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Dental stem cells and their application in dental research: A review

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Abstract

Promising advancements in dental therapies aimed at replacing, repairing, and regenerating dental tissues have resulted from recent innovations in cell and molecular-based dentistry. Additionally, fresh approaches to the study of human tooth organogenesis have also been established. In recent days, five subpopulations of dental and oral stem cells have been identified, including dental pulp SCs (DPSCs), SCs from human exfoliated deciduous teeth (SHEDs), periodontal ligament SCs (PDLSCs), dental follicle progenitor SCs (DFPCs), and SCs from apical papilla (SCAPs). Teeth are one of the most accessible and least invasive sources of stem cells. Despite being unique, these populations exhibit traits common to MSCs, such as the capacity for self-renewal and the capacity to split into at least three separate lineages. Here in this article, the different sources of Dental stems cells and their characteristic features are discussed.

Keywords: Dental stem cells; Dental pulp stem cells; Human exfoliated deciduous teeth; Dental follicle progenitor; Periodontal ligament stem cells

1. Introduction

Stem cell is a dynamic environment with a specialized function, it helps to regulate the balance between quiescent and proliferative states of stem cells by controlling self-renewal, proliferation, and differentiation. Adult stem cells are responsible for producing new cells to replace worn-out ones. Thus, the growth and maintenance of stemness is indispensable to maintain the structure and function of an organ. The decline in stem cell population and/or stemness results in ageing phenotype by reduced turnover of tissues and multi organ dysfunction. The severity of dysfunction is more in tissues like brain, heart and skeletal muscle due to their post-mitotic quiescent nature. Since these cells do not divide in tissues and can potentially persist for a lifetime, they are more likely to accumulate damaged macromolecules and ROS, a hallmark of ageing.

Human body is dependent on a variety of rare stem cells which function to replace somatic cells and tissues as they get damaged, diseased, die, or otherwise lost. Replacement of these lost cells declines progressively with age because of stem cell aging and attrition. One way, in which stem cells age is by telomere erosion, the lack of telomerase leads to telomere shortening, change in chromatin structure and results in replicative senescence.

In this perspective, age-dependent decline in the activities and/or number of adult stem cells has to be improved and replaced. Stem cell-based therapy to replace lost and/or damaged cells in post-mitotic organs is the current focus of intense research. The two most promising approaches involve transplantation of exogenous stem cells and promoting proliferation of endogenous stem cells.

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Therapeutic application of adult stem cells is still unclear and which types of stem cells are most potent for use in therapy. There is, as yet no stem cell type or method of delivery universally applicable for therapy.

The aim of our review of literature about Dental stem cell types and analyzing their possible application in clinical research as well in tissue regeneration research. The more chances of dental stem cells as better candidate when compared to existing adult stem cells due to their origin, as they are thought to be derived from migrating neural crest cells during early development and have been shown to harbor various populations of multipotent stem/progenitor cells and can be used as autolous source and its availability.

1.1. Dental Pulp Stem Cells (DPSCs)

DPSCs have been the major focus area for various studies since it has been proven to be safe and highly promising source of adult stem cells in tissue engineering (1). DPSCs identification and isolation was first described by Gronthos et al in 2000 (2) from third molar perivascular dental pulp, it can also be isolated from various sites like inflamed pulp tissue (3) , super numerary tooth (4), and from natal tooth (5).

1% of the total cell of dental pulp constitutes DPSC and was first proposed by Fitzgerald et al (6).it is also considered as an important source of mesenchymal cells (7). it has both ectoderm and mesoderm characteristics due to its ectomesenchymal embryonic origin (8). It has the ability to transform into odontoblasts, adipocytes, neural cells, osteoblast, chondrocytes and myoblast like cells in vitro and has high proliferative rate than that of BMSCs (2). DPSCs in dental pulp are capable of multilineage differentiation (9). DPSCs in adult pulp are quiescent and will be activated proceeding injuries (10). Human DPSCs under the skin of immunocompromised mice formed pulp/dentin like tissue with odontogenic differentiation (11-14). Their characteristics are similar to BMMSCs (Bone marrow mesenchymal cells) (15-19) with less osteogenic and adipogenic potentials (2, 20). It has been put through various studies in regenerative medicinal field such as cerebral ischemia (2,21,22), dental and bone loss defects (23,24), the nervous system (25), digestive system (26) and the endocrine system (27).

Isolated DPSC show high expression of CD MARKERS for mesenchymal adult stem cells such as CD 29, CD44, C90, CD 73, CD 105 CD13 (stromal associated markers) (28-31), low positive for hematopoietic markers such as CD 34, CD 45 and no expression for endothelial markers such as CD 31, CD 14 & CD 106 (8). DPSCs extracted from natal teeth also exhibit immunophenotypic features and has multidirectional differentiation potential (32), along with positive expression of SOX2 an embryonic cell marker. In ED enzymatic approach, DPSCs have higher proliferative capacities and differentiation potential (jang et al, 2016), so these enzymes have major impact on the proliferative and differentiation rate (Dadtgurdia et al 2018) as, even the time duration of its activity is essential as it could cause cell death.

1.2. Application

Procedures that can be regenerated through DPSC are Mineral tissue (33), lamellar bone (34,35), mineralized bone like tissue with blood capillaries created by scaffold containing self-assembling peptide hydrogel (Chan et al) (36). DPSC can be possibly used as therapeutic material in regenerative endodontics. 3D scaffolds have also been used in regeneration of DPSCs in human root canals implanted in mice (37). DPSCs are used in bone regenerative procedures (38-43) (DPSC with mature osteogenic phenotype), Nakamura et al. DPSC with Mature Osteogenic phenotype has more responsive to pulsating fluid shear stress than that of DPSCs with immature osteogenic phenotype. These might perform mature bone cell - specific functions in bone adaptation to mechanical loading *in vivo.*

MODIFIED DPSCs a combination of genetic and cell therapy which is said to have an greater potential and effective treatment modality when compared with non-engineered therapy (44). This therapy involves the primary stem cell that over-express tissue specific genes making to produce therapeutic protein on site of regeneration (44). Modified DPSCs improves brain injury, Sulphate sodium induced ulcerative colitis (7). The regenerative mechanisms are studied through stem cell labeling techniques such as green fluorescent protein (GFP) (45), BrdU labeling (45), superparamagnetic Iron oxide (46) fluorescent-based tracing (47) immunological effects. Stem cell therapy have shown encouraging results in treatment of immune related diseases (48,49) which suggests that they might have a role in immune regulation of the host. Various studies showed that, DPSCs have immunomodulatory function similar to that of MSCs, which makes it a good candidate in treatment for immune and inflammation related diseases as it can suppress t cell proliferation like MCSc (50). inhibit the production of interferons, interleukin 17 (51,52). DPSCs could be good enough to prevent/ treat T cell alloreactivity associated with hematopoietic or allogenic transplantation. it was also proven that, DPSCs have better inhibitory responses to tcells than BMSCs (53) and inhibit acute allogenic immune response by release of TGF-Beta (5.4). DPSCs can induce activated Tcells apoptosis by Fasligand expression (55).

1.3. Stem cells from human exfoliated deciduous teeth (shed)

SHED are multipotent stem cells, discovered by Dr. Songtao Shi in 2003. SHED was shown to be more capable of differentiating into a range of cell types than DPSCs, including osteoblast-like, odontoblast-like, adipocytes, and brain cells, according to Miura et al. (56). According to Abbas et al. (57), SHED may have originated from the neural crest. These cells' primary function appears to be the development of mineralized tissue, which can be exploited to speed up the regeneration of orofacial bone (58). A naturally exfoliated deciduous tooth is similar to an umbilical cord in some ways, according to recent research. It contains stem cells that could provide a special source of stem cells for potential clinical applications. Additionally, recently emerging evidence suggests that cell-fusion events could explain some of these observations. The cell-surface molecules STRO-1 and CD146 (MUC18), two early mesenchymal stem-cell markers previously discovered to be present in BMSSCs and DPSCs, were discovered to express in ex vivo-expanded SHED (59).

Previous research has demonstrated that adult teeth's dental pulp tissue contains a population of DPSCs that may differentiate into odontoblasts and adipocytes, as well as express nestin and GFAP, and eventually form a dentin/pulp-like complex when transplanted into living tissue (57). In terms of their physiological functions, tissue composition, and developmental processes, deciduous teeth differ greatly from permanent teeth. The fact that SHED differ from DPSCs in terms of their greater rate of proliferation, larger cell-population doublings, sphere-like cell cluster formation, osteoinductive capacity in vivo, and inability to reassemble a dentin-pulp-like complex is not surprising. The SHED population of multipotent stem cells appears to be younger than the postnatal stromal stem-cell populations that have been previously studied (59) .

1.4. Shed types and applications

- Adipocytes: They may be employed in plastic surgery as well as to treat a variety of orthopedic and spine disorders, Crohn's disease, and other ailments of the cardiovascular system (60).
- Animals' complete teeth have been grown using chondrocytes and osteoblasts (56).
- Mesenchymal stem cells (MSCs) have been utilized successfully to treat spinal cord damage and to provide paralyzed human patients the ability to feel and move again. Additionally, they can be utilized to treat neuronal degenerative conditions including Parkinson's disease, cerebral palsy, Alzheimer's disease, and other conditions of a similar nature (56).

1.4.1. Advantages

- Painless isolation, Autologous transplantation; thus, immunosuppressive therapy is unnecessary (61).
- Compared to cord blood banking, SHED banking is more affordable and could be useful in conjunction with cord cell banking (61).
- Unlike embryonic stem cells, cells are not susceptible to the same ethical considerations (61)

1.4.2. Eligibility

- Primary incisors and canines that are pathology-free and have at least one-third of their roots still present are eligible for SHED isolation. However, deciduous molars removed early for orthodontic reasons may present an opportunity to use these teeth for stem cell banking (62).
- Primary molar roots are not advised for sampling because they take longer to resorb, which may result in an obliterated pulp chamber that contains no pulp and, therefore, no stem cells (61)

1.4.3. Periodontal ligament stem cells: (pdlsc)

Seo et al. isolated them for the first time in 2004, PDLSCs, or periodontal ligament stem cells, are a promising tool for periodontal regeneration. They are found in the perivascular area of the periodontium. The characteristics of PDLSCS are those of stem cells, such as their small size, slow cellular cycle, immunomodulatory capabilities, and in vitro multilineage differentiation capacity.

1.4.4. Properties

Instead of neural crest cells, PDLSCs derived from mature periodontal ligaments have MSC-like stem cell characteristics (63). Although PDLSCs lack expression of CD45, CD34, and CD14 or CD11b, CD79a, or CD19 and HLA class II (68), they do exhibit MSC surface markers CD105 (64-68), CD90 (64-66,68,69), and CD73 (57,70). In terms of morphology, differentiation potential, cell phenotype (expression of pericyte-associated markers CD146, neural/glial antigen-2, and CD140B), and the capacity to develop capillary-like structures in vitro, PDLSCs found in the perivascular wall of periodontal ligaments are comparable to pericytes (71). Although it is thought that neural crest cells are the source of PDLSCs, matured PDLSCs exhibit immunomodulatory features and are comparable to bone marrow MSCs (66). Due to

the lack of HLA-II DR or T cell costimulatory molecules (CD80 and CD86), PDLSCs have low immunogenicity. PDLSCs require additional research, evaluation of the effectiveness, and in-depth examination of the relationships between numerous growth factors.

Origin

PDLSCs were primarily recovered from the middle third of the root surface following extraction of permanent teeth. But Wang and associates (65) showed that some PDL tissue was still present in the alveolar socket. When compared to traditional root surface-derived PDLSCs (r-PDLSCs), alveolar bone derived PDLSCs (a-PDLSCs) demonstrated a larger capacity for proliferation as well as a stronger potential for osteogenic and adipogenic differentiation. PDLSCs derived from deciduous teeth (d-PDLSCs) had greater proliferation, stronger adipogenic potential, and osteogenic potential than PDLSCs derived from permanent teeth (p-PDLSCs) (72,73). D-PDLSCs could also form a cementum-PDL structure when implanted in a nude mouse (74).

When compared to BMMSCs, PDLSCs derived from periodontal ligaments of extra teeth were more effective in forming colonies and had the ability to differentiate into adipocytes and osteoblasts. Furthermore, when transplanted into mouse calvaria defects, PDLSCs isolated from periodontal granulation tissue (75,76) in periodontitis patients produced Stro-1 and CD146 and promoted new bone formation.

In comparison to PDLSCs taken from healthy periodontal tissue (h-PDLSCs), PDLSCs produced from inflammatory periodontal tissues (i-PDLSCs) displayed higher proliferation (77) and faster migration (78), but lower osteogenic capacity (77) and reduced cementogenesis potential.

1.4.5. Age of donor

PDLSCs from older donors demonstrated a lower ability for regeneration than those from younger donors (79). It is important to pay attention to how aging affects stem cell characteristics, especially before applying PDLSCs autologously to older patients. When Zhang and colleagues (80) evaluated the biological characteristics of PDLSCs taken from donors of various ages, they discovered that the proliferative, migratory, and differentiation capabilities of PDLSCs decreased with donor age.

PDLSCs from older donors (over 41 years old) expressed less Stro-1 and CD146 and failed to form cementum-PDL-like structures in vivo, showing that the number and regenerative capacity of stem cells declined with donor age. Because chronic periodontitis patients are often older than 40 years old and the regeneration capacity of PDLSCs may have been reduced, donor age is important for autologous PDLSC transplantation.

Stem Cells From Apical Papilla (SCAPS)

First discovered by Sonoyama et al from an incompletely developed tooth (81). Cells present in the apical region of an immature permanent tooth has greater population of Msc and has good proliferative potential, low immunogenicity (82). There is a lot of evidence that SCAP can produce cells from several lineages, including osteogenic, odontogenic, adipogenic, chondrogenic, hepatogenic and could be an hopeful source of stem cell-based therapies (81-84).

Characteristic

SCAP has different phenotype and characteristics subpopulation (82). example: STRO -1, CD146 Subpopulation. Evidence shows that SCAP has higher rate of proliferation compared with DPSCs and PDLSCs and lower rate of proliferation than DFSCs (81-83,85,86)

SCAPs have higher ability tommigrate than DPSCs (81). SCAP show positive markers for CD12, CD14, CD29, CD44, CD49, CD 51, STRO-1, OCT3/4 (ocramer binding transcription factor), CD56, CD61, CD 71, CD 90 (82,83,87-89). SCAPs exhibit higher levels of anti-apoptotic protein survivin, has longer telomere length and telomerase activity, all of this interlinked which increase cell proliferation (82,92).

Significantly more chemokines, neurotrophins, and proteins involved in transcription and metabolic activities are secreted by SCAPs than by bone marrow mesenchymal stem cell (BMMSCs) (93). SCAPs exhibit low amounts of the immunological molecules swine leukocyte antigen (SLA) class I molecules and SLA class II DR molecules however is has ability to inhibit t cell through an apoptotic independent mechanism (94).

1.4.6. Therapeutics

SCAPs can be utilised for pulp- dentin regeneration, periodontal regeneration, bone and neutal regeneration. reports showed continued root development in imature permanent teeth with pulp necrosis by differentiating into odontoblasts sugesting SCAPs survive in pulp necrosis (81,95,96).

1.4.7. Dental Follicular Stem Cells (DFPC)

During the earliest stages of tooth development, the dental follicle (DF) is a loose band of connective tissue that surrounds the dental papilla and enamel organ (97). It is a cranial neural crest-derived ectomesenchyme tissue that plays a critical role in tooth development. Periodontium tissue, such as cementum, alveolar bone, and periodontal ligament (PDL), can develop from DF (98).

In 1992, dental follicular cells with a fibroblast-like appearance were initially isolated from rat molars (99). Later, in 2005 (100), a population of plastic adherent cells and colony-forming cells was isolated from the DF of human third molars. These cells are classified as dental follicle progenitor/stem cells (DFPCs), a novel type of dental MSCs, because they possess characteristics resembling those of the traditional MSCs.

1.4.8. Differentiation potential

DFPCs, which originate from the neural crest, can differentiate into osteoblasts, adipocytes, chondrocytes, cementoblasts, periodontal ligament cells, and neuronal cells (101,102). As a result, DFPCs are thought to be a promising candidate for tissue engineering and regenerative medicine.

The cloning of three different DF cell lines, each with their own special traits, highlighted the heterogeneity of DFPCs (103). The first line was extremely prolific without exhibiting mineralization behavior, suggesting that it might have contributed to the lineage of the PDL. Extremely high alkaline phosphatase (ALP) activity in the second line indicated an undifferentiated condition. Due to their ability to mineralize, the third cell line may give rise to cementoblasts or the alveolar bone osteoblastic lineage (103).

Role of dfsc in tooth-bone interface (TBI):

Acellular cementum, PDL, and cryptal bone must be properly formed for the tooth-bone interface (TBI) to operate. Due to their role in the formation of TBI, DFPCs also play a significant role in the remodeling of the alveolar bone and the formation of periodontium tissue. While exerting regulatory effect on monocyte/osteoclast lineage differentiation and function, DFPCs can differentiate into osteoblasts to contribute to the creation of alveolar bone (104,105).

Advantages

- Impacted third molars can be removed without harming DFPCs. DFPCs are simple to access because third molar extractions are less intrusive and harmful to healthy dentition.
- Second, DFPCs are a subset of adult stem cells that are drawn from tissue that is still forming. They might have more potential for multilineage differentiation.
- Third, research revealed that DFPCs were more capable of proliferating than dental pulp stem cells (DPSCs) (106).
- DF tissue can be successfully cryopreserved and used as a long-term resource for DFPCs (107).

2. Conclusion

DSCs have been studied not only limited to dental research, but DSCs have also been explored for the regeneration of other tissues and organs, including the cornea, liver, pancreas, vascular system, and bones. Additionally, the potential treatment of neurodegenerative illnesses has been investigated in relation to these cells. Within dentistry, DSCs have been investigated for the formation of new teeth, repair of maxillofacial bone defects, regeneration of pulp following necrosis, and therapy of periodontitis. Although DSCs have only been used in scientific study up to this point, it is anticipated that this method will soon become commonplace and mark a significant advancement in dentistry. Application of DSCs in everyday dental procedures, more research on their differentiation processes and uses is required.

Compliance with ethical standards

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Disclosure of Conflicts of Interests

The authors declare no conflict of interest and there is no financial interest to report.

Statement of ethical approval

The study is exempt from human ethical approval from the institute.

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