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(Review Article)

Current overview on stem cells in dentistry

Neeru Rani [1], Mrinalini [2,*] and Seema Bukhari [2]

[1] *UG Student, Manav Rachna Dental College, Faridabad, Haryana, India.*

[2] *Department of Conservative Dentistry and Endodontics, Manav Rachna Dental College, FDS, MRIIRS, Sec - 43, Delhi, Surajkund, Badkhal Road, Faridabad, Haryana, India.*

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Abstract

In recent times, stem cell therapy has developed as an advanced and much more promising scientific research topic, and also evoked great expectations in development of new treatment modalities. The two crucial properties of stem cells i.e., the capacity to self-regenerate for a long-period without senescence and pluripotency, the ability to divide into one or more types of specialized cells, makes it a very emerging and demanding tool of tissue engineering and regenerative medicine. The aim of stem cell-based treatments is to restore normal anatomy and function of damaged teeth or their components through a regenerative process. The goals of regenerative dentistry include regeneration of pulp tissues, continued root formation, assisted transplantation and replantation, root bioengineering, reconstruction of periodontal tissue, and tissue engineering of the pulp-dentin complex. In order to obtain stem cells from dental tissue, it is necessary to establish appropriate methods for obtaining, isolating, culturing, and replicating stem cells. One of the most commonly stored stem cells is SHEDs. This is because they are readily available and similar to cord blood cells. SHED banking is not subject to the same ethical constraints as embryonic stem cells and provides individuals and their immediate family with an autologous source of stem cells. New approaches should first be tested in subcutaneous or renal capsule implants, followed by confirmation of results in root canal models to identify problems and reduce costs.

Keywords: Stem cell therapy; Pulp-dentin complex; Regenerative endodontics; Stem cells from human exfoliated deciduous teeth; Mesenchymal stem cells

1. Introduction

Bone and dental tissue loss and defects due to trauma or disease are prevalent global problems, severely affecting the health and life quality of the entire population and imposing large economic loads on societies (1). Presently, the gold-standard treatment of bone defects is autogenous bone transplantation (2). In the case of oral disease, the available mainstream therapies are periodontal treatment, dental prostheses, and dental implants (3). However, the limitation of sources, the morbidity of the donor site, and the difficulty in graft harvest seriously restrain the transplantation of autogenous bone graft (4). Furthermore, the treatment modalities currently present for oral diseases can only improve the clinical diagnostic state and cease the progression of the disease but are still unable to regenerate lost parts of damaged tissues (5). Therefore, there is a great need for new research and technologies to achieve sterling regeneration of bone and dental tissues.

Stem cells are immature, unspecialized cells of the human body that have the ability of proliferation, regeneration and develop into many different cell lineages via differentiation. These cells can divide asymmetrically i.e., after cell-division, one cell remains as a stem cell while another cell (daughter cell) becomes a germ cell. Stem cells can remain dormant

* Corresponding author: Mrinalini

Department of Conservative Dentistry and Endodontics, Manav Rachna Dental College, FDS, MRIIRS, Sec - 43, Delhi, Surajkund, Badkhal Road, Faridabad, Haryana, India.

for long periods before cell-division starts again (6). There are different types of human stem cells including totipotent, pluripotent, multipotent, oligopotent, unipotent and can be found both in adult and embryo cells. As development potential decreases in each step of specialization, unipotent stem cells, unlike pluripotent stem cells, cannot differentiate into many cell types (7). Totipotent cells with highest potential of differentiation have the ability to divide and differentiate into whole organisms. They are used in various biological fields such as regenerative medicine, mammalian breeding, and conservation (8). The product of fertilization i.e., zygote is an example of a totipotent stem cell. Pluripotent stem cells (PSCs) can proliferate indefinitely and can differentiate into cells of all three germ layers. That's why nowadays PSCs are becoming the demanding source for stem cell therapies in a variety of diseases and injuries (9). The two types of human PSCs investigated for clinical use are Embryonic stem cells (ESCs) and Induced pluripotent stem cells (iPSCs) (10). Oligopotent stem cells can divide into cells of various types, like myeloid stem cells that can differentiate into white blood cells (WBCs) but not red blood cells (RBCs) (11). Multipotent stem cells with constricted spectrum of differentiation have the ability to differentiate into all cell types within one particular lineage. For example, hematopoietic stem cells which have the ability to differentiate into any type of blood cells (12). Unipotent stem cells are characterized by the narrowest differentiation capacity so that's why this unique property therefore makes it an encouraging candidate for therapeutic application in regenerative medicine. They have the special property of dividing repeatedly but can form only one type of cell e.g. Dermatocytes (7).

2. Methods

An online-based search was conducted on Scopes, Medline, Google scholar, and PUBMED. To limit our area of search to some required articles, the term review article (published in the past 20 years) was used to filter the search. Different keywords used for article search are "dental stem cells", "stem cells from human exfoliated deciduous teeth (SHED)", "dental pulp stem cells (DPSCs)", "periodontal ligament stem cells (PDLSCs)", "stem cells from apical papilla (SCAP)", "use of stem cells in dentistry" and "scope of stem cells in endodontics". Articles related to our topic are selected and sorted by publication date. About 200 articles have been screened for this review article to get necessary knowledge updates. The relevant information and data were compiled with the aim of imparting basic knowledge about stem cells and their therapeutic modalities and their future scope in dentistry.

2.1. Stem cells mechanism

According to body needs, stem cells can differentiate into specific types of cells. The four main sources of stem cells are fetal tissues, adult tissues, embryonic tissues, and induced pluripotent stem cells (iPSCs) i.e. genetically reprogrammed differentiated somatic cells (13). After fertilization, a blastocyst is formed, the inner surface of which is lined with embryonic stem cells. Blastocysts are composed of two distinct cell types, the trophectoderm (TE) and the inner cell mass (ICM). Blastocysts regulate the ICM Micro-environment and TE continues to form the extraembryonic support structures necessary for successful embryogenesis**.** Until the TE begins to form the specialized structures for support, the ICM cells will remain proliferative, undifferentiated, and fully pluripotent (14). ICM gives rise to Human embryonic stem cells (hESCs). During embryogenesis, cells form an aggregation called the germ layer which includes ectoderm, mesoderm, and endoderm, later on, all ultimately differentiate into cells and tissues of the fetus (15). After hESCs differentiate into one of the germ layers, they transform into multipotent stem cells, whose potential was restricted only to cells of the germ layer. In human development this procedure lasts for short-time duration. Thereafter, Pluripotent stem cells will emerge as undifferentiated cells throughout the body, and their major ability is the formation of the next generation of stem cells under specific physiological conditions and proliferation through differentiation into specialized cells. The process of specialization can be influenced by internal signals, which are controlled by genes present in DNA, and external signals, like physical contact between cells or chemical secretion by surrounding tissue (7).

2.2. Stem Cells in Dentistry

Teeth are the noninvasive, simply accessible, natural origin of stem cells. There are four main human dental stem cells that have been separated from oral cavity i.e. Stem cells from Human exfoliated deciduous teeth (SHED) (16), Dental pulp stem cells (DPSCs) (17), Stem cells from apical papilla (SCAP) (18), Periodontal ligament stem cells (PDLSCs) (19).

2.2.1. Stem cells from human exfoliated deciduous teeth (SHED)

SHEDs were first isolated in 2003 by Miura *et al*. They confirmed that SHED can differentiate into different cell types ranging from dental pulp-related cells to other cell lineages including osteoblasts, adipocytes, neuronal-like cells and endothelial cells. SHED has high differentiation potential and supports the formation of mineralized tissue that can be used to promote orofacial bone regeneration (16).

2.2.2. *Dental pulp derived stem cells (DPSC)*

DPSCs are a mesenchymal type of stem cells obtained from the pulp of permanent teeth and They are the typical source of dental-derived stem cells (20). They were first isolated and characterized by Gronthos *et al.* in 2000 from human teeth (17). They have potential to transform into osteogenic, myogenic, chondrogenic, adipogenic and neurogenic components both in-vitro and in-vivo and are capable of differentiating into dentin and pulp-dentin like complex, in-vivo (17). Using dental pulp organ culture techniques, recently immature dental pulp stem cells (21) which are a pluripotent subpopulation of DPSCs have been isolated.

2.2.3. *Stem cells from apical papilla (SCAP)*

In 2006, SCAPs was first isolated by Sonoyama *et al.* from the root apical papilla region of human dentition. These are the mesenchymal stem cells residing in the apical papilla of the developing permanent teeth with immature roots. These cells have high proliferative, migratory, and regenerative potential (20). Contains odontoblast-like and fibroblast-like cells with MSC markers such as CD24, CD 146, CD 44 and STRO-1 and also differentiate into dentin-pulp complexes, in-vivo (20,22). SCAPs aid in apexogenesis, which can occur in immature permanent teeth afflicted with abscesses and periradicular periodontitis. SCAPs found in the apical papilla survive such pulpal necrosis due to their proximity to blood vessels in the periapical tissue. Therefore, despite endodontic irrigation, SCAP is able to generate primary odontoblasts that terminate root formation under the control of the remaining Hertwig's epithelial root sheath (HERS) (18).

2.2.4. *Periodontal ligament stem cells (PDLSC)*

In 2004 Seo et al. (20) successfully isolated and reported the existence of multipotent postnatal stem cells in the periodontal ligament (PDLSCs) of human beings. When transplanted into rodents, PDLSCs showed the ability to generate cementum-like structures, peripheral nerves, periodontal ligament-like structures in alveolar bone, blood vessels and contributing to periodontal tissue repair. Turbiani et al. in 2008 (23) suggested that PDLSCs has regenerative potential that can be used in regenerative dentistry as implantable biomaterials for tissue engineering. Whereas Li et al. in 2008 (24) reported that when PDLSCs were transplanted onto bioengineered dentin, as result of it there is formation of cementum and periodontal ligament-like tissue.

2.3. Clinical application of stem cells in endodontics

Everyday people around the world lose their teeth due to many reasons, be it due to injury or negligence and as a result they have to compromise their oral health. Although currently we have several prosthetic methods to replace missing teeth, such as artificial dentures and dental implants, still they are not always as comfortable as natural teeth and can interfere with our normal eating and speaking habits. Nowadays, the re-establishment of missing or diseased teeth with the help of a modern stem cell-based tissue manipulation method can be considered a promising technique (25).

2.3.1. *Stem cell in dental implants*

Regrowing missing teeth in the mouth is the goal of a stem cell dental implant (26). Baby teeth and wisdom teeth that have been exfoliated are the sources of the majority of dental stem cells (27). Both baby teeth and adult teeth have dental stem cells in their pulp. After extraction or exfoliation, these teeth were routinely thrown for many years. Many patients now have the choice to keep these teeth for potential future treatments thanks to this new information. The best sources of dental stem cells are currently thought to be infant teeth and wisdom teeth (28).

2.3.2. *Healing and Regeneration damaged coronal dentin and pulp*

Currently, no endodontic restorative material has been able to reproduce all of the mechanical and physical characteristics of tooth structures. Under these circumstances, if tooth-tissue regeneration can be achievable, it will make it easier for physiologic dentin to form an essential component of the tooth, thereby rebuilding the integrity of the structure, microleakage, decreasing interfacial failure, and other consequences that may arise. Similarly, young permanent teeth that need apexification or apexogenesis are ideal candidates for pulp regeneration because they permit the finishing of lateral and vertical root development, enhancing the prognosis over the long term (28).

2.3.3. *Regeneration of Periodontal tissue*

In craniofacial regenerative biology, the periodontium has always been given top importance, because of its complex structure and complete regeneration of periodontium. All the available tissue regenerating procedures, including allografts, autologous bone transplants, and alloplastic substances have some drawbacks and are not usable in each clinical state. As a result, cell-based bone regeneration therapy will be a viable treatment option. The unresolved problem with these methods is how well any reconstituted periodontium can operate and preserve its integrity during mastication over an extended period of time. However, because there are currently inadequate treatments for severe periodontitis, any future dental stem cell-based therapy will likely undergo extensive clinical testing (28).

2.3.4. Repair of genetic oro-facial disorders/diseases

Many clinical treatments modalities for conditions involving aberrations of the brain, retinal, hepatic, bone, and tissue tend to concentrate exclusively on a few specific tissue areas of the human body. However, oro-facial symptoms can occur with several of these illnesses. Most oro-facial illnesses have been demonstrated to be predominantly caused by mutations. Genetic correction, which would provide a long-term cure for conditions like sickle cell anemia in patients, is one of the key goals of current stem cell therapy. Another effective application is to investigate tooth stem cells taken from individuals showing various dental syndromes and a range of craniofacial skeletal syndromes to enhance our knowledge of the molecular nature of diseases ranging from Treacher-Collins syndrome and Cleidocranial dysplasia syndrome. In this way, it may be possible to develop targeted medicines in future to cure or maybe prevent some of these complications. Given the success of these tissue-developing endeavors, their application to cell transplant therapies and gene corrections for oro-facial illnesses can be anticipated to yield even great benefit (28).

2.3.5. Regeneration of Temporomandibular joint (TMJ)

All dental specialists will find tissue-engineered bone transplants to be helpful. The oral maxillofacial and craniofacial surgeons would benefit most from future dental tissues that may also incorporate manufactured cranial sutures and Temporomandibular joints (28).

2.3.6. Continued root formation

Further study is required to confirm the involvement of root apical papilla-derived stem cells in ongoing root production however, clinically based researches indicate that it is likely to play a crucial part in root formation (28).

Endodontic treatment of permanent dentition having necrosed pulp using progenitor cells and suitable biomaterials can re-establish the lost pulpal tissues. However, the cost of treatment and the feasibility of transferring progenitor cells to donor sites can be the main barriers to the clinical implementation of such methods. Dentists are the most crucial doctors in providing their patients with potentially life-saving treatments derived from stem cells or their own primary or permanent teeth.

3. Conclusion

Latest researches, discoveries, and advancements in and around stem cells provide an excellent opportunity for medicine-based researchers that stem cells, whether received from the earliest cellular forms or any adult tissues, hold great expectations and promises that extend far beyond regenerative medicine. It should be mandatory in all dental institutions to add stem cells and regenerative therapies to their curriculum as dental doctors play a crucial role in enhancing patient's knowledge regarding stem cells treatment, tooth regenerative medicine, stem cell-based research, and the usefulness of stem cell storing for future use in regenerative therapies. Therefore, there is a great need for clinical trials of stem cell therapy to provide better options for replacing missing teeth.

Compliance with ethical standards

Disclosure of conflict of interest

There are no conflicts of interest.

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