Review Article

Recent Advances of Stem Cells in Dentistry

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Abstract

Stem cells (SCs) have an ultimate potential of regenerating tissues and organs due to their salient properties. In the contemporary years, emergence of novel tissue bioengineering therapies and gene editing technologies has been a breakthrough in the field of SC research. A combination of these paradigm-shifting technologies with dental SCs definitely has brighter prospects in the upcoming decades. The goal of the current study of literature is to highlight the latest technologies and regenerative applications of SCs in the field of dentistry.

Keywords: Dental stem cells, gene therapy, regeneration

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Introduction

Stem cells (SCs) are an undifferentiated type of cells that has an innate capability to multiply into a multi-lineage type of cells through mitotic differentiation (stemness).[1-3] According to the traditional definition, these cells possess the potent capacity of indefinite "self-renewal" and they differ in terms of their location in the body and the variety of cells they can replicate.[4] Tissue-specific proteins in the cytoplasm indicate morphological differentiation of SCs microscopically.[5]

Recent researches in dentistry have revealed that SCs in order to maintain tissue homeostasis actively reside or differentiate in specific tissue sites known as "SC niche" which are especially located in the oral and maxillofacial region.[6,7] The quiescent SCs reactivate themselves and self-renew/repair the tissues they are present in such as teeth, bone marrow, skin, hair follicles, pancreas, intestine, and brain when there is any injury/damage.[8,9]

The oral cavity has a rich reservoir of SCs which are certainly accessible. Thus, the exceptional properties of SCs aid in the development of novel revolutionary tissue-engineering technologies such as manipulation of extracellular and *in vitro* cells so as to regenerate injured or diseased tissues and organs.[10-13]

Newer tissue bioengineering therapies using SCs thereby regenerate teeth[14,15] and it's associated structures including the alveolar bone,[16-18] dental pulp, and periodontal structures.[19] Recently, regenerative strategies are implemented in various structures such as the tongue,[20] salivary gland,[21] orofacial/craniofacial musculature,[16-18,22,23] and also the temporomandibular joint (TMJ).[24-28]

In addition, numerous translational studies incorporating various bioactive tissue-engineering elements in the dental-related SCs are being done in animal models for regeneration of tissues/organs.[29,30]

Types of Stem Cells

Embryonic stem cells

They are procured from the blastocyst (5–7 days) and have the potential to differentiate into all three primordial germinal layers, namely the ectoderm, endoderm, and mesoderm. Embryonic germ cells arise from the primitive cells of gonadal ridge (5–9 weeks) of fetuses.[31,32]

Fetal stem cells

These are a type of embryonic cells consisting of fetal hematopoietic SCs, progenitor cells of islets of pancreas, and neural crest SCs typically found in fetal organs.[31]

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Infant stem cells

These multipotent cells are derived from the cord blood (umbilical cord blood SCs [UCbSCs]) and Wharton's jelly (umbilical cord matrix SCs). UCbSCs have the innate potential to differentiate into neurons and hepatocytes, whereas the matrix cells have typical SC markers of prospective usage.[31]

Adult stem cells

These Adult SCs are undifferentiated cells. They collectively comprise the hematopoietic SCs, mesenchymal SCs, SCs of epidermis (skin and hair), SCs of bone and cartilage, SCs of the eye, liver, gut, pancreas and neuronal SCs.[31]

Dental-derived adult stem cells

They include the dental pulp SCs (DPSCs), Stem cells from human exfoliated deciduous teeth (SHED), SCs from apical papilla (SCAP), dental follicle progenitor cells, periodontal ligament SCs, SCs from human natal dental pulp, and gingival mesenchymal SCs; in addition, SCs can also be obtained from supernumerary teeth or in teeth surgically extracted for orthodontic purposes.[1,33]

Induced pluripotent stem cells

These induced pluripotent SCs (iPSCs) are analogous to embryonic SCs (ESCs) in differentiation and can develop to form all types of germinal layers; however, these cells are not subjected to ethical limitations because they are produced by using vectors to transfect the genes found in ESCs into a donor cell.[31,32,34]

Dental SCs (DSCs) are a valuable source in the field of regenerative medicine because they are simple to acquire with minimal invasiveness. Furthermore, they exhibit long-term genetic stability with higher malleability and are capable of *in vitro* expansion.[35] Their effective interaction with growth factors and scaffolds along with the secretion of immune receptors and cytokines possesses immunomodulatory[36-39] properties which shall be used in the treatment of various allergic, autoimmune, and inflammatory diseases.[40]

Whereas, the mesenchymal tissues possess numerous types of adult SCs which are referred to as multipotent mesenchymal stromal cells (MSCs). These MSCs possess the ability to differentiate into limited cell types/lineages.[41,42] These somatic cells when genetically[43,44] or chemically[45] manipulated generate artificially iPSCs.

Gene Therapy Using Stem Cells

SC gene therapy is centered on a concept where genetically impaired SCs are reprogrammed to normal SCs using various gene editing or gene addition procedures.[46,47] Genetic diseases such as Marfan's syndrome and osteogenesis imperfecta can be treated using modification of MSCs.[48]

In the recent years, the emergence of clustered regularly interspaced short palindromic repeats-associated protein 9 (CRISPR/Cas9) gene editing technology has been a breakthrough in the field of dentistry.[49] This is a DNA-free approach which can be done both *in vivo* and *in vitro*.[50] Genes that suppress the tumor-promoting properties are identified using CRISPR technology and are used in the treatment of oral cancer.[51] Various researches are being done due to its increased accuracy and efficiency in identifying genes associated with the pathobiology of oral cancer.[50,52,53] In addition, prevention of periodontitis,[54] dental plaque,[55] dental caries,[56] downregulation of pain signal pathways,[57] and inactivation, incubation, and even eradication of viral genes in infected cells can be achieved using CRISPR system.[58,59]

Applications of Stem Cell in Dentistry

Whole tooth bioregeneration

An *in vitro* combination of adult SCs with adult epithelial and embryonic cells along with tooth-inducing mesenchymal cells produces an embryonic tooth primordium. Otherwise, tooth germ models can be developed from harvested tooth buds combined with regenerative constituents.[60,61] These bioengineered primordia can be transplanted into tooth sockets immediately after extraction which might potentially develop into a whole tooth. Thus, various researches have predicted the possibility of transplantation of bioengineered tooth germs into the tooth sockets of the oral cavity.[62,63]

Regeneration of muscle tissue

The DPSCs have the capability to differentiate into myogenic cells where in that process the microRNAs have a crucial role.[64] the microRNAs have a crucial role. DPSCs, when injected into the skeletal muscles of undernourished mice, bind to the blood vessels and muscle fiber receptors *in vivo* resulting in an increased area of muscular fibers with reduced collagen content.[65]

Temporomandibular joint regeneration

Injured articular disc cartilage can be repaired by using chondrocytes derived from DPSCs.[66-69] Moreover, activity of alkaline phosphatase spiked on the 14th day after which proteoglycans were noted on the 21st day resulting in the strong expression of Type I and II collagen matrix indicating chondrogenesis.[69,70] In addition, a significant improvement in the mechanical properties of cultivated DPSCs in scaffold using chitosan/alginate was noted which was compared to the natural TMJs' disc.[26]

Cartilage regeneration

Specific cells of DPSCs in the pulp exhibit chitosan and Type II collagen which possess similar characteristic features of bone. About 30% of these SCs transform into chondrocytes which can be used for the regeneration of cartilages.[71] Thus, at an earlier stage, DPSCs can be differentiated into dentinoblasts, osteocytes, or chondrocytes and in later stages could be differentiated into osteoblasts.[72]

Nerve regeneration

MSCs derived from SCs from human exfoliated deciduous teeth (SHED) assist in healing of wounds.[73] DPSCs due to

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their active differentiation have paracrine effects promoting self-regeneration of axons and neurons resulting in nerve repair.[74-77] Studies have shown effective regeneration of facial nerve in mice and other animal models using DPSCs with collagen scaffolds.[78,79]

Regenerative endodontics

DPSCs aid in regeneration of healthy pulp tissue. DPSC can be easily manipulated *in vitro,* and it has proven to reconstruct a tissue similar to pulp both *in vivo* and *ex vivo*.[33,80]

Three-dimensional cell printing of pulp complexes

According to previous researches, the seed cells, three-dimensional (3D) printed pulp complex growth factors, and scaffold are the most essential components required for regeneration of pulpal tissues. The seed cells include the Stem cells from apical papilla, human deciduous tooth pulp SCs, and importantly pulpal SCs (DPSCs). Growth factors aid in the regeneration of blood vessels wherein the scaffold transports them to an appropriate microenvironment.[81]

In spite of the successful progression in 3D cell cultivation, provision of nutrient supply and oxygen to other pulpal cells in the root canal still remains a substantial challenge which entails further research. In addition, SCs' culture in 3D has an ultimate potential to regenerate tissues and organs which paves the way for the construction of visceral organs *in vivo* such as the heart, brain, and liver. Furthermore, creation of *in vitro* 3D pulpal tissues and study models through 3D cultivation of SCs can be done in the upcoming decades.[82]

Conclusion

Although the therapeutic applications of SCs are developing in a gradual pace, SC researches on the whole have exponentially increased. The application of SCs in treatment of various diseases and tissue regeneration has brighter prospects. Transferring of autologous cells enables the repair of damaged tissues and their functions. The future of individualized and regenerative medicine is SC-based technological advancements in therapeutic, reconstructive, orthopedic, and cosmetic applications. However, because SC technology is still in its infancy, interdisciplinary collaboration is necessary to develop successful therapeutic applications. Due to their accessibility, pliability, and increased proliferative capacity, DSCs have gained interest in the recent times.

DSCs come in a variety of forms, and yet, they are free from the moral dilemmas that are present in other SC sources. Together with a deeper understanding of DSC biology, tissue-engineering techniques along with gene therapy will offer effective tools for a wider range of DSC-based applications in various therapeutic approaches. We firmly believe that SCs, gene therapy along with tissue-engineering therapies shall significantly advance during the upcoming decades.

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Conflicts of interest

There are no conflicts of interest.

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