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Stem Cells in Regenerative Dentistry

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Introduction

Stem cells are self-replicating cells with the ability to differentiate into many cell types *[1]*. Loss of tooth structure and surrounding tissues are commonly results from caries, periodontal diseases and traumatic injuries. Self-healing ability of dental structures is limited which necessitates more effective treatment modalities *[2]*. Regeneration of pulp and periodontal tissue is an attractive approach for alternative management modalities of damaged tissues. It aims to restore the function as well as structures of dental tissues *[3]*. Dental stem cells are characterized by easy isolation, responsiveness to expansion, retaining stemness and ability to promote pulpal as well as periodontal regeneration *[4]*. Recently, Dental stem cells were utilized in multiple *in vitro* and *in vivo* studies and showed an ability to regenerate dental structures with important challenges *[1, 5]*.

Sources of Dental Stem Cells

Tooth extraction for many reasons may act as an easy and accessible source for obtaining stem cells. It is easily practiced method and doesn't need more surgical intervention asobtaining stem cells from bone marrow. Furthermore, after oral surgery procedures, some tissue can be maintained to isolate stem cells for further regeneration *[6, 7]*.Inner layers of the pulp and periodontal ligament (PDL) may act as good sources for human dental stem cells. They have high plasticity and regeneration ability ranging from 30 to 50%, with better immunoregulatory behavior in comparison to bone marrow stem cells *[8][9]*.In addition, deciduous teeth extracted from children represent a good source of stem cells *[10]*.

Dental stem cells can be isolated from dental follicles. Studies have shown that dental follicle stem cells (DFSCs) were able to promote regeneration of cementum, PDL and alveolar bone *in vitro* and *in vivo [11, 12]*.Third molar tooth is the best source for the isolation of dental pulp stem cells (DPSCs) *[13]*. Human stem cells may be obtained from bone marrow however it is a more invasive technique and it doesn't give a large number of stem cells. It is usually obtained from the iliac crest *[14]*.

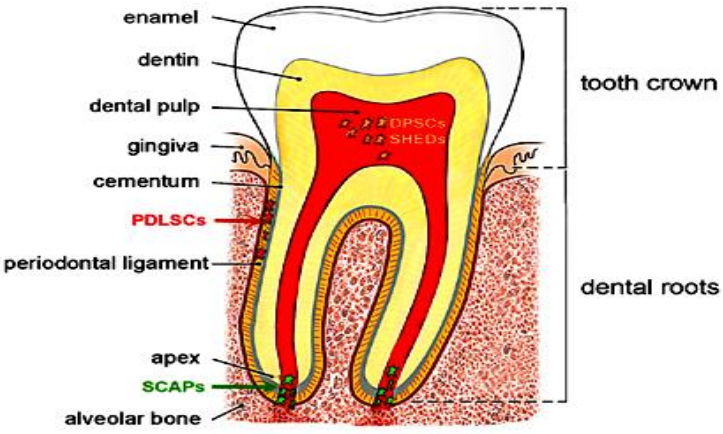

Figure (1): Stem cells obtained from human teeth. PDLSCs (Periodontal ligament stem cells), DPSCs (Dental pulp stem cells). SCAPs (stem cells from alveolar papilla), SHEDs (Stem cells from human exfoliated deciduous teeth).

Different Criteria of Stem Cell with a Dental Origin

DPSCs showed high expression of stem cell markers as CD90, CD73, CD105, CD29, CD13, and CD44 surface antigens. They were able to differentiate into Odontoblast-like cells, osteoblasts, adipocytes and neural cells *[13]*. Periodontal ligament stem cells (PDLSCs) are positive for STRO-1, CD146, CD73, CD90, and CD105 and can differentiate into Osteoblast-like cells, adipocytes, collagen-forming cells *[15, 16]*. In addition, stem cells isolated from the human pulp of

exfoliated deciduous teeth (SHED) can differentiate into osteoblasts, odontoblasts, adipocytes and neural cells so they can regenerate dentin, boneand non-mesenchymal tissue *[17, 18]*. Stem cells derived from apical papilla (SCAPs) are positive for stem cell markers as STRO-1, CD146, and CD24 and can differentiate into. Odontoblasts. Finally, DFSCs showed positivity for STRO-1, CD105, CD90, nestin, notch-1 and can enhance regeneration of PDL, cementum and alveolar bone *[19]***.**

Isolation of Stem Cells

No master isolation technique is superior to others. Researchers are seeking an efficient isolation technique that is able to maintain a sufficient number of stem cells that maintain the high regenerative ability. Enzymatic digestion of tissues is a good technique for a proper *in vitro* expansion of stem cells to obtain asufficient number for biomedical regeneration *[20]*.Isolation of each type of dental stem cells was reported. DFSCs and DPSCs showed comparative expansion rate, morphology, expression of stem cell markers and in vitro differentiation capacity *[21]*.

Application of Stem Cell in Dental and Periodontal Regeneration

Periodontitisis a common chronic inflammatory disease of the tooth supporting structure that is associated with loss of attachment and tooth mobility *[22]*.Periodontal regeneration aims to achieve significant phases of wound recuperating related toperiodontal improvement to reestablish lost tissues to their unique structure and function *[23, 24]*. PDLSCs were transplanted into surgically created periodontal defects and they showed high regeneration potential and differentiation into PDL cells *[25]*. Human periodontal stem cells were able to promote periodontal regeneration in mice *[26]*. Furthermore, autologous and allogenic stem cells were able to act as a treatment modality for periodontal diseases in animals as miniature swine and dog models *[27, 28]*. Despite the overallagreementascertained in preclinical animal studies assessing the potential of PDLSCs in regeneration of periodontal tissues, few human clinical studies were conducted *[29, 30]*.Transplantation of PDLSCs into immunocompromised mice showed an increased ability to regenerate cementum and PDL *[26]*.

Bone marrow derived stem cells obtained from extra oral tissue were utilized for periodontal regeneration. They showed regeneration ability for about 20% of cementum and alveolar bone in surgically created class III defects in dogs *[31]*.Combination of PDLSCs from human deciduous teeth with dentin blocks showed high regeneration potential with formation of cementum as well as PDL-like structures *[10]*.The regenerative potential of mesenchymal stem cells and PDL progenitor cells was tested by Kramer et al. They reported that PDL-like tissue can be developed from periodontal progenitor cells and from mesenchymal stem cells *[32]*.

DFSCs are the most common cells obtained from third molar teeth and were able to act as pioneeringcandidates for dental and periodontal regeneration. It can produce mineralized tissues and complex structures similar to dentin, dental pulp andPDL in xenograft models *[33]*. Combination of DFSCs cells with dentin matrix was transplanted into rate alveolar bone defect and they were able to enhance periodontal tissue and root formation *[34]*. *Nakashima et al* reported that Human DPSCs acted as safe and effectivecells for complete pulpregeneration in humans with irreversible pulpitis with no adverse events or toxicity *[35]*.

Endodontic treatment modalities lack the ability of pulp regeneration and are associated with loss of pulp vitality. New pulp regeneration techniques were introduced in the dental field to enhance the preservation of tooth structure and function *[36, 37]*.

In pulpal inflammation, DPSCs give rise to a new generation of odontoblasts that replace the disintegrated odontoblasts after attraction by signal molecules released from the pulp. This can help pulp regeneration and form reparative dentin. The reparative ability of periodontal tissue and pulp is not completely sufficient to totally replace the damaged tissue *[2, 35, 38]*. *Cordeiro et al* prepared dentin slices *invitro*and seeded them with stem cells and implanted them into immunocompromisedmice subcutaneously *[17]*. *Batouli et al* utilized stem cell in pulp regeneration as they transplant pulp stem cells into mice, after 16 weeks, they found that DPSCs enhanced new pulp tissue formation with fibroblasts, osteoblasts and newly formed blood vessels *[39]*. Application of stem cells in pulp regeneration still have some challenges as the signals that drive stem cells differentiation are not clarified[40]. Another study performed by *d'Aquino et al* Showed that *in vivo* transplantation of DPSCs showed differentiation into osteoblasts, endothelial cells and eventually to bone containing vessels *[41]*. Transplantation of DPSCs with granulocyte-colony stimulating factor in dog teeth after pulpectomy showed enhanced regeneration of entire pulp and new dentin formation *[42]*.

Challenges of Stem Cell Therapy in Dental Tissues Regeneration

Neural and vascular regeneration is one of the highlighted challenges in pulp regeneration with stem cells *[37]* which are limiting the success of dental and periodontal regeneration. Rapid development of vascularization to provide nutrition of the newly formed tissue is required *[17]*. Another challenge in stem cell application in dentistry is their mechanism in stimulation of dental tissue regeneration and the possible methods to overcome the technical problems still need further studies and clarification.

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