

STEM CELLS IN DENTISTRY

Abstract

Creating complex structures known as organoids and spheroids through 3D cell culture methods is one of the most intriguing developments in the field of bio science research. These three-dimensional setups closely resemble in vivo environments, where cells can proliferate and engage with their environment. This results in our better understanding of both the spatial and temporal patterns of organ development and organ functioning. Research on stem cells is increasing, and both the medical and dental fields have researched them in great detail. Since their discovery, stem cells have drawn a lot of attention for their ability to self-renew and differentiate into other types of cells. The human body's richest source of stem cells is the mouth cavity. In the realm of dentistry, adult mesenchymal stem/stromal cells (MSCs) have been found in a number of oral and maxillofacial tissues. It is anticipated that oral stem and mucosal cells would be a prime source for genetically altered cells, including induced pluripotent stem (iPS) cells. Furthermore, since stem cell and tissue engineering therapies in dentistry continue to draw increasing clinical attention and offer new approaches to treating disorders and replacing missing tissues, oral tissues are anticipated to be both a source and a therapeutic target for stem cells. Oral stem cell collection is simple as the mouth cavity is so easily accessible. Dental pulp, exfoliated deciduous teeth, periodontal ligaments, the apical papilla, dental follicles, gingival epithelial tissue, and gingival connective tissue are the major sources to include oral stem cells. The potential application of these oral stem cells in regenerative medicine is highlighted by the fact that these cells are known to be essential for several forms of dental tissue regeneration, including the regeneration of dentine and periodontal ligaments after injury. The history of stem cells, various stem cells that are pertinent to dentistry, their benefits and drawbacks, the state of dental applications today, and the banking and storage of dental stem cells are all covered in this chapter.

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I. INTRODUCTION

Numerous pathologies, including periodontal disorders, dental caries, fractures, traumas, and even hereditary changes, can cause tooth loss. The recipient's own body tissues, allogenic transplants, alloys of metals, or synthetically manufactured implants are some of the therapeutic options. However, they have drawbacks like the possibility of malfunction and short service periods. The integration of bone, bone quality and bone quantity all have a significant role in the success of implants. The major setback of grafting autologous tissue is the morbidity and trauma of donor site. The question of whether there is a material that can replace the missing piece while also having acceptable endurance thus becomes crucial. Stem cells are the solution to this problem. Dentistry plays a crucial role for stem cell research. Since stem cells can easily be produced and encouraged to develop into any cell type in culture, it has been observed that they may play a notable role in future medical and dental treatments.[1]

II. BACKGROUND

Stem cell treatment has drawn a lot of interest in the dental industry due to the wide range of opportunities for autologous cell-based therapies. Due to the shortcomings of present methods, scientists are investigating the possible use of stem cells for the regeneration and restoration of lost dental components. To advance stem cell therapy into the therapeutic realm, endeavor to establish directed differentiation techniques that accurately represent the embryological developmental processes of dental tissue will be required.

III. WHAT ARE STEM CELLS

Stem cells (SCs) are undifferentiated cells that have the capacity to self-renew and differentiate into various kinds of cells. There are basically three types of SCs: totipotent, pluripotent, and multipotent [2], depending on the ability to differentiate:

1. Totipotent SCs have the ability to develop into extraembryonic and embryonic tissues [3].
2. Pluripotent SCs (PSCs) have the capacity to develop into the three embryonic germ layers—endoderm, mesoderm, and ectoderm—when exposed to certain environmental factors [4].
3. Multipotent SCs can only differentiate into a small number of cells that are specialized [5].

IV. HISTORY

In 1868, the term “stem cell” appeared in the works of German biologist Haeckel for the first time.[6] The term stem cell was coined by Wilson.[7] In 1908 a histologist named Alexander Maksimov from Russia, mentioned about stem cells of hematopoietic origin at hematologic society in Berlin,[8] where term “stem cell” was introduced to use scientifically.

V. TYPES OF STEM CELLS

The two primary types of stem cells are adult and embryonic stem cells (ASCs and ESCs, respectively). The blastocyst, which is an early stage of the embryo, is where ESCs are

formed from. Mesenchymal stem cells (MSC) and hemopoietic stem cells (HSC) are adult stem cells (ASCs), which are located in adult tissues, and have a limited capacity for replication.

Cells or HSC: Dental stem cells have traits common to mesenchymal stem cells. They produce odontoblasts, which in turn generate dentin, osteoblasts, adipocytes, cartilage, bone, skeletal muscle, and smooth muscle. According to studies, dental stem cells can change their origin to produce both ectodermal tissues (neurons or epithelial-like stem cells) and endodermal tissues (endothelial cells, hepatocytes, and insulin-generating cells).[1]

The following dental stem cells have been identified from various dental structures:

- Adult dental pulp stem cells (DPSC)
 - SHED
 - Stem cells from the papilla's apical portion (SCAP)
 - Stem cells from the periodontal ligament (PDLSC)
 - Dental follicle stem cells (DFSC).
1. DPSCs, or mesenchymal stem cells, are found in dental pulp. DPSCs have the capacity for both chondrogenesis and osteogenesis in vitro. They have the ability to differentiate in vivo into both dentin and a complex that resembles dentin pulp. Immature dental pulp stem cells, a pluripotent subpopulation of DPSC generated during dental pulp organ culture, were also found.

Due to the following factors, DPSCs are presumed to have potential for dental tissue engineering:

- Easy access to the surgical site for collection and low morbidity following dental pulp extraction.
 - When compared to nondental stem cells, DPSCs may produce a lot more normal dentin tissues in a short amount of time.
 - Recombined with many scaffolds and can be safely cryopreserved.
 - Have immuno-privilege and anti-inflammatory capabilities helpful for the allotransplantation experiments.[9]
2. **SHED:** According to Miura et al.[10], SHED had a stronger capacity for cell differentiation than DPSCs, including the ability to transform into adipocytes, neural cells, osteoblast-like, odontoblast-like, and adipocyte-like cells. The genesis of SHED from the neural crest was studied by Abbas et al. [11]. These cells' primary function appears to be the production of mineralized tissue, which can be used to accelerate orofacial bone repair.

Following are the categories of stem cells that can be found in shedded deciduous teeth of human:

- Adipocytes, which are used to treat a variety of orthopedic and spine disorders, Cardiovascular conditions, Crohn's disease, and possibly cosmetic surgery issues.
- Chondrocytes and osteoblasts are employed to help animals develop healthy teeth.[10]

- In order to address spinal cord injuries and aid patients who are paralyzed in regaining feeling and movement, mesenchymal stem cells (MSCs) are employed. They can also be used to treat other comparable illnesses that are caused by neuronal degeneration, such as Parkinson's disease, cerebral palsy, and Alzheimer's disease. MSCs are more capable of healing than other adult stem cell varieties.[10]
3. **SCAP:** Permanent teeth with developing roots have MSCs in the apical papilla. They were found by Sonoyama et al. and are known as SCAP.[9] SCAP are capable of forming odontoblast-like cells that produce dentin in vivo and are most likely the primary cell source for odontoblasts that make root dentin. The SCAP encourages apexogenesis. SCAP remains capable of producing primary odontoblasts, which complete root formation under the direction of the surviving Hertwig epithelial root sheath, even after endodontic infection. [12]
 4. **PDLSCs:** According to Seo et al. [13], human periodontal ligament (PDLSC) includes several pluripotent postpartum stem cells. PDLSCs aid in restoring periodontal tissue in rodents by producing a cementum or PDL like structure. For a ready source of MSCs, these cells can also be isolated from cryopreserved periodontal ligaments while still maintaining their stem cell properties, including single-colony strain generation, regeneration of tissue like cementum or periodontal ligament, appearance of MSC surface markers, multipotent differentiation.
 5. **DFSC:** The dental follicle that surrounds the growing tooth germ has been regarded as a tissue with multiple potency because of its capacity to produce bone, cementum and periodontal ligament. The parent cells of the dental follicle (DFPC) develop into neurons, adipocytes, osteoblasts or cementoblasts. For tissue engineering purposes such as bone and periodontal regeneration, DFPCs now have more potential.[1]

Advantages and disadvantages of different stem cells

TYPES	ADVANTAGES	DISADVANTAGES
DPSCs	Complex formation resembling dentin and pulp, potential for odontoblastic differentiation, source of reparative dentin	Wide span of proliferation rates, variable cell shapes and sizes, should be gathered from healthy adult tooth
SHED	Most proliferative one among the five stem cells, easily available, capacity of osteoinduction, potential for odontoblastic differentiation	Unable to form complex resembling dentin and pulp
SCAP	Complex formation resembling dentin and pulp, Source of root dentin, ability to differentiate into odontoblasts, and superior cell source to DPSCs for tissue regeneration	Not easily available
PDLSCs	Easily available, cementum and PDL-like formation	Deficit in odontogenic potential
DFPCs	Cementum and PDL-like formation	Deficit in odontogenic potential

VI. APPLICATIONS IN ORAL DISEASES

Dental stem cells have a wide range of potential clinical applications that could materialize in the near future. Research on dental stem cells currently focuses on regenerating periodontal ligament following periodontal disease; regenerating dentine, pulp, and teeth; alveolar bone; ; regenerating salivary glands; repairing faults of the craniofacial structure; and even treating lichen planus.

- 1. Tooth Regeneration:** In the treatment of tooth defects and tooth loss, progenitor cells of dental origin are employed to rebuild some dental tissues. These cells have ability to develop into lineages dental cell. Studies currently concentrate on full tooth regeneration utilizing a method that involves implanting a artificial tooth germ and letting it grow in an adult mouth. One of two ways for regenerating teeth uses traditional tissue regeneration, in which the deployment of cells in a carrier medium in vitro under the influence of a stimulus results in tissue regeneration. The second technique uses dental epithelial and mesenchymal cells in vivo after direct implantation and is based on knowledge of general embryogenesis and physiological tooth growth during childhood.[1]
- 2. Utilizing Dental Stem Cells to Treat Periodontitis:** There are no periodontal treatments existing right now that can help rebuild the afflicted area and the missing periodontal tissue into a healthy and useful structure. Since PDLSCs can differentiate into cementoblasts and osteoblasts and can stimulate the production of tissue surrounding the surface of dental implants, in vivo experiments using scaffold-assisted PDLSC transplantation in immunocompromised animal models have demonstrated the regeneration of periodontal tissue.[14,15] After using PDLSCs on three persons, Chen et al.[16] observed a substantial improvement in the damaged area. In a recent study, Chen et al.[17] autologously transplanted PDLSCs and DPSCs into 30 patients, demonstrating that doing so is safe and does not cause any side effects.
- 3. Using Dental Stem Cells to Regenerate Bone:** Maxillofacial bone repair with DPSCs has also been examined by D'Aquino et al.[18] to fill up the gaps left by the extraction of impacted third molars in seven patients and implanted autologous DPSCs along with a collagen scaffold. Three months later, there were areas of bone regeneration. Giuliani et al.[45] shown that though the bone matrix was histologically distinct from the native alveolar bone the transplanted area was made up of compact and uniformly vascularised bone three years after the procedure. Despite the histological variation, chewing pattern and tooth function were unaffected.
- 4. Using Dental Stem Cells to Regenerate Pulp:** Research has been done to find an efficient method for pulp regeneration following endodontic therapy. Presently, two methods are being researched: revascularization of pulp canal, which attracts MSCs to the site of trauma, and DPSCs autologous transplantation linked to scaffolds. However, histological investigation reveals that no tissue creation resembling pulp has occurred following the revascularization of root canal and pulp chamber. Cementum, periodontal, and bone-like tissues make up the majority of the cases instead of pulp-like tissues.[19] In a research using a canine model, a subset of DPSCs (CD105+) with SDF-1 [20] was transplanted and pulp like tissue with nerves and blood vessels were restored in the tooth root .

5. **Salivary Gland Regrowth Following Radiation Treatment:** The ability of salivary gland tissue to regenerate after atrophy has made it possible to identify and isolate cell types that contain salivary gland stem cells. Stem cells extracted from mouse salivary glands can repair saliva production in salivary glands damaged to radiation. In view of the substantial breakthroughs in the field of stem cell research, stem cell-based therapy has significant promise for the treatment of human xerostomic illnesses.
6. **Lichen planus:** Lichen planus has traditionally been treated in difficult and unsatisfactory ways. Studies have recently concentrated on the immunosuppressive effects of MSCs on different immune cell varieties. According to these findings, mesenchymal stem cells may be systemically applied or locally infused to treat patients of oral lichen planus.
7. **Regeneration of the mandible condyle:** Damage to the temporomandibular joint disc or condyle (condylar osteochondral defect) brought on by trauma or arthritis may cause patients to feel pain and have difficulty eating normally. Rat BMSCs produced through chondrogenesis and osteogenesis and then encased in a biocompatible polymer were used to successfully build a mandibular condyle. Low-intensity pulsed ultrasound was used to hasten the regeneration of the rabbit mandibular condyle by generating chondrogenic and osteogenic BMSCs. These studies provide an early evidence suggesting for the potential stem cell-based tissue engineering of damaged articular condyles in the setting of conditions like rheumatoid arthritis.[21]

VII. STEM CELL BANKING

The procedure of conserving stem cells derived from patients' primary and wisdom teeth is known as dental stem cell banking. The use of dental stem cells in regenerative medicine has the potential to be a key research technique. Developed nations are where the trend is gaining the most acceptances.

1. Companies like Store-A-Tooth (Provia Laboratories, Littleton, Massachusetts, USA) and StemSave (Stemsave Inc, New York, USA) are focusing on international expansion of stem cell banking businesses.
2. In 2005, "Three Brackets" (Suri Buraketto) was the name of Japan's first tooth bank. Nagoya University in Kyodo, Japan, also developed a tooth bank in 2007.
3. In September 2008, Hiroshima University and Taipei Medical University launched the country's first tooth bank.
4. The Norwegian Institute of Public Health and the University of Bergen collaborated to establish the Norwegian Tooth Bank, which began stocking shedded primary teeth from 100,000 Norwegian infants in 2008.[9]
5. The National Health Surveillance Agency (ANVISA) of Brazil enables the storage of SHEDs and SCs obtained from placenta and cord blood in private facilities with the necessary operational license.
6. Steamed recently opened operations in Mumbai and Delhi, introducing the idea of dental stem cell banking in India.

VIII. CONCLUSION

Dentists now have the chance to play a key role in the treatment of medical disease as well as dental pathosis thanks to advances in researches of dental stem cell. Dental stem cells can be used in a variety of ways, but there are also certain restrictions. Currently, the use of DSCs is limited to scientific study, but it is anticipated that this procedure will soon become commonplace, marking a significant advancement in dentistry. To use these cells in standard dentistry practice, more research is required on the mechanisms underlying DSC differentiation and its uses.

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