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Review

Innovations in dentistry: Mesenchymal stem cell therapies

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ABSTRACT

The human body contains various types of cells, each with different functions to ensure a healthy life. Stem cells, which can transform into all cells within the organism and form the structure of all tissues and organs in the body, are defined as primary cells. These stem cells, which can renew and differentiate into specific cell types continuously, are present in every area of the body where needed. Due to their ability to transform and divide, stem cells play a crucial role in the regeneration of all tissues and organs that are diseased or damaged in the human body. Generally, there are two types of stem cells. One type is embryonic stem cells, whose acquisition and use involve legal and ethical issues. The other type is adult stem cells, including dental stem cells. Dental tissues are a rich source of mesenchymal stem cells (MSCs), adult stem cells found in connective tissue. Mesenchymal stem cells are of particular interest in cell-based therapies due to their characteristics and potential. With advances in technology and medical science, stem cell research in dentistry has become a promising field. This review provides an overview of MSC sources in dentistry.

Keywords: Dentistry, mesenchymal stem cells, stem cells.

Throughout history, the discovery of stem cells and advancements in cellular and molecular biology have paved the way for the development of novel strategies for regenerating various tissues.[1] Regenerative medicine, similar to tissue engineering, aims at the regeneration, repair, or replacement of damaged tissues and has established itself as a rapidly advancing field within healthcare under a distinct framework.[2] In the modern era, stem cell therapies hold immense and rapidly expanding potential for the effective treatment of diverse medical conditions within the realm of regenerative medicine.[3] In recent years, stem cell and tissue engineering applications have gained significant prominence in medicine for the regeneration and repair of bodily structures.[1]

Stem cells are the fundamental cells that form the structure of all tissues and organs in the human body. Defined as master cells with the unique ability to transform into any cell type within the organism, stem cells are present in every region of the body and play a crucial role in the regeneration of diseased or damaged tissues and organs.[3] Characterized as undifferentiated master cells capable of transforming into various cell types under suitable conditions in the body or in a laboratory setting, stem cells are believed to divide indefinitely throughout life, replacing other cells.[4] Their remarkable ability to undergo unlimited division establishes stem cells as the body's enduring guardians.

Stem cells are a population of undifferentiated cells characterized by their ability to self-renew (extensive proliferation), clonality (often originating from a single cell), differentiate into various cell and tissue types, and proliferate.[5]

Stem cells, which have the ability to continually renew themselves and differentiate into specific cell types, are primarily categorized into embryonic stem cells and adult (somatic) stem cells. Embryonic stem cells are derived from the blastocyst of a human embryo and are pluripotent.[4] Although embryonic stem cells are considered a valuable source due to

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their differentiation potential, ethical concerns regarding the use of embryonic tissues and their neoplastic potential (teratoma) have led to restrictions on their use.[1]

Adult stem cells, also known as somatic stem cells, are undifferentiated cells found among differentiated cells in a tissue or organ. They can self-renew and differentiate into specialized cell types within the tissue or organ they reside in.[6] Adult stem cells, also referred to as multipotent stem cells, are obtained from adult tissues.[5] The main tasks of adult stem cells are to repair the tissue they reside in and maintain the continuity of the tissue.[6]

Adult stem cells appear to be more applicable in stem cell-based therapies and regenerative medicine among different types of stem cells. This is as adult stem cells do not raise ethical concerns, show less tumorigenic potential compared to embryonic counterparts, and have lower immunogenicity, making them promising candidates for regenerative treatments.[7,8]

Adult stem cells are found in the bone marrow, periosteum, muscle, fat, brain, and skin tissues. Among stem cell sources obtained from somatic tissues, mesenchymal stem cells (MSCs) have gained importance.[1] Mesenchymal stem cells are adult stem cells that possess the ability to differentiate into other cell types and self-renew.[7] Multipotent adult stem cells such as MSCs have been the preferred type for cellular therapies and have been used for therapeutic purposes in clinics for approximately 15 years.[8] Only a few centers worldwide are currently producing MSCs for clinical use, and all necessary processes for MSC production must be carried out according to internationally accepted good manufacturing practice standards.[9] Mesenchymal stem cells are found in various tissues throughout the body, including bone marrow, umbilical cord, adipose tissue, dental pulp, placenta, and amniotic fluid. They have the ability to migrate from their source tissue to a damaged tissue within the body.[10] Mesenchymal stem cells, which can be obtained from various tissues, are resilient cells that are suitable for expansion.[11]

The characteristics of MSCs can be listed as follows:

- Having the ability to differentiate into various tissues,
- Possessing the capability for differentiation (transdifferentiation) into cell types such as neurons, hepatic, and pancreatic cells,
- Repairing damage in the surrounding environment,
- Ability to migrate to damaged areas in other tissues for repair,
- Not stimulating the immune system due to their immunosuppressive/ non-immunogenic properties.[12]

Today, MSCs are being used as the main therapeutic agent in clinical trials for treating various diseases.[13] Despite their many advantages, the most significant disadvantage for clinical use is the need for extensive expansion *in vitro* culture for weeks due to their limited numbers. This process incurs high costs and requires substantial technological infrastructure and expertise. Consequently, only a few centers worldwide are capable of producing MSCs suitable for clinical use.[14]

Dental tissues are a rich source of MSCs suitable for tissue engineering applications. Additionally, alternative sources of MSCs exist in the oral and maxillofacial regions.[1] Various adult stem cell populations have been identified in various dental tissues, often referred to as dental stem cells (DSCs). Dental stem cells can also be collected from tooth extraction under local anesthesia or from diseased or inflamed tooth-supporting tissues, and they possess similar properties to stem cells obtained from healthy tissues. Therefore, DSCs are seen as a promising source of adult stem cells.[7]

Due to sharing similar characteristics with MSCs, DSCs have garnered significant interest in the treatment of MSC-related diseases.[15] Undoubtedly, stem cell research endeavors conducted within ethical and legal frameworks hold paramount importance, particularly in the fields of medical science, dentistry, and, of course, humanity as a whole.

CLASSES AND CHARACTERISTICS OF DENTAL STEM CELLS

Until now, seven types of DSCs have been identified in the literature:[16]

- Dental pulp stem cells (DPSCs),[17]

- Stem cells from human exfoliated deciduous teeth (SHED),[18]
- Periodontal ligament stem cells (PDLSCs),[19]
- Dental follicle progenitor cells (DFPCs),[20]
- Stem cells from the apical papilla (SCAP),[21,22]
- Gingival mesenchymal stem cells (GMSCs),[23]
- Human natal dental pulp stem cells (NDP-SCs).[24]

All of these cell populations share similar characteristics such as fibroblast-like cell morphology, colony formation, and high proliferation potential, while their differentiation potentials vary from one another.[25]

Dental pulp stem cells

The dental pulp is an important source of stem cells used in stem cell research.[25,26] The presence of stem cells in dental pulp was first proposed by Yamamura[27] in 1985 and first identified by Gronthos et al.[16] in 2000. They compared these to bone marrow-derived MSCs in terms of their colony-forming and differentiation abilities, reporting that dental pulp MSCs exhibited a greater capacity for colony formation and that their differentiation potentials differed from those of bone marrow-derived MSCs. Dental pulp stem cells were isolated and identified as cells capable of generating dense calcified colonies and sporadic nodules, exhibiting a high degree of proliferation and clonogenic potential.[27]

Dental pulp stem cells are among the most extensively studied DSC sources due to being the first isolated dental source, their ease of access, and their satisfactory outcomes in terms of proliferation and differentiation under both live tissue and laboratory conditions.[28] Dental pulp stem cells possess all the necessary characteristics required for therapeutic applications.[29] Dental pulp stem cells are multipotent MSCs capable of high proliferation, clonability, and exhibiting high plasticity without losing their multipotent properties even after passaging.[30]

Histologically, DPSCs are located around the dentin-pulp and are closely interconnected. Functionally, these cells can regenerate dentin and provide oxygen, nutrition, and innervation to the dentin tissue. Dentin tissue, in turn, protects the soft pulp tissue and together ensures the continuity of the tooth's shape and function.[1]

Among the main sources of pulp stem cells are impacted/wisdom teeth, extracted/shed deciduous teeth, and teeth extracted due to orthodontic treatment or trauma, periodontal disease. Wisdom teeth are often used in DPSC studies due to their indication for extraction and easy accessibility. Furthermore, due to being the last to develop, wisdom teeth are deemed to be abundant in pulp tissue if intercepted during their early developmental stages.[30] In the dental pulp, undifferentiated root cells responsible for dentin repair are present throughout life. Dental pulp stem cells constitute a highly heterogeneous group of cells with varying morphologies and sizes.[31]

Dental pulp stem cells can differentiate into adipocytes, osteoblasts, chondroblasts, neurons, smooth muscle cells, skeletal muscle cells, and odontoblast-like cells under cell culture conditions. Additionally, they can be cryopreserved without losing their multipotent differentiation capabilities.[15] The high cell viability rates obtained after thawing demonstrate that DPSCs can be cryopreserved for future use in sample storage banks when needed.[32] In addition to their dentinogenic properties, dental pulp cells also possess adipogenic, chondrogenic, neurogenic, osteogenic, and myogenic characteristics.[31]

Stem cells from human exfoliated deciduous teeth

Deciduous teeth differ from permanent teeth in many aspects such as their functions, developmental origins, and tissue structures.[2] Stem cells found in deciduous teeth are isolated from the dental pulp of incisors. These cells exhibit high plasticity and can differentiate into neurons, adipocytes, osteoblasts, and odontoblasts. Stem cells in deciduous teeth contribute to bone formation and also produce dentin under *in vivo* conditions.[15]

Children typically develop 20 deciduous teeth, which are eventually replaced by permanent teeth after their roots dissolve and they fall out. The process of permanent teeth eruption spans over seven years or more.[33] During this process, the crown portion of the exfoliated deciduous teeth retains a live pulp residue. In a study conducted by Miura et al.[31] in 2003, DPSCs derived from exfoliated deciduous teeth were identified in the pulp residues of extracted incisors in 7-8-year-old children. In this study, it was indicated that stem cells derived from deciduous tooth pulp contribute to new bone formation. The formation of new bone was attributed not directly to the differentiation of stem cells into osteoblasts but rather to their osteoinductive effect on osteogenic cells. This information suggests that deciduous teeth not only serve as placeholders for permanent teeth but also induce new bone formation during the eruption of permanent teeth.

Recent scientific studies have suggested that DSCs derived from exfoliated deciduous teeth may serve as an ideal source of stem cells for the treatment of damaged dental and bone tissues, and potentially for the treatment of nerve tissue damage or degenerative diseases.[18,34]

It has been determined that exfoliated deciduous teeth, which are unique stem cell sources, resemble umbilical cord blood in clinical applications.[35] The primary advantage of using SHED is that these stem cells can be non-invasively obtained from exfoliated deciduous teeth, which are routinely extracted during childhood and often discarded as medical waste without any ethical concerns.[36]

It has been noted that stem cells obtained from deciduous tooth pulp exhibit a higher proliferation rate and cell population compared to adult tooth pulp. These stem cells are comprised of more immature multipotent cells. However, it has been observed that they cannot form complex pulp-dentin structures like DPSCs.[30] It's quite popular to store deciduous teeth as a potential source of stem cells for the future. Stem cells derived from deciduous teeth can be preserved in banks for up to 20-25 years. To utilize deciduous teeth as a source of stem cells, they must remain vital, meaning they should not undergo necrosis. Deciduous teeth that fall out naturally typically do not cause bleeding and have lost their pulp vitality. It's healthier and more efficient to collect these cells when the tooth is still alive, for example, when it has just started to become mobile. These cells could potentially be used in the treatment of various diseases such as organ transplantation, cancer, heart, skin, muscle, bone and blood disorders, genetic and metabolic diseases, Alzheimer's, Parkinson's, and others.[4]

Periodontal ligament stem cells

The periodontal ligament is a soft tissue that lies between two mineralized tissues: the teeth and the alveolar bone. It is surrounded by two hard tissues, cementum, and bone, and it connects the teeth to the alveolar bone with fibers that attach to the two mineralized tissues.[37] The continuous dynamic nature of periodontal tissues has directed researchers towards stem cell studies in periodontal tissues.[29] In 2010, Feng et al.[23] were the first to apply PDLSCs in periodontal treatment clinically. The periodontal ligament not only provides structural support to the teeth but also plays a crucial role in facilitating tooth nutrition, maintaining tissue balance, repairing injured structures, and perceiving mechanical forces.[16]

The periodontal ligament, a complex structure containing various cell types, is challenging to rebuild, especially considering its interaction with bone and teeth. Within the periodontal ligament, there are also STRO-1(+) cells. Periodontal ligament stem cells can acquire adipogenic, osteogenic, and chondrogenic phenotypes *in vitro*.[15]

Periodontal ligament stem cells are obtained from the root surfaces of extracted teeth and can differentiate into periodontium-like tissues and cells. These cells are capable of forming colonies, but their *in vitro* osteogenic differentiation potential is reported to be low. However, when transplanted into mice, they have been shown to promote tissue regeneration and periodontal repair.[30] Studies have indicated that MSCs derived from the periodontal ligament could serve as an autologous source for bone regeneration. Stem cells obtained from healthy periodontal tissues have exhibited similar characteristics to those obtained from periodontal defect sites, and furthermore, these stem cells have been observed to share similar properties with stem cells derived from bone marrow and dental pulp.[4]

The periodontal ligament harbors cell populations capable of differentiating into cementoblast-like and osteoblast-like cells. Under appropriate culture conditions, these multipotent stem cells can differentiate into cementoblast-like cells, adipocytes, and fibroblasts. When transplanted into immunocompromised mice, PDLSCs have demonstrated tissue regeneration and periodontal repair abilities. Stem cells isolated from the root surfaces of extracted teeth exhibit a low osteogenic differentiation potential under *in vitro* conditions.[1]

Dental follicle progenitor cells

The dental follicle is the mesenchymal tissue surrounding the developing tooth germ.[1] The dental follicle is an ectomesenchymal that surrounds the enamel organ and dental papilla before the eruption of permanent teeth during the developmental process.[31] Stem cells derived from dental follicle tissue were first isolated by Handa et al.[37] from bovine tooth germs. This tissue contains periodontal (cementum, periodontal ligament, and alveolar bone) stem cells.[31,38,39] It is believed that the dental follicle plays an important biological role during the process of tooth eruption into the oral cavity.[38] During tooth root development, cementum, periodontal ligament, and alveolar bone are formed by DFPCs.[1]

In 2005, Morsczeck et al.[17] reported the presence of precursor cells in the dental follicle tissue obtained from impacted molar teeth in humans. Dental follicle progenitor cells are located in the epithelial layer of the dental follicle that separates from the dentin during the early stages of periodontal development, specifically at the Hertwig epithelial root sheath. During the transition from stem cell to precursor cell, the most primitive stem cells exhibit the highest proliferation and the lowest differentiation potential, whereas precursor cells have a lower proliferation potential but can differentiate easily. Therefore, it is evident that progenitor dental follicle cells, despite having a lower proliferation potential, can more readily differentiate into dental tissues.[30] Stem/progenitor cells obtained from the intraoral/maxillofacial region serve as a valuable source for tissue engineering and regeneration of hard and soft tissue defects in that area. In the intraoral/maxillofacial region, the use of gingival tissue for obtaining multipotent cells from healthy tissues adjacent to defects offers several advantages. These include the non-invasive approach and ease of collection, suggesting it as an alternative tissue source.[35] The heterogeneous nature of dental follicle cells is believed to offer a significant advantage in regenerative therapies.[36]

Stem cells from the apical papilla

The tissue at the apex of developing permanent teeth, possessing specific physical and histological characteristics, is known as the apical papilla. Stem cells isolated from this tissue are referred to as stem cells from the apical papilla.[1] Stem cells derived from the apical papilla are obtained from the dental papilla of unerupted wisdom teeth or teeth with open apices during the early stages of tooth development.[38]

There is an apical cell-rich zone between the apical papilla and the dental pulp, where both dental pulp and apical papilla contain stem cells and progenitor cells.[1] According to a study by Sonoyama et al.,[35] the apical papilla, while histologically distinct from pulp tissue, contains a unique and potent type of MSC. Apical papilla stem cells were first isolated by them in 2008 from the apical papilla of impacted third molar teeth in patients aged 18-20 years. The isolation of apical papilla stem cells is performed by gently separating the apical papilla from the root surface of the third molar teeth during extraction before apex development is complete. The apical papilla is then sectioned into small pieces and subjected to enzymatic digestion to obtain single-cell suspensions. Human third molar teeth, easily accessible sources of SCAP, have the capacity to differentiate into osteogenic, odontogenic, neurogenic, adipogenic, chondrogenic, and hepatogenic cell lineages.[15]

These cells exhibit a higher proliferation rate compared to PDLSCs and are more effective for tooth regeneration.[1] It has been found that SCAPs exhibit a higher proliferation capacity compared to DPSCs isolated from the same tooth, indicating a greater potential for substantial tissue regeneration due to their higher proliferation potential.[1,35] The dental papilla possesses a greater number of adult stem cells. It has been stated that SCAP, when used in conjunction with PDLSCs, promotes the formation of connective tissue.[30]

The apical papilla stem cells have been found to possess the capability to contribute not only to the formation of dental tissues but also to the formation of various other tissues.[40]

Gingival mesenchymal stem cells

The gingiva is a mucosal barrier that covers the alveolar bone, the retromolar area, and the teeth, playing a role in oral immunity.[40] Gingival mesenchymal stem cells were first isolated from the spinous layer of human gingiva by Zhang et al.[36] in 2009. The isolated cells possess the ability to form colonies, self-renew, and differentiate into multiple lineages. Gingival mesenchymal stem cells originate from the spinous layer of the gingiva. They not only express specific MSC markers but also extracellular matrix proteins.[15]

Gingival tissue can be considered an important alternative due to its ability to yield a high number of stem cells from the patient without causing irreversible tooth loss. Additionally, the ease of obtaining gingival tissue through minimally invasive methods is also a significant advantage.[16]

Human natal dental pulp stem cells

Natal teeth, which are observed in newborn babies, are classified as such due to their emergence at birth. Natal teeth either lack root development entirely or exhibit minimal root development. In comparison to permanent teeth, they are structurally smaller. They are quite rare, as the rate of babies being born with teeth is estimated to be around 2-3 per thousand births.[26]

Human natal dental pulp stem cells are a unique type of DSC that can only be isolated from the teeth of newborns. In 2010, Karaöz et al.[24] isolated NDP-SCs from two natal teeth of a healthy newborn. The crown of the tooth was broken and removed to expose the pulp, which was then digested with collagenase enzyme to obtain a single-cell suspension. Natal dental pulp stem cells exhibited a higher proliferation rate compared to SHED and DPSCs. Although they possess a higher proliferation capacity compared to DPSCs, NDP-SCs cannot form the dentin-pulp complex. However, they can induce bone and dentin formation.[40,41]

In conclusion, as research in stem cells and organ regeneration in modern medicine began in the 1950s, it has since experienced rapid advancement. Stem cells have become a focal point in regenerative medicine research for better understanding the biology and formation of diseases and discovering new treatments. Stem cells also hold significant potential in dentistry for uncovering and applying alternative treatment options. This is as human teeth have limited regeneration capacity when diseased or traumatized, a challenge that stem cell-supported therapies are believed to overcome. Thus, an easily isolatable and cultivable stem cell source is required. Dental stem cells, obtained from oral tissues through simple, non-invasive procedures under local anesthesia, serve as an excellent source of stem cells. Therefore, DSCs emerge as an ideal stem cell source for dental research and offer a good alternative to other MSCs used in regenerative medicine. The ease of obtaining DSCs compared to other stem cell sources, coupled with their high differentiation potential, has led to an increase in their experimental and clinical use in regenerative medicine. With the increasing focus on research in this field, it is evident that DSCs could serve as important resources for cellular therapy in numerous diseases in the future and could be widely utilized.

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