MedCrave
Step into the World of Research

Journal of Stem Cell Research & Therapeutics

Review Article

Open Access

CrossMark

The future in dental medicine: Dental stem cells are a promising source for tooth and tissue engineering

Abstract

Since the discovery of dental mesenchymal stem cells (DMSCs), there has been an extensive amount of research into their proliferating capabilities. DMSCs are extracted from exfoliated deciduous teeth, wisdom teeth, postnatal teeth, the periodontium, and alveolar bone. DMSCs have been shown to heal periodontal diseases and improve bone augmentation. DMSCs are accessible to all dentists. These qualities make DMSCs a promising source for tooth regeneration. There are numerous studies discussed in this article that offer encouraging evidence for the development of dental tissue regeneration. Eight different DMSC types are classified in this review: Dental Pulp Stem Cells (DPSCs), Stem cells from Human Exfoliated Deciduous teeth (SHEDs), Periodontal Ligament Stem Cells (PDLSCs), Dental Follicle Stem Cells (DFSCs), Stem Cells from the Dental Apical Papilla (SCAPs) Alveolar Bone–Derived MSCs (ABMSCs), Tooth Germ Progenitor cells (TGPCs), and Gingival MSCs (GMSCs), respectively. The discovery of DMSCs for regenerative medicine has attracted a profound amount of research. Additional clinical experimentation is required to test their medical and dental practicalities. This article is a review of the characterization, isolation, and the literature of previous studies on dental stem cell capabilities in regenerative medicine and their clinical applications for future dental practitioners.

Keywords: tissue engineering, mesenchymal stem cells, dental stem cells, regenerative dentistry, tooth regeneration

Volume 5 Issue 2 - 2019

Jonathan D Caracappa,[1,2] Vincent S Gallicchio[2]

[1]Department of Economics, College of Business, USA
[2]Department of Biological Sciences, College of Science, USA

Correspondence: Vincent S Gallicchio, Department of Biological Sciences, College of Science, Clemson University, Clemson, SC, USA 29636, Email vsgal@clemson.edu

Received: February 28, 2019 | **Published:** March 26, 2019

Introduction

The oral cavity is an accurate indicator of a patient's oral health. There is a strong correlation between the effects of chronic oral inflammation and general health. Prevailing and advancing medicine has rapidly increased human life expectancy, which has led to an increasingly aging society. Since human beings are living longer, there is a growing demand for dental medicine. More specifically, tooth loss, a burden millions of people deal with every day, is a major problem that compromises human oral health as well as individual overall health, as it contributes to poor nutrition and eventual debilitation as a person ages overtime. There are several prosthetic methods for treatment of tooth loss, which include fixed and/or removable prostheses, either tooth implants or implant bone.[1] However, many patients remain unsatisfied with these current dental prosthetic methods. One major flaw of artificial dentures is their poor function and inability to stay in a patient's mouth.[2] Dental implants require an extensive costly surgery. Even further, dental implants may not feel the same as natural teeth and cannot simply be splinted to the neighboring tooth.[3] Advancing modern medicine has allowed current researchers to do that which was once unimaginable: re–growing teeth. This notion, which was once a topic in science fiction, is now emerging into the stem–cell research field, which will take the next major transition into dental stem cell therapy.

Background

Stem cells are undifferentiated cells capable of proliferation, self–maintenance, production of different specialized cells, self–repair of tissues from injury, and the capability to develop into a variety of cell types throughout the body.[4] Stem cells replicate via self–renewal.[5] These cells vary in their location and specialized functions. The term stem cell first emerged in German biologist Haeckel's scientific research in 1868.[6] Columbia University Professor Dr. Edmund Wilson coined the term "stem cell" in his research of cell development and inheritance in 1896. Stem cells were proposed for scientific use when Russian histologist Alexander Maksimov claimed the existence of hematopoietic stem cells at a Berlin conference in 1908.[7] In 1961, while studying the effects of radiation on the bone marrow of mice, James Till and Ernest McCulloch discovered multipotent stem cells.[8] In 1974, Dr. Friedenstein and his research team discovered a cell population of mesenchymal stem cells in bone marrow.[9]

Stem cells have growing applications in tissue engineering and regenerative medicine. Tissue engineering is the intertwining of bioscience and engineering intended to create biological materials for the conservation, restoration, and improvement of tissue function.[10] The ultimate goal of tissue engineering is to replicate and produce functional replacement tissue by intending to provide a stimulus to the body's cells, in which the cells will either regenerate the tissues naturally or artificially grown in culture, which is transplanted as natural tissue. These procedures are based on the stem cells' ability to proliferate and differentiate. They are also dependent on a stable construction of bio–scaffolds and a natural tooth homeostatic environment.[10,11]

Stem cells are divided into three different groups: embryonic stem cells (ESC), adult stem cells (ASC), and induced pluripotent stem cells (iPSC). Embryonic stem cells are derived from embryos, developed from eggs, and are fertilized via *in vitro*. Ethical concerns question their use because researchers are arguably killing a human being, since these stem cells come from the intracellular mass held within the blastocyst. Embryonic stem cells are pluripotent: capable of differentiating into all cell types in the body. Induced pluripotent stem cells (iPSC) are pluripotent stem cells artificially generated via genetic manipulation of somatic cells.[12] iPSC cells can be created from non–pluripotent cells, which are fully differentiated, and possess pluripotency synonymous to ESCs. [12]

ASCs are undifferentiated somatic cells found throughout the body, which replace and replenish dying cells by cell division. ASCs

naturally reside in adult and juvenile tissues. There are nine different types of ASCs found throughout the body: hematopoietic, mammary, intestinal, endothelial, neural, olfactory, neural crest, testicular, and mesenchymal stem cells. Adult stem cells naturally reside in adult and juvenile tissues. Both ASCs and iPSC are derived from each individual patient's cells; this ensures the cells are biocompatible and can aid in drug screening and disease modeling.[13]

Mesenchymal stem cells

Tooth development or odontogenesis is a process involving the collaboration of reciprocal and sequential signals between the epithelial and mesenchymal tissue, respectively.[14] The signaling between these two types of tissue promotes morphogenesis by activating a subpopulation of mesenchymal cells, which differentiate into odontoblasts, thus forming primary dentin. Adult stem cells are found throughout the body, sometimes referred to as somatic stem cells or postnatal stem cells. Since the discovery of bone marrow mesenchymal stem cells (BMMSCs), there has been a quest to find alternative sources of MSCs in different tissues of the body. Through extensive research, populations of MSCs can be obtained from a variety of locations: skeletal muscle,[15] umbilical cord blood,[16] synovium,[17] the liver,[18] adipose,[19] the lungs,[20] amniotic fluid,[21] tendons,[22] placenta,[23] skin,[24] breast milk,[25] and teeth. Of all locations listed above, teeth are the most viable source to obtain MSCs because of their easy–to–access location inside the oral cavity. The formation of dental tissue requires two different cell types: the odontoblasts from mesenchymal stem cells, and ameloblasts from epithelial stem cells.[26] During tooth development, odontoblasts are responsible for the formation of dentin while ameloblasts form the enamel matrix.[26] Ameloblasts are the only ectodermal cells that contribute to odontogenesis. These cells disappear after tooth eruption, which eliminates the chance of *in vivo* production of enamel.

In animal models, the epithelium tissue was harvested from 3rd molar of young animals. The epithelium of the individual cells was enzymatically separated and propagated, *in vitro*.[26] The cells were joined with locally harvested mesenchymal cells and were exposed to biomaterials.[27–29] Biomaterials, or bio scaffolds, are artificial structures inserted into the body where the tissue can grow into its respective organ. Furthermore, the tooth germ from a child was needed for this procedure since the stem cells were in the roots of the erupting tooth. This research offers promising results for dental tooth and tissue engineering. Thus, the demand for more accessible mesenchymal stem cells other than MSCs located in bone marrow has encouraged scientists to explore dental tissues. These cells all display multiline age differentiation potential (multipotency), self–renewal, and immunomodulatory properties. MSCs have the ability to differentiate into the three mesodermal lineages: mesodermal,[30] endodermal,[31] and ectodermal.[32] In 2006, the Mesenchymal and Tissue Stem Cell Committee of *the International Society for Cellular Therapy* (ISCT) listed the criteria to characterize MSCs.[33] These MSCs must be "plastic–adherent" in a normal culture environment and be able to differentiate into chondroblasts, adipocytes, and osteoblasts *in vitro.* MSCs must display positive expression of CD105, CD73 and CD90 while expressing negative hematopoietic markers for CD45, CD34, CD14 or CD11b, CD79alpha or CD19 and HLA–DR surface molecules.[33] The expression of these specific protein cell surface markers confirms cell identity and cell type. Cell surface markers are a way of labeling and identifying a specific cell/tissue type found throughout the body. These markers are especially important during differentiation of the various cell types.

There is a rich variety of stem cells in the dental tissues that can be applied to regenerative medicine and tissue engineering. These cells are called dental mesenchymal stem cells and are cataloged based on their location:

1) Dental Pulp Stem Cells, DPSCs[34] (located inside pulp cavity of tooth)
2) Stem cells from Human Exfoliated Deciduous teeth, SHEDs[35](located inside pulp cavity of tooth)
3) PerioDontal Ligament Stem Cells, PDLSCs[36] (located on the periodontal tissue)
4) Dental Follicle Stem Cells, DFSCs[37] (located around tooth germ of developing tooth)
5) Stem Cells from the Dental Apical Papilla, SCAPs[38] (located in upper dental papilla)
6) Alveolar Bone–Derived MSCs, ABMSCs[39] (located on alveolar bone in maxilla and mandible jaw)
7) Tooth Germ Progenitor cells, TGPCs[40] (deciduous teeth of 3rd molars)
8) Gingival MSCs, GMSCs[41] (gingiva of the periodontium)

Dental pulp stem cells (DPSCs)

Dental Pulp Stem Cells (DPSCs) are located within the pulp cavity of teeth.[42] The regenerative nature of the dental pulp has encouraged scientists to research the pulp complex of the tooth. In 2000, DPSCs were first identified from the pulp tissue.[34] These cells had similar phenotypic traits to bone marrow stem cells (BMSCs). Researchers found that DPSCs can regenerate a dentin–pulp complex with a mineralized matrix lined with odontoblasts and fibrous connective tissue containing blood vessels, which closely resembles the dentin–pulp structure in a normal tooth.

Gronthos et al.[42] harvested DPSCs from the 3rd molars of patients between 19–29 years old, and display the following characteristics: higher proliferation rate *in vitro,* synonymous expression protein markers to bone marrow mesenchymal stem cells, and similar fibroblast structure.[42] These teeth are the last permanent molars to form, which explains the existence of stem cells within the pulp complex. Gronthos et al.[42] also found that DPSCs could create ectopic dentin and affiliated pulp tissue *in vivo* and differentiate into neural–like cells and adipocytes. In their study, Gronthos et al.[42] found that *ex vivo* expanded DPSCs generate a dentin/pulp– like configuration *in vivo.* This evidence suggests that DPSCs possess multi–lineage differentiation and self–renewal.

This same research group performed an experiment *in vivo*, which exhibited DPSCs creating bone when implanted into hypodermal sites with HA/TCP powder into immune compromised mice. They observed, in 6 weeks, a dentin–pulp–like structure that strongly resembles a human tooth. Additionally, the long–term storage of these stem cells was tested. After two years stored, DPSCs were able to differentiate into pre–osteoblasts, constructing woven bone tissues.[43] The DPSCs expressed certain surface antigens to confirm cellular integrity.[44]

A functional bio–scaffold is crucial for the development of implanted stem cells because it serves as the template for tissue growth. Without a suitable bio–scaffold, the stem cells do not have an adequate foundation for growth and development. In addition, the proper

microenvironment must be established to promote differentiation. Scientists have recently seeded DPSCs onto 3–dimensional scaffold materials: a fibrous titanium mesh, a porous ceramic, and a spongeous collagen.[42] The DPSCs were implanted into mice for 6 or 12 weeks. The stem cells did not form a dentin–pulp–like complex, but instead formed a structure synonymous to connective tissue.[44] Although the DPSCs did not form the mineralized bone structure, a softer, cartilage–like tissue developed.

Future biomaterial engineer's biggest challenge is finding the most appropriate and suitable bio–scaffold for clinical application. The evidence presented above demonstrates that DPSCs are highly proliferative, clonogenic, and capable in regenerating tissue; all qualities that define postnatal human dental pulp as stem cells. The data presented here demonstrates that postnatal dental pulp contains cells that are clonogenic, highly proliferative, and capable of regenerating a tissue, properties that effectively define them as stem cells.[45]

Stem cells from human exfoliated deciduous teeth, SHEDs

Stem cells from Human Exfoliated Deciduous Teeth (SHEDs) are another type of DMSC. Moreover, SHEDs are a specific mesenchymal stem cell located in the pulp cavity of deciduous (baby) teeth. In 2003, researchers discovered a population of SHEDs that differentiate into neurons, odontoblasts, and adipocytes.[46] Researchers observed that this cell population has a higher proliferation rate and higher number of population doublings; compared to DPSCs and bone marrow stromal stem cells (BMSSCs).[46]

Therefore, SHEDs are easy to extract from younger patients. This special quality of SHEDs makes them a readily available plethora of potent stem cells that can be altered for clinical manipulation. These stem cells show the ability to survive, after *in vivo* transplantation, in a mouse's nervous tissue (expression of neural markers).[46] A significant increase in blood vessel density is observed. SHED can trigger bone formation and generate dentin.[46] However, SHEDs lack the ability to regenerate directly into osteoblasts. Instead, SHEDs induce formation.[46]

Extracted (exfoliated) teeth are a surprisingly prolific resource for tissue engineering and autologous stem cell transplantation.[46] The abundance and proliferation of SHEDs makes them an ideal input for tooth regeneration. SHEDs are an unforeseen source of potent cells because they are capable of delivering enough cells for potential clinical therapies. They are applicable to tissue regeneration, tooth engineering, and autologous stem cell transplantation.[46] SHEDs also differentiated into anastomosed blood vessels with the host vasculature.[47] These cells displayed high plasticity and osteo–inductive ability.[47] In essence, SHEDs are a viable of stem cells for dental pulp engineering.[47]

Periodontal ligament stem cells, PDLSCs

Periodontal Ligament Stem Cells (PDLSCs) are found within the periodontium.[48] The function of periodontal ligament is to connect teeth to the alveolar bone, thus creating a supportive foundation. PDLSCs have been noted to produce the alveolar bone and cementum.[48,49] The tissue has strong connective fibers that keep the teeth in place. The main clinical application of PDLSCs is to repair normal function of teeth by restoring periodontal support in the periodontal ligament (PDL), alveolar bone, gingiva, and the cementum.[48,49] PDLSCs possessed the following mesenchymal stem cell markers: STRO–1 and CD146/MUC18.[48] PDLSCs differentiated, under specific cultures conditions, into adipocytes, collagen–forming cells, and cementoblast–like cells.[48] To obtain stem cells; the periodontal ligament is extracted from the roots of teeth from which the stem cells are isolated. PDLSCs have been noted to produce the alveolar bone and cementum. Like other stem cells, they can differentiate *in vitro* into a variety of tissues types: chondrocytes, adipocytes, and osteoblasts.[50]

PDLSCs are a reservoir of pluripotent stem cells that can form mineralized nodules, respond to bone–inductive factors *in vitro,* and they express osseous/cementum–associated markers.[48] PDLSCs possess the capacity to form mineralized nodules, expression of bone/cementum–associated markers, and response to bone–inductive factors *in vitro*.[48] PDLSCs have been promising in regenerating damaged bone, cementum, and functional periodontium. One study combined and transplanted PDLSCs and stem cells from the dental apical papilla (SCAPs) into six inbred male minipigs. PDLSCs and SCAPs generated a root/periodontal complex, which was capable of supporting a porcelain crown.[51] These cells were implanted into a scaffold and transplanted in the alveolar bone of adolescent pigs.[51]

In another study, PDLSCs were transplanted into immuno–deficient mice.[48] These mice developed bone–like structures, cartilage, periodontal ligament, and cementum. A study conducted in miniature swine tested the regenerative properties of these progenitor cells.[52] A periodontal lesion was made to the swine first molar area via surgical extraction of bone. PDLSCs were expanded and then implanted *in vivo* onto the periodontal gingiva tissue.[52] PDLSCs regenerated the lesion area and the surrounding tissue. This study proves a foreseeable future in treatment for gum disease, a burden that half of adults 30 and older suffer. This experiment proves the viability and practicality of PDLSCs to treat periodontal infections.

Dental follicle stem cells, DFSCs

Dental follicle stem cells (DFSCs) are ecto–mesenchymal derived tissues that develop locally around the tooth germ.[53] The dental follicle is a dental sac containing the developing tooth containing DFSCs. These progenitor cells have suitable lineages to form osteoblasts, cementoblasts, and periodontal ligament cells.[53] In previous studies, DFSCs have been isolated from dental follicle in adult 3rd molars.[53] DFSCs are very similar to the other DMSCs.[53] DFSCs also have a high proliferation rate, and create hard and soft tissue both *in vivo* and *in vitro*.[53,54] These progenitor cells can regenerate tissues of the periodontium: periodontal ligament, alveolar bone, and cementum.[53]

An *in vitro* study of DFSCs combined with dexamethasone created dense calcified nodules and appeared to resemble membrane–like configurations.[53] DFSC's characteristics closely resemble the properties of cementoblasts stimulated by enamel matrix derivatives and BMP□2/□7.[55] Specific staining and expression of certain markers showed that DFSCs can differentiate into adipocytes and chondrocytes.[55] These findings suggest that DFSCs have suitable stem cell therapy qualities with prolific differentiation potential.

An *in vivo* study transplanted DFSCs onto porous ceramic discs into immuno–compromised rats.[53] The DFSCs created cement woven bone tissue pattern. Osteocyte–like cells and cementocyte–like cells were embedded within the formed tissues. This experiment did not produce the calcified tissues (dentin, cementum, and bone) that are essential for normal tooth function.[53] In summary, the *in vivo* transplantation did not produce a functional hard tissue. *In vivo* transplantation shows the shortcomings of DFSCs. Although mineralized bone matrix did

not form, a less mineralized medium was created More research is required to discover a more viable bio–scaffold for clinical use.

Stem cells from the dental apical papilla, SCAPs

Stem cells from the Dental Apical Papilla (SCAPs) are isolated from the upper dental papilla. The development of the tooth relies on the apical papilla, which is a soft tissue located on the top of developing adult teeth.[51] SCAPs are a more recently discovered progenitor cell arising from developing tissue.[51] SCAPs exhibit higher plasticity than other MDSCs.[51] They are induced by overlapping dental lamina during odontogenesis originating from ecto–mesenchymal tissue.[56,57] These stem cells are responsible for the development of the tooth structure and the pulp tissue. SCAPs form a concentrated area of cells between the pulp complex and the apical papilla.[58] In addition, they have higher mineralization and proliferation rate potential than DPSCs.[37,59] SCAPs express usual MSC markers: CD90, CD105, CD73, and STRO–1. These cell markers are the minimum required criteria to be classified as mesenchymal stem cells.

SCAPs offer a more superior tissue regeneration than DPSCs.[51] SCAPs also have high proliferation potential, reflected from high telomerase activity.[60] SCAPs harvested from one single tooth are capable in providing large populations of stem cells that are considered sufficient for human transplantation.[60]

An *in vitro* experiment performed in a three–dimensional cell culture system showed that SCAPs can be differentiated into odontoblasts in the appropriate microenvironment. Ikeda et al.[61] cultured dental papilla from impacted human molars and found that mesenchymal stem cells localize inside the dental papilla. These cells have the capacity to be cultured, utilized, and expanded for osseous tissue engineering.[61] In another study, researchers used HA/TGT (hydroxyapatite/tricalcium phosphate) combined with PDLSCs and SCAPs in mice. The result was the formation of cementum/Sharpey's fibers, and dentin.[26] This discovery signifies the capabilities of SCAPs combined with other DMSCs in regenerative medicine, especially revascularization and regenerative endodontic therapy.

Alveolar bone–derived mesenchymal stem cells, ABMSCs

Alveolar Bone Derived Mesenchymal Stem Cells (ASMSCs) are located in the alveolar bone.[39] This is the foundational structure where teeth naturally reside and are adjacent to periodontal ligament of compact bone. ASMSCs reside within the osseous tissue. One study successfully isolated and cultured ASMSCs. Extracted ASMSCs displayed plastic adherence, colony formation, and spindle□shaped fibroblast□like morphology. ASMSCs expressed the following surface markers: CD105, CD73, CD90, and STRO□1 while not expressing the hematopoietic markers CD45, CD34, and CD14.[39,62,63] These markers confirm the surface antigens that code for MSCs.

Expanded ASMSCs *in vitro* have been found to differentiate into osteoblasts lineages and exhibit ALP expression.[39] Treating human ABMSCs with orbital shear stress,[64] low□frequency pulsed electromagnetic fields,[65] interferon□induced transmembrane protein,[66] low fluid dynamic shear stress,[67] low□intensity pulsed ultrasound,[68] nicotine[69] and dichloromethane fraction of Dipsaci Radix[70] have all enhanced osteogenesis in ASMSCs, respectively. Furthermore, ABMSCs displayed adipogenic and chondrogenic differentiation potentials analogous to those of other DSCs.[64,71] ABMSCs can be easily harvested during dental implant surgery.[63] This cell source gives ABMSCs an advantage to other cell types applicable to clinical trials. These recent progresses confirm the feasibility of using ASMSCs in clinical applications to treat bone defects.[63]

Tooth germ progenitor cells, TGPCs

Tooth germ progenitor cells (TGPCs) are another type of dental stem cell that has positively impacted tissue regeneration.[40] TGPCS are found in the dental mesenchyme of wisdom teeth during the late bell stage of odontogenesis, recognized for morpho–differentiation and histo–differentiation.[72] TGPCs showed high proliferation activity and capability to differentiate *in vitro* into cells of three germ layers including osteoblasts, neural cells, and hepatocytes.[40]

Like other DMSCs, TGPCs show high proliferation and can differentiate *in vitro* into neural cells, osteoblasts, and hepatocytes.[41] Contrasting from other DMSCs, TGPCs can differentiate into hepatocyte–like cells. TGPCs are an ideal raw material for treating liver diseases and regenerating the liver. In 2008, Ikeda et al.[40] showed a substantial therapeutic effect of engrafted TGPCs that prevented the inclination of liver fibrosis.[40] TGPCs aided in restoring proper liver function in tetrachloride–treated rats.[39]

TGPCs have been expanded for 60 population doublings and were found to retain their proliferation rate and spindle shape–like morphology. TGPCs express the following MSC markers: STRO–1, CD29, CD44, CD73, CD90, CD105, CD106, CD166.[73] In addition, TGPCs exhibit a propensity for pluripotency–associated gene expression (*sox2, nanog, oct4, c□myc, and klf4*), signifying a mesenchymal phenotype.[40,74,75] Although this review focuses on dental stem cells for tooth regeneration, TGPCs are one significant example of DMSCs differentiating into dental mesenchymal tissues and non–dental mesenchymal tissues.

Gingival mesenchymal stem cells, GMSCs

Gingival MSCs have been praised in recent years for their readily accessible tissue[76] GMSCs are extracted using a minimally invasive cell–isolation technique.[76] The gingival gum is a unique tissue because of their quick and scarless wound healing abilities. In 2017, GMSCs were isolated from the gingival lamina propria. Gingival tissue originates from the dental follicle propria, perifollicular mesenchyme, and neural crest ectomesenchyme. Obtained GMSCs are de–epithelized and the lamina propria is removed, gathered, and minced to isolated GMSCs.[77]

GMSCs have the ability for *in vivo* osseous formation, related gene expression, multilineage differentiation, and self–renewal.[78] GMSCs have also demonstrated the ability to differentiate into several specialized cell types: chondrocytes, adipocytes, osteoblasts, and also endothelial and neural pathways when cultured *in vitro,* respectively.[77,78] GMSCs have stem cell specific genes, the expression of mesenchymal cell surface markers, and a higher population doubling time.[78] GMSCs obtained *in vitro* also exhibit many similar characteristics to MSCs from bone marrow.[78] These include plastic adherent cells with fibroblast–like morphology, colony forming ability, multipotent differentiation, and multilineage differentiation.

These characteristics make GMSCs a good candidate for many clinical applications.[41] Wang et al.[79] extracted GMSCs and implanted them into rats. Using histochemically analysis, immunohistochemical analysis, and images of fluorescence microscope; these results infer

that MSCs derived from gingival tissue have high potential for stem cell–based therapy in osseous reconstruction in clinical applications, respectively (80).[79] GMSCs can be used to treat many areas of regenerative medicine including tendon, periodontal, and bone defect regeneration; oral mucositis, integumentary wound repair, collagen–induced arthritis and contact hypersensitivity, and antitumor effect.[78] GMSCs are an abundant and easily accessible DMSC that can be a significant resource for use in regenerative medicine and tooth engineering.

Conclusion

Stem cells of dental origin are a harbinger of rich stem cells that have the qualities to be used in clinical applications. Although there has been much progress in stem cell biology, there are several limitations of dental stem cells. The first limitation is the possibility of immune rejection unless autologous cells or the use of immunosuppressive drugs are being facilitated and recommended. The second limitation is that the majority of research performed has been accomplished using only animal models. Thus, their extensive clinical application has yet to be confirmed. The third limitation is the struggle to identify, isolate, modify, and grow stem cells reliably in the lab. Finally, teeth–like structures cannot substitute real teeth. Researchers still need to engineer blood vessels and nerves that coincide with the dental stem cells, that of which has not been successfully attainable. Dental stem cell research, like other innovative technologies, has its challenges and risks. For the future of dental stem cells in dental practice to be achievable researchers and healthcare practitioners must assess the risks and meet the challenges. This literature review catalogues the eight main types of DMSCs that exist within the oral cavity that are notable for their regenerative capabilities: Dental Pulp Stem Cells (DPSCs), Stem cells from Human Exfoliated Deciduous teeth (SHEDs), Periodontal Ligament Stem Cells (PDLSCs), Dental Follicle Stem Cells (DFSCs), Stem Cells from the Dental Apical Papilla (SCAPs), Alveolar Bone–Derived MSCs (ABMSCs), Tooth Germ Progenitor cells (TGPCs), Gingival MSCs (GMSCs). All of these cells are easily accessible and offer incredible multipotency. DMSCs, used as stem cell therapies, have shown clinical application in countless areas of medicine including tendon regeneration, integumentary wound repair, peri–implantatitis, oral mucositis, antitumor effect, periodontal regeneration, osseous defect regeneration, contact hypersensitivity, and collagen–induced arthritis. This overwhelming evidence proves the prolific relevance and abilities of DMSCs in regenerative medicine and tissue engineering.

Acknowledgments

None.

Conflicts of interest

Authors declare that there is no conflicts of interest.

References

1. Koh RU, Rudek I, Wang H. Immediate implant placement: positives and negatives. *Implant Dent*. 2010;19(2):98–108.
2. Pellecchia M, Pellecchia R, Emtiaz S. Distal extension mandibular removable partial denture connected to an anterior fixed implant-supported prosthesis: a clinical report. *J Prosthet Dent*. 2000;83(6):607–612.
3. Misch CE. Short dental implants: a literature review and rationale for use. *Dent Today*. 2005;24(8):64–66,68.
4. Potten CS, Loeffler M. Stem cells: attributes, cycles, spirals, pitfalls and uncertainties. Lessons for and from the crypt. *Development.* 1990;110(4):1001–1020.
5. Slack J. Origin of stem cells in organogenesis. *Science.* 2008;322(5907):1498–1501.
6. Yamaizumi M, Mekada E, Uchida T, et al. One molecule of diphtheria toxin fragment A introduced into a cell can kill the cell. *Cell*. 1978;15(1):245–250.
7. Maximow A. The lymphocyte as a stem cell, common to different blood elements in embryonic development and during the post-fetal life of mammals. *Folia Haematologica.* 1909;8:125–134.
8. McCulloch EA, Till JE. Perspectives on the properties of stem cells. *Nat Med.* 2005;11(10):1026–1028.
9. Friedenstein AJ, Gorskaja JF, Kulagina NN. Fibroblast precursors in normal and irradiated mouse hematopoietic organs. *Exp Hematol*. 1976;4(5):267–274.
10. Khetan S, Burdick J. Cellular encapsulation in 3D hydrogels for tissue engineering. *J Vis Exp*. 2009;(32):1590.
11. Schneider RK, Puellen A, Kramann R, et al. The osteogenic differentiation of adult bone marrow and perinatal umbilical mesenchymal stem cells and matrix remodelling in three-dimensional collagen scaffolds. *Biomaterials*. 2010;31(3):467–480.
12. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell*. 2006;126(4):663–676.
13. Ebert AD, Liang P, Wu JC. Induced pluripotent stem cells as a disease modeling and drug screening platform. *J Cardiovasc Pharmacol.* 2012;60(4):408–416.
14. Irma T, Vaahtokari A, Partanen A. Regulation of organogenesis. Common molecular mechanisms regulating the development of teeth and other organs. *Int J Dev Biol*. 1995;39:35–50.
15. Williams JT, Southerland SS, Souza J,et al. Cells isolated from adult human skeletal muscle capable of differentiating into multiple mesodermal phenotypes. *Am Surg*. 1999;65(1):22–26.
16. Erices A, Conget P, Minguell JJ. Mesenchymal progenitor cells in human umbilical cord blood. *Br J Haematol.* 2000;109(1):235–242.
17. De Bari C, Dell'Accio F, Tylzanowski P,et al. Multipotent mesenchymal stem cells from adult human synovial membrane. *Arthritis & Rheumatism*. 2001;44(8):1928–1942.
18. Campagnoli C, Roberts IA, Kumar S, et al. Identification of mesenchymal stem/progenitor cells in human first-trimester fetal blood, liver, and bone marrow. *Blood.* 2001;98(8):2396–2402.
19. Zuk PA, Zhu M, Mizuno H, et al. Multilineage cells from human adipose tissue: implications for cell-based therapies. *Tissue Eng.* 2001;7(2):211–228.
20. Noort WA, Kruisselbrink AB, in't Anker PS, et al. Mesenchymal stem cells promote engraftment of human umbilical cord blood–derived CD34 cells in NOD/SCID mice. *Exp Hematol.* 2002;30(8):870–878.
21. Scherjon SA, Kleijburg-van der Keur C, Noort WA, et al. Amniotic fluid as a novel source of mesenchymal stem cells for therapeutic transplantation. *Blood.* 2003;102(4):1548–1549.
22. Salingcarnboriboon R, Yoshitake H, Tsuji K, et al. Establishment of tendon-derived cell lines exhibiting pluripotent mesenchymal stem cell-like property. *Exp Cell Res.* 2003;287(2):289–300.
23. Scherjon SA, Kleijburg□van der Keur C, de Groot□Swings GM, et al. Isolation of mesenchymal stem cells of fetal or maternal origin from human placenta. *Stem Cells.* 2004;22(7):1338–1345.

24. Shih DT, Lee D, Chen S, et al. Isolation and characterization of neurogenic mesenchymal stem cells in human scalp tissue. *Stem Cells*. 2005;23(7):1012–1020.

25. Patki S, Kadam S, Chandra V,et al. Human breast milk is a rich source of multipotent mesenchymal stem cells. *Human cell.* 2010;23(2):35–40.

26. Lymperi S, Ligoudistianou C, Taraslia V, et al. Dental stem cells and their applications in dental tissue engineering. *Open Dent J*. 2013;7:76–81.

27. Young CS, Terada S, Vacanti JP, et al. Tissue engineering of complex tooth structures on biodegradable polymer scaffolds. *J Dent Res*. 2002;81(10):695–700.

28. Honda MJ, Shimodaira T, Ogaeri T, et al. A novel culture system for porcine odontogenic epithelial cells using a feeder layer. *Arch Oral Biol.* 2006;51(4):282–290.

29. Honda MJ, Tsuchiya S, Sumita Y,et al. The sequential seeding of epithelial and mesenchymal cells for tissue-engineered tooth regeneration. *Biomaterials.* 2007;28(4):680–689.

30. Pittenger MF, Mackay AM, Beck SC, et al. Multilineage potential of adult human mesenchymal stem cells. *Science.* 1999;284(5411):143–147.

31. Sato Y, Araki H, Kato J, et al. Human mesenchymal stem cells xenografted directly to rat liver are differentiated into human hepatocytes without fusion. *Blood*. 2005;106(2):756–63.

32. Kopen GC, Prockop DJ, Phinney DG. Marrow stromal cells migrate throughout forebrain and cerebellum, and they differentiate into astrocytes after injection into neonatal mouse brains. *Proc Natl Acad Sci USA.* 1999;96(19):10711–10716.

33. Dominici M, Le Blanc K, Mueller I, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy.* 2006;8(4):315–317.

34. Gronthos S, Mankani M, Brahim J,et al. Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo. *Proc Natl Acad Sci USA*. 2000;97(25):13625–13630.

35. Miura M, Gronthos S, Zhao M, et al. SHED: stem cells from human exfoliated deciduous teeth. *Proc Natl Acad Sci USA.* 2003;100(10):5807–5812.

36. Seo B, Miura M, Gronthos S, et al. Investigation of multipotent postnatal stem cells from human periodontal ligament. *Lancet*. 2004;364(9429):149-55.

37. Morsczeck C, Götz W, Schierholz J, et al. Isolation of precursor cells (PCs) from human dental follicle of wisdom teeth. *Matrix Biology.* 2005;24(2):155–165.

38. Sonoyama W, Liu Y, Fang D, et al. Mesenchymal stem cell-mediated functional tooth regeneration in swine. *PloS one*. 2006;1(1):e79.

39. Matsubara T, Suardita K, Ishii M, et al. Alveolar bone marrow as a cell source for regenerative medicine: differences between alveolar and iliac bone marrow stromal cells. *J Bone Miner Res*. 2005;20(3):399–409.

40. Ikeda E, Yagi K, Kojima M, et al. Multipotent cells from the human third molar: feasibility of cell□based therapy for liver disease. *Differentiation.* 2008;76(5):495–505.

41. Zhang Q, Shi S, Liu Y, et al. Mesenchymal stem cells derived from human gingiva are capable of immunomodulatory functions and ameliorate inflammation-related tissue destruction in experimental colitis. *J Immunol.* 2009;183(12):7787–7798.

42. Gronthos S, Mankani M, Brahim J, et al. Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo. *Proc Natl Acad Sci USA*. 2000;97(25):13625–13630.

43. Peng L, Ye L, Zhou X. Mesenchymal stem cells and tooth engineering. *Int J Oral Sci.* 2009;1(1):6.

44. Papaccio G, Graziano A, d Aquino R, et al. Long□term cryopreservation of dental pulp stem cells (SBP□DPSCs) and their differentiated osteoblasts: a cell source for tissue repair. *J Cell Physiol.* 2006;208(2):319–325.

45. Shamel M, Mahmoud M Al Ankily, Mahmoud M Bakr. Proliferative Capacity and Differentiation Potential of Isolated Postnatal Human Dental Pulp Stem Cells in Diabetic Patients. *J Stem Cell Res*. 2017;1(3):1–6.

46. Miura M, Gronthos S, Zhao M, et al. SHED: stem cells from human exfoliated deciduous teeth. *Proc Natl Acad Sci USA*. 2003;100(10):5807–5812.

47. Cordeiro MM, Dong Z, Kaneko T, et al. Dental pulp tissue engineering with stem cells from exfoliated deciduous teeth. *J Endod.* 2008;34(8):962–969.

48. Seo B, Miura M, Gronthos S, et al. Investigation of multipotent postnatal stem cells from human periodontal ligament. *Lancet*. 2004;364(9429):149–155.

49. Seo B, Miura M, Sonoyama W, et al. Recovery of stem cells from cryopreserved periodontal ligament. *J Dent Res*. 2005;84(10):907–912.

50. Gay IC, Chen S, MacDougall M. Isolation and characterization of multipotent human periodontal ligament stem cells. *Orthod Craniofac Res*. 2007;10(3):149–160.

51. Sonoyama W, Liu Y, Fang D, et al. Mesenchymal stem cell-mediated functional tooth regeneration in swine. *PloS one.* 2006;1(1):e79.

52. Liu Y, Zheng Y, Ding G, et al. Periodontal ligament stem cell□ mediated treatment for periodontitis in miniature swine. *Stem Cells.* 2008;26(4):1065–1073.

53. Morsczeck C, Götz W, Schierholz J, et al. Isolation of precursor cells (PCs) from human dental follicle of wisdom teeth. *Matrix Biol*. 2005;24(2):155–165.

54. Huang G, Gronthos S, Shi S. Mesenchymal stem cells derived from dental tissues vs. those from other sources: their biology and role in regenerative medicine. *J Dent Res.* 2009;88(9):792–806.

55. Kémoun P, Laurencin-Dalicieux S, Rue J, et al. Human dental follicle cells acquire cementoblast features under stimulation by BMP-2/-7 and enamel matrix derivatives (EMD) in vitro. *Cell Tissue Res.* 2007;329(2):283–294.

56. Huang GT, Ricucci D, Lin LM. *Endodontic infections in incompletely developed teeth.* 2nd ed. Endodontic microbiology. 2017.

57. Orban B. Oral histology and embryology. South Med J. 1955;48(1):99.

58. Kikuchi H, Suzuki K, Sakai N, et al. Odontoblasts induced from mesenchymal cells of murine dental papillae in three-dimensional cell culture. *Cell Tissue Res.* 2004;317(2):173–185.

59. Sonoyama W, Liu Y, Yamaza T, et al. Characterization of the apical papilla and its residing stem cells from human immature permanent teeth: a pilot study. *J Endod.* 2008;34(2):166–171.

60. Shi S, Gronthos S, Chen S, et al. Bone formation by human postnatal bone marrow stromal stem cells is enhanced by telomerase expression. *Nat Biotechnol.* 2002;20(6):587–591.

61. Ikeda E, Hirose M, Kotobuki N, et al. Osteogenic differentiation of human dental papilla mesenchymal cells. *Biochem Biophys Res Commun.* 2006;342(4):1257–1262.

62. Mason S, Tarle SA, Osibin W. standardization and safety of Alveolar bone–derived stem cell Isolation. *J Dent Res.* 2014;93(1):55–61.

Citation: Caracappa JD, Gallicchio VS. The future in dental medicine: Dental stem cells are a promising source for tooth and tissue engineering. *J Stem Cell Res Ther.* 2019;5(2):30–36. DOI: 10.15406/jsrt.2019.05.00131

63. Park J, Kim JC, Kim Y, et al. Acquisition of human alveolar bone derived stromal cells using minimally irrigated implant osteotomy: in vitro and in vivo evaluations. *J Clin Periodontol*. 2012;39(5):495–505.

64. Lim KT, Hexiu J, Kim J. Synergistic effects of orbital shear stress on in vitro growth and osteogenic differentiation of human alveolar bone-derived mesenchymal stem cells. *Biomed Res Int*. 2014;2014:316803.

65. Lim K, Hexiu J, Kim J, et al. Effects of electromagnetic fields on osteogenesis of human alveolar bone-derived mesenchymal stem cells. *Biomed Res Int*. 2013;2013:296019.

66. Kim B, Kim H, et al. IFITM1 increases osteogenesis through Runx2 in human alveolar-derived bone marrow stromal cells. *Bone.* 2012;51(3):506–514.

67. Lim K, Kim J, Seonwoo H, et al. Enhanced osteogenesis of human alveolar bone-derived mesenchymal stem cells for tooth tissue engineering using fluid shear stress in a rocking culture method. *Tissue Engineering Part C Methods*. 2013;19(2):128–145.

68. Lim K, Kim J, Seonwoo H. In vitro effects of low-intensity pulsed ultrasound stimulation on the osteogenic differentiation of human alveolar bone-derived mesenchymal stem cells for tooth tissue engineering. *Biomed Res Int.* 2013;2013:269724

69. Kim B, Kim S, Kim H, et al. Effects of nicotine on proliferation and osteoblast differentiation in human alveolar bone marrow-derived mesenchymal stem cells. *Life Sci.* 2012;90(3–4):109–115.

70. Kim B, Kim Y, Zadeh H, et al. Effects of the dichloromethane fraction of Dipsaci Radix on the osteoblastic differentiation of human alveolar bone marrow-derived mesenchymal stem cells. *Bioscience, Biotechnology, and Biochemistry*. 2011;75(1):13–19.

71. Pekovits K, Kröpfl JM, Stelzer I. Human mesenchymal progenitor cells derived from alveolar bone and human bone marrow stromal cells: a comparative study. *Histochem Cell Biol*. 2013;140(6):611–621.

72. Nanci A. *Ten Cate's Oral Histology-E-Book: Development, Structure, and Function*. 9th ed. Elsevier Health Sciences; 2017.

73. Liu J, Yu F, Sun Y, et al. Concise reviews: Characteristics and potential applications of human dental tissue derived mesenchymal stem cells. *Stem Cells*. 2015;33(3):627–638.

74. Yalvac ME, Ramazanoglu M, Rizvanov AA, et al. Isolation and characterization of stem cells derived from human third molar tooth germs of young adults: implications in neo-vascularization, osteo-, adipo-and neurogenesis. *Pharmacogenomics J.* 2010;10(2):105–113.

75. Yalvaç ME, Ramazanoglu M, Tekguc M, et al. Human tooth germ stem cells preserve neuro-protective effects after long-term cryo-preservation. *Curr Neurovasc Res*. 2010;7(1):49–58.

76. Venkatesh D, Kumar KM, Alur JB. Gingival mesenchymal stem cells. *Journal of oral and maxillofacial pathology: JOMFP*. 2017;21(2):296–298.

77. Yang H, Gao L, An Y, et al. Comparison of mesenchymal stem cells derived from gingival tissue and periodontal ligament in different incubation conditions. *Biomaterials.* 2013;34(29):7033–7047.

78. Fawzy El-Sayed KM, Dörfer CE. Gingival mesenchymal stem/progenitor cells: a unique tissue engineering gem. *Stem Cells Int.* 2016;2016:7154327.

79. Wang F, Yu M, Yan X, et al. Gingiva-derived mesenchymal stem cell-mediated therapeutic approach for bone tissue regeneration. *Stem Cells Dev.* 2011;20(12):2093–2102.