root development.<sup>13,14</sup> Various other studies also support the fact that DPSCs have significantly greater osteogenic potential and the capacity to produce a comparatively high volume of mineralized matrix as compared with other MSCs, thus suggesting that these cells show promise for regenerative dental therapies.<sup>15</sup> In another attempt at tooth regeneration, epithelial and MSCs with a collagen scaffold *ex vivo* have been implanted into the cavity of adult mice. All dental structures were observed with this technique.<sup>16,17</sup>

### Periodontal Tissue Regeneration

Periodontal diseases can cause destruction of tooth-supporting structures, i.e., PDL, cementum, and alveolar bone. The goal of periodontal treatment is to stop the progression of the disease and regenerate the structure and function of the damaged tissues. Conventional non-surgical or surgical treatments, such as scaling and root planing, open flap debridement, and osseous surgery can control the progression of periodontal disease.

Periodontal regeneration has been defined as the regeneration of alveolar bone, PDL, and cementum over a previously diseased root surface. Several treatment modalities have been developed to achieve periodontal regeneration, including guided tissue regeneration, use of bone grafts, application of growth factors and host modulating factors, and the combination of the above methodologies. Although there is some evidence showing that periodontal regeneration can be achieved

by employing these techniques, all regenerative treatment modalities have shown limited success, especially in challenging clinical situations.

The concept that the stem cells may reside in the periodontal tissues was proposed approximately 20 years ago by Melcher,<sup>18</sup> who queried whether the three cell populations of the periodontium (cementoblasts, osteoblasts, and PDL fibroblasts) were derived from stem cells. The studies of McCulloch<sup>19-21</sup> in 1987 identified a small population of progenitor cells adjacent to blood vessels within PDL. These cells demonstrated some classical cytological features of stem cells, including small size, responsiveness to stimulating factors, and slow cycle time. When *ex vivo* expanded, PDL SCs are implanted *in vivo* with a suitable scaffold, atypical cementum/PDL-like structure forms.<sup>22,23</sup>

### Immunosuppression

In addition to regenerative properties, dental stem cells are also immunosuppressive and immunomodulatory in a number of situations. They interfere with different pathways of the immune response by means of direct cell-to-cell interactions and soluble factor secretion. They inhibit cell proliferation of T-cells, B-cells, natural killer (NK) cells, and dendritic cells in certain situations. Along with that, these MSCs can stop a variety of immune cell functions: Cytokine secretion and cytotoxicity of T and NK cells; B-cell maturation and antibody secretion; dendritic cells maturation and activation; as well as antigen presentation. Various studies have been designed to test the efficacy of MSC therapy in two different immune settings: The prevention or treatment of allograft rejection episodes and the ability to suppress abnormal immune response in autoimmune and inflammatory diseases. These include treatment of autoimmune diseases, such as Crohn's disease, ulcerative colitis, rheumatoid arthritis, lupus diseases, type 1 diabetes mellitus, multiple sclerosis, prevention of allograft rejection, enhancement of the survival of bone marrow and kidney grafts, and treatment of resistant graft *vs* host disease.<sup>24,25</sup>

### Neural Tissue Regeneration

Nervous tissue presents inherent difficulties for its effective regeneration. Because the origin of DPSC is within the neural crest, they can be differentiated into neural crest-derived cells including neuron and glia cells. The DPSCs also secrete a wide variety of chemokines and neurotrophins, which promote neuronal cells to survive and differentiate. In various studies, evidence has shown that human DPSCs engraftment recovered neuronal tissue damage of central nervous system injuries. Thus, these stem cells can be a new future for treatment of nervous

system diseases, such as spinal cord injury, stroke, and neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases.<sup>26</sup>

### Diabetes

The DPSC can be used to produce insulin-producing cells and were used successfully to construct the recombinant insulin-producing cells.<sup>27</sup>

In another study, DPSCs were separated and cultured. The multilineage differentiation capacity was observed. Compared with the control group, insulin secretion was increased significantly by these bioengineered islet cells.<sup>28</sup> Govindasamy et al<sup>29</sup> explored the potential of DPSCs to differentiate into pancreatic cell lineage resembling islet-like cell aggregates. The DPSC-derived islet cell aggregates have been observed to release insulin in a glucose-dependent manner, thus confirming functionality.

### Myocardial Infarction (Heart Attack)

Although various advances in prevention and treatment of myocardial infarction (MI) have occurred, but this still remains one of the major causes of mortality. Stem cell therapy-based options can provide a promising alternative to the conventional therapies for this life-threatening condition. In this regard, cardiomyocyte differentiation of DPSCs has been studied by different researchers.<sup>30,31</sup>

The capacity of the stem cells derived from the bone marrow stem cells (BMSCs), adipose tissue cells, and DPSCs to differentiate into cells with a cardiac phenotype was evaluated by Arminan et al.<sup>30</sup> The result showed that MSCs could change into cardiomyocytes and support the potential use of MSCs in stem cell-based cardiac therapies. The expression of cardiac specific markers like Troponin-1, beta-myosin heavy chain, atrial natriuretic peptide, and alpha sarcomeric actinin were also detected in DPSCs. The therapeutic potential of DPSCs in the repair of MI was also evaluated by Gandia et al.<sup>31</sup> The cardiac function also improved by the percentage of change in the anterior wall thickening, left ventricular fractional area change, reduction in the infarct size, and increased angiogenesis.<sup>31</sup> The angiogenesis was also increased relative to the control-treated animals.

### Repairing Craniofacial and Skeletal Bone

The SHED were transplanted with a carrier (hydroxyapatite/tricalcium phosphate) into the calvarial defects in immunocompromised mice, which showed repair of the defects with substantial bone formation concluding that SHED, derived from neural crest cells, may exert osteogenesis. The SHED might be a suitable resource for orofacial bone regeneration.<sup>32</sup>

For reconstruction of cranial bone loss, transplant of bone autograft is the treatment of choice. However, it is inadequate for large defects, and is associated with several risks as rejection, infection, graft or flap failure, and even donor site morbidity. Use of MSCs for bone reconstruction has been an active growing area that can facilitate bone healing in difficult circumstances, and possibly in the near future, it will replace conventional therapeutic modalities for the repair of large cranial defects.<sup>33</sup> In another attempt to regenerate bone in a significant osseous defect, various stem cells from deciduous teeth, using platelet-rich plasma as a scaffold were used, and results demonstrated that stem cells from deciduous teeth, dental pulp, and bone marrow with PRP have the ability to form bone. This preclinical study suggests role of stem cell therapy in orthopedics and oral maxillofacial reconstruction for clinical application.<sup>34</sup>

To examine the efficacy of SHED in regenerating orofacial bone defects, isolated stem cells from pig deciduous teeth were engrafted into the critical-size bone defects in swine mandible models. Results indicated that stem cells from miniature pig deciduous teeth (an autologous and easily accessible stem cell source) were able to engraft and regenerate bone to repair critical-size mandibular defects at 6 months postsurgical reconstruction.<sup>35</sup>

In a comparative study, to investigate cell-based effective bone engineering and the correlation between the osseointegration of dental implants and tissue-engineered bone using DPSCs, BMSCs, and periosteal cells, different materials were implanted in the mandibular defects and the sites were allowed to heal. The DPSC showed the highest osteogenic potential and may be a useful cell source for tissue-engineered bone around dental implants.<sup>36</sup>

### Corneal Repair

*In vitro* studies have shown that SHED cells and limbal stem cells express similar markers. When transdifferentiated corneal cells from dental stem cells were transplanted onto damaged ocular surface, successful repair of scarred rabbit cornea was observed. Thus this shows that transplanted dental stem cells may have potential to be used in humans with bilateral corneal damage and/or total limbal stem cell deficiency.<sup>37,38</sup>

### Tissue Ischemia

Angiogenesis was found to be improved when stem cells from swine deciduous and permanent teeth were used to treat ischemia in a hind limb ischemia mouse model, as the cells helped to increase the blood supply and contributed to the formation of a new capillary network.<sup>39</sup>

## Wound Healing

The SHEDs were reported to help accelerate wound healing when associated with fibroblast growth factor.<sup>40</sup>

## DISCUSSION

Obtaining SHEDs is simple and convenient, with little or no trauma.<sup>2</sup> Every child loses primary teeth, which creates the perfect opportunity to recover and store this convenient source of stem cells—should they be needed to treat future injuries or ailments. Moreover, using one's own stem cells creates few, if any, risks for developing immune reactions or rejection following transplantation and also eliminates the potential of contracting disease from donor cells. Stem cells can also be recovered from wisdom teeth that need extraction and permanent teeth, which are extracted for orthodontic reasons. It is best to recover stem cells when a child is young and healthy because the cells at that time are strong and proliferative. Banking on one's own tooth-derived stem cells is a reasonable and simple alternative to harvesting stem cells from other tissues.

## CONCLUSION

Stem cell therapy is emerging as a revolutionary treatment modality to treat diseases and injury, with wide-ranging medical benefits. Current research in regenerative medicine is directed toward using dental stem cells to treat diabetes mellitus, impaired vision, extensive burns, cardiomyopathies, neurodegenerative diseases (Parkinson's disease, Alzheimer's disease), muscular dystrophy, baldness, lupus erythematosus, and pulp/tooth regeneration.

There is much research left to be conducted, but the existing research has clearly shown that dental stem cells have immense scope and magnitude for stem cell therapies.

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