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Dental Tissue-Derived Mesenchymal Stem Cells in Tissue Engineering

Doku Mühendisliğinde Diş Dokusundan Türetilmiş Mezenkimal Kök Hücreler

ABSTRACT

Tissue engineering (TE) is an interdisciplinary field that applies the principles of engineering and life sciences toward the development of biological substitutes that restore, maintain, or improve tissue or organ function. TE provides newly regenerated tissues by the appliance of cells, scaffold, and signaling molecules. In tissue engineering applications, mesenchymal stem cells are among the most-used populations. The stem cell is a multipotent cell, which can proliferate and differentiate to a specific cell. These cells can form many different tissue types. Since the discovery and characterization of multipotent mesenchymal stem cells (MSCs) from bone marrow (BM), MSC-like populations from other tissues have now been characterized based on the 'gold standard' criteria established for BMMSCs. Dental issues have been considered as a potential source for the isolation of MSC-like populations. To date, many unique populations of dental tissue-derived MSCs have been isolated and characterized. This article will review the current dental sources of MSCs, and the properties of these dental tissue-derived MSCs.

Key Words: Tissue Engineering (TE), Dental Tissue, Mesenchymal Stem Cells (MSCs).

ÖZET

Doku mühendisliğ, "Mühendislik ve yaşam bilimlerinin ilkelerini, doku işlevini veya bütün bir organı restore eden, koruyan veya geliştiren biyolojik ikamelerin gelişimine uygulayanan disiplinler arası bir alandır." Doku mühendisliği hücreleri, iskele ve sinyal moleküllerini kullanarak yenilenmiş dokular oluşturur. Mezenkimal kök hücreler, doku mühendisliği uygulamalarında en çok kullanılan popülasyonlar arasındadır. Kök hücre multipotent bir hücre olup, spesifik hücreye çoğalabilir ve farklılaşabilir. Bu hücreler birçok farklı doku tipini oluşturma kapasitesine sahiptir. Kemik iliğinde multipoten mezenkimal kök hücrelerin keşfinden beri, diğer dokulardaki mezenkimal kök hücreler tanımlanmıştır. Diş dokuları, mezenkimal kök hücrelerin izolasyonu için potansiyel bir kaynak olarak kabul edilmiştir. Bugüne kadar, diş dokularından bircok mezenkimal kök hücre izole ve karakterize edilmiştir. Bu makale, mezenkimal kök hücrelerin dental kaynaklarını ve bu dental dokudan türetilmiş mezenkimal kök hücrelerin özelliklerini gözden geçirecektir.

Anahtar Sözcükler: Doku Mühendisliği, Diş Dokusu, Mezenkimal Kök Hücreler.

Abdulkareem ALMARRAWI

ORCID: 0000-0002-9163-6973

Bülent Ecevit Üniversitesi Diş Hekimliği Fakültesi, Ağız, Diş ve Çene Cerrahisi Anabilim Dalı, Zonguldak, Türkiye

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İletişim Adresi/*Corresponding Adress:*
Abdulkareem ALMARRAWI
Bülent Ecevit Üniversitesi Diş Hekimliği Fakültesi, Ağız, Diş ve Çene Cerrahisi Anabilim Dalı, Zonguldak, Türkiye
E-posta/*e-mail*: a-marrawi@hotmail.com

INTRODUCTION

The partial or complete loss of an organ or tissue in an individual represents a major clinical problem, and one of the most frequent, devastating, and costly problems in human health care. The difficulties associated with the surgical replacement of the organ are principally the shortage of donor organs and the increased risk of infection associated with implanting foreign materials (1). The artificial generation of tissues, organs, or even more complex living organisms was throughout the history of mankind a matter of myth and dream. During the last decades, this vision became feasible and has been recently introduced in clinical medicine (2). A new field, tissue engineering, applies the principles of biology and engineering to the development of functional substitutes for damaged tissue has made significant progress in the last years (1).

TISSUE ENGINEERING

The field of tissue engineering aims to regenerate damaged tissues, instead of replacing them, by developing biological substitutes that restore, maintain, or improve tissue function (3-6). So tissue engineering is defined as an interdisciplinary field that applies the principles of engineering and life sciences toward the development of biological substitutes that restore, maintain or improve tissue or organ function (1). Successful and effective tissue engineering requires three components to ensure the development of a new organ (7,8).

1-Cells:

Mesenchymal stem cells (MSCs) are the most successful candidate (9).

2- Scaffolds:

The scaffold is used to enable cells to function appropriately to produce the required extracellular matrix and ultimately a tissue of the desired geometry, size, and composition are briefly considered here (10). The scaffold must be biocompatible and biodegradable, support cell attachment and growth, and subsequently facilitate new tissue and organ development (11, 12).

Many materials have been designed and constructed for tissue engineering approaches natural materials (collagen, elastin, fibrin, alginate, silk, glycosaminoglycans such as hyaluronan, and chitosan) (13,14). They offer a high degree of structural strength, are compatible with cells and tissues and biodegradable, but are often difficult to process and afflicted with the risk of transmitting animal-associated pathogens or provoking an immunoresponse (13).

Synthetic polymers or inorganic materials and composites (polylactic acid, polyglycolic acid, and their copolymer, poly lactic-co-glycolic acid) (13,15). Provide excellent chemical and mechanical properties and allow high control over the physicochemical characteristics, such as molecular weight, a configuration of polymer chains, or the presence of functional groups (13). Pre-clinical studies on animal models using all of the aforementioned categories have shown promising results in dental tissue regeneration (16).

Recently, novel biomaterials with more sophisticated designs that can be reinforced by bioactive elements have appealed to scientists (17–20). Some examples include the coating of bone scaffolds with fluoridated hydroxyapatite (19), adding various ion substitutes to bioactive glasses (18), and incorporation of bone morphogenetic protein into various bio-matrices to enhance osteogenesis (21). Moreover, biodegradable hydrogels that profit from their tissue-like properties and cross-linking potential can also be used for the efficient incorporation of biological agents (22,23).

3- Signaling molecules:

This includes using either biological or synthetic materials to lead repair processes and cell growth (7). Signaling molecules can stimulate cellular proliferation and cellular differentiation. Bone morphogenetic proteins (BMPs) family members are used sequentially and repeatedly throughout embryonic tooth development, initiation, morphogenesis, cytodifferentiation, and matrix secretion (24). Other investigations have been demonstrated the effect of dexamethasone in cultures with dental stem cells, where these cells in combination with dexamethasone can differentiate into osteoblasts, adipocytes, or chondrocytes (25). Recently has been improved the role of 17β-estradiol on cementoblasts activity (26).

STEM CELLS

Stem cells are unspecialized cells characterized by the ability to renew themselves through mitotic cell division and differentiate into a diverse range of specialized cell types (27).

Over the last few years, medicine has begun to explore the possible applications of stem cells and tissue engineering towards the repair and regeneration body structures (28). It is becoming ever clearer that this conceptual come up to therapy, named regenerative medicine, will have its place in clinical practice in the future (29).

It has been shown that stem cells will play an important role in future medical treatments because they can be readily grown and induced to differentiate into any cell type in culture. Stem cells are cells that can renew themselves through mitosis and can differentiate into several specialized cells (29).

According to developmental stages, stem cells can be divided into embryonic stem cells and adult stem cells. Differentiation and proliferation of embryonic stem cells constitute the basis of animal development. The further differentiation of adult stem cells is the prerequisite of tissues and organs' repair and regeneration (27).

1- Embryonic Stem Cells:

Embryonic stem cells are pluripotent cells derived from the early mammalian embryo with the capacity to proliferate extensively and differentiate into cells with features of all three embryonic germ layers (mesoderm, endoderm, and ectoderm) (30). Despite their developmental potential, the use of embryos to obtain human embryonic stem cell lines raises serious ethical and religious concerns because embryos are destroyed to obtain them (31,32), and technically these cells are difficult to control and grow and they might as well form tumors after their injection (33).

A very recent development, with potentially a profound significance for clinical therapy, has been the generation of induced pluripotent stem (iPS) cells from somatic cells. The method for iPS cell induction is "ground-breaking" because somatic cells are converted directly into pluripotent cells through the introduction of four genes: Oct-4, Sox2, c-Myc, and Klf4 (34). iPS cells are similar to ES cells in morphology, proliferation and differentiation capacity, and genomic and epigenomic states (35).

2- Adult Stem Cells:

Adult stem cells have been identified in numerous tissue niches in the postnatal organism and are thought to function in replenishing cell loss as a consequence of tissue damage and death (36).

Since their discovery, it has been recognized that the developmental capabilities of adult stem cells are greater than initially thought. In addition to being responsible for the maintenance of tissue homeostasis in their host tissue, it has also been demonstrated that they can differentiate into other cellular lineages beyond their tissue(s) of origin (37).

Whilst these cells exhibit a more restricted proliferation and differentiation potential compared to embryonic stem cells, they are easily accessible, immunocompatible, and are not associated with ethical concerns (30).

The presence of stem cells in the adult was first discerned by Till and McCulloch, who were investigating the mechanisms by which the bone marrow could regenerate after exposure to radiation. However, adult stem cell research remains an area of intense study, because their potential for therapy may apply to a myriad of degenerative disorders (31).

MESENCHYMAL STEM CELLS (MSCs)

Mesenchymal stem cells (MSCs) are adult stem cells able to give rise to multiple specialized cell types (38,39). Mesenchymal stem cells (MSCs) are spindle-shaped cells. MSCs were initially reported as fibroblast-like cells that could be isolated from bone marrow (40).

Alexander Friedenstein was the first to evidence the presence of a population of nonhematopoietic cells that were capable of autorenovation and bone differentiation in the bone marrow (41). Subsequently, others showed the bone-marrow-derived cells isolated according to Friedenstein's technique, also possessed high potency of proliferation and pluripotency of differentiation into mesenchymal tissues, and therefore Caplan used the term ''mesenchymal stem cell'' (MSC) to describe them (42). Further studies have established mesenchymal stem cells as a heterogeneous cell population in which each individual cell varies in its gene expression, differentiative capacity, expansion potential and phenotype (43,44). Moreover, all of them do not seem to fulfill the stem cell criteria. Therefore, they are preferred to be called ''multipotent stromal cell'' with the same acronym "MSC" (44).

Mesenchymal stem cells (MSCs) are a heterogeneous population and are defined as being derived from mesenchymal tissue and by their functional capacity to

form colonies and to differentiate into bone, cartilage, and adipose cells in vitro (45,46). These cells participate in tissue homeostasis, remodeling, and repair by ensuring the replacement of mature cells that are lost during physiological turnover, injury, or disease (47).

In addition to bone marrow, MSC populations can be readily obtained from skeletal muscle (48) and a variety of other tissues, such as umbilical cord blood (49), synovium (50), the liver (51), adipose tissue (52), the lungs (53), amniotic fluid (54), tendons (55), placenta (56), skin (57), and breast milk (58).

At present, any cell population which meets the following characteristics, irrespective of its tissue source, is generally referred as MSC: morphologically, they adhere to plastic and have a fibroblast-like appearance; functionally, they have the ability of self-renewal and could differentiate into cells of the mesenchymal lineage (osteocyte, chondrocyte, and adipocyte), also into cells of the endoderm (hepatocytes) and ectoderm (neurons) lineages under proper cell culture conditions; phenotypically, they express more than 95% of the population express the CD105, CD73, CD90 surface antigens and that less than 2% of the population expresses the pan-leukocyte marker CD45, the primitive hematopoietic progenitor and endothelial cell marker CD34, the monocyte and macrophage markers CD14 and CD11, the B cell markers CD79 and CD19, or HLA class II (59).

DENTAL TISSUE- DERIVED MSCs

MSC-like populations have also been isolated from a variety of human dental tissue. To date, eight unique populations of dental tissue-derived MSCs have been isolated and characterized (40,60).

Postnatal dental pulp stem cells (DPSCs) were the first human dental MSCs to be identified from pulp tissue (61). Gradually, other dental MSC-like populations, such as stem cells from human exfoliated deciduous teeth (SHED) (62), periodontal ligament stem cells (PDLSCs) (63), dental follicle progenitor cells (DFPCs) (64), alveolar bone-derived MSCs (ABMSCs) (65), stem cells from apical papilla (SCAP) (66), tooth germ progenitor cells (TGPCs) (67), and gingival MSCs (GMSCs) (68), were also reported.

Recently, oral MSCs have also been harvested from dental tissue that is not healthy, such as fractured teeth and teeth affected by caries or irreversible pulpitis or aggressive periodontitis (69–72).

The properties of MSCs derived from dental tissues were found similar to those of MSCs derived from bone marrow (BM-MSCs) and skin (62,73). However, as the dental stem cells have a neural crest origin, they have higher neurogenic capacities than other MSCs (74). It is considered that stem cells derived from dental tissues have analogous properties to that of neural crest (61). Previously, human dental stem cells were successfully differentiated into neuron-like cells, both in vitro and in vivo (61,62,75-77).

The dental tissue-derived stem cells possess potent capacities to differentiate into odontogenic cells and generate reassembly dental tissue structures. Given the innate capacity of dental-derived MSC like cells to ectopically generate structures resembling the tissues from which they are derived in vivo, these progenitor cell populations represent promising candidates for oral tissue regeneration (78-80).

The major attractions towards using dental MSCs are ease of access, less invasive approach for harvest, ability to produce higher colony-forming units (CFUs), and a higher cell proliferation rate and survival time than bone marrow-derived MSCs (81,82).

1- Dental pulp stem cells (DPSCs):

The regenerative potential of the human dentin/pulp complex to form reparative dentin following a carious lesion or mild traumatic injury suggests the presence of dentinogenic progenitors that are responsible for dentin repair (83).

Recently, a mesenchymal stem cell (MSC) population has been isolated from dental pulp tissue and is generally referred to as the dental pulp stem cells (DPSCs). Pulpal fibroblasts only show monopotency with the ability to differentiate into odontoblasts, while the DPSCs are multipotent (84). They were first isolated from pulp tissue of permanent human teeth and were designated postnatal DPSCs (61).

Human DPSCs are commonly obtained from extracted wisdom teeth (61), primary teeth (72), and have also successfully been obtained from supernumerary teeth (85). DPSCs have also been obtained from this inflamed pulp successfully, and their properties are similar to those of DPSCs obtained from normal pulp tissue (71,86).

Lei et al. 2014 found that DPSCs are highly potent cell populations that can differentiate into specialized lineages toward functional tissue regeneration. Importantly, these cells show the potential to retain their stem cell-like properties after long-term in vivo transplantation (87).

Han et al. 2017 demonstrated that long-term preserved dental pulp tissues harvested from the extracted wisdom teeth can be an excellent autologous stem cell source for the generation of definitive endoderm (interphase during endodermal differentiation from stem cells) and endodermal cells. Preservation of dental tissues would be worthwhile for use as an autologous stem cell resource in tissue engineering (88).

2- Stem cells from human exfoliated deciduous teeth (SHED):

The transition from deciduous to permanent teeth is a very unique and dynamic process in which the development and eruption of permanent teeth synchronize with the resorption of the roots of deciduous teeth (62,89).

The development and eruption of permanent teeth are coordinated with the resorption of the roots of deciduous teeth. This process starts at about 6 years and stops after 12 years of age. In this period, all of the 20 deciduous teeth are normally replaced (90).

The recent discovery has evaluated that fresh dental pulp tissues of human exfoliated deciduous teeth preserve the MSC population, termed SHED (62).

Since SHED has been identified and characterized as MSCs, deciduous dental pulp tissues have been considered a promising stem cell source. Exfoliated deciduous teeth possess advantages of minimal invasiveness and easily accessible tissue source in comparison with other human tissues such as bone marrow and adipose tissue (62).

SHED or deciduous teeth stem cells express multipotency into several lineage cells including of dentin/bone-forming cells (62, 89-91), endothelial cells (91), neural cells (62,92) and myocytes (93) in vitro and in vivo. SHED was also applied for tissue-engineering in large animal models including bone defects, muscular dystrophy, and dentin defects (94-96), as well as small animal models including bone defect and spinal cord injury (97-99).

Ma et al. 2012 found that the cryopreservation of dental pulp tissues of human exfoliated deciduous teeth does not affect the biological, immunological, and therapeutic functions of SHED. Therefore, the cryopreserved approach of deciduous dental pulp tissues not only serves as a most clinically desirable banking approach but also provides a sufficient number of SHED for critical therapeutic benefits to stem cell-based immune therapy and tissue engineering in regenerative medicine (100).

Also, Yin et al. 2016 showed that a lentiviral TERT gene transduction could establish a stable SHED cell line that is completely multipotential; even after long-term in vitro passaging, no evidence of genetic instability or malignant biological behavior of these cells was observed. These findings provide novel strategies to prevent senescence and maintain the stemness of ex vivo-maintained SHED for potential clinical therapies, although attention should be paid to the biological behavior of these cells (101).

Recently several studies were performed to evaluate "multipotency" and "stemness" of SHED-derived insulin-secreting cell aggregates (102–104). Kim et al. 2016 confirmed that SHED cells produce insulin successfully (105).

3- Periodontal ligament stem cells (PDLSCs):

The periodontal ligament's known ability to establish new attachment fibers between the cementum and bone to achieve regeneration (106), implies that progenitor cells, and possibly stems cells, exist within the periodontal ligament cell populations (107).

In 2004, a pioneer study demonstrated that the PDL contains stem cells, generally termed PDL stem cells or PDLSCs, that have the potential to differentiate into cementoblast-like cells, adipocytes, and collagen-forming cells in vitro and to generate new cementum/PDL-like compartments in vivo (108). PDL stem cells (PDLSC) display cell surface marker characteristics and differentiation potential are similar to bone marrow stromal stem cells and DPSC (108).

Recently, PDLSCs haven been successfully cultured through different extraction methods, showing that PDL is a suitable source of stem cells, with the consequent potential use in regenerative medicine (109).

Human PDLSC expanded ex vivo and seeded in three-dimensional scaffolds (fibrin sponge, bovine-derived substitutes) were shown to generate bone (110).

Lei et al. 2014 provided evidence that PDLSCs (dental pulp stem cells and PDL stem cells) are highly potent cell populations that can differentiate into specialized lineages toward functional tissue regeneration. Importantly, these cells show the potential to retain their stem cell-like properties after long-term in vivo transplantation (87).

Also, recent findings suggest that PDLSCs could be isolated from both healthy and inflamed young PDL tissue; the inflamed PDLSCs retain their regenerative potential for cementum and related PDL tissues,

suggesting an alternative rich source (i.e., teeth extracted for periodontitis reasons) of mesenchymal stem cells (MSCs) for cytotherapeutic use due to the large number of periodontitis patients involved (111). The use of PDLSCs involves less religious and ethical concerns than using MSCs derived from bone marrow because they are easily obtainable from medical waste, i.e., the teeth extracted for orthodontic, impaction, or irreversible periodontic reasons (16). Therefore, PDLSCs represent a unique population of MSCs that may facilitate translational research and have future clinical application in, but not limited to, periodontal regenerative medicine (16,112).

4- Dental follicle progenitor cells (DFPCs):

The dental follicle (DF) is a loose connective tissue sac surrounding the enamel organ and dental papilla of a developing tooth germ before eruption (113). Dental follicles originate from ectomesenchymal cells, and contain the periodontal precursor cells that give rise to periodontal tissue consisting of cementum, periodontal ligaments, and alveolar bone during tooth development (114,115).

Recently, mesenchymal stem cells (MSCs) from dental follicles were isolated and differentiated into clonogenic, plastic-adherent, fibroblast-like cells (116,117). Moreover, the multiple differentiation potential of DFSCs has demonstrated by experimental studies (64,118,119).

The strong osteogenic ability of those cells makes them potentially useful in repair bone defects especially the reconstruction of bone under inflammatory conditions like bone loss associated with periodontal disease (120-124). Furthermore, the neurogenic potential of some follicular cells indicates that they may be useful for treating neurodegenerative diseases based on cell therapy (119).

Recently, Sung et al. 2016 isolated MSCs from human dental follicles (DFCs) from the extracted wisdom teeth, and differentiated them into cardiomyocytes in vitro using SAHA (suberoylanilide hydroxamic acid) induction media (125).

5- Alveolar bone-derived mesenchymal stem cells (ABMSCs):

Representing a key component of the periodontium, the human alveolar bone proper arises from the tooth follicle (126). SCs were isolated from the human alveolar bone (ABMSCs), and these cells were obtained from marrow samples obtained during wisdom tooth extraction, surgery for bone fracture jaw deformity, dental implants or dental cyst extraction (127) ABMSCs ware able to differentiate into osteoblastic lineages (127). A recent study showed that PDLSCs from the PDL regions adjacent to the alveolar bone may even have better regenerative qualities compared to the same PDLSCs adjacent to root surfaces (128). Another study found that the ABMSCs are available in unlimited amounts with minimally invasive procedures, and compared with BMSC, ABSC have a higher rate of proliferation and comparable differentiation, therefore, ABSC can be used for regeneration of the craniofacial complex (129). Recently, Wang et al 2018 isolated the MSCs from human alveolar periosteum (130).

6- Stem cells from apical papilla (SCAPs):

The dental papilla located at the apex of developing human permanent teeth (131). It is only present during root development before the tooth erupts into the oral cavity (132). It has been known that dental papilla contributes to tooth formation and eventually converts to pulp tissue (133). A recent scientific finding is the discovery and isolation of a new population of mesenchymal stem cells residing in the apical papilla of incompletely developed teeth, which may explain why apexogenesis can occur in these infected immature permanent teeth. These cells are referred to as stem cells from apical papilla (SCAPs), and they have the capacity for multiple differentiation (131,134,135).

Chen et al. 2013 demonstrated that SCAPs displayed a higher proliferation rate and a greater mineralization capacity than those of PDLSCs, and it might help understand the development of tooth root and periodontium (136). The higher proliferative potential of SCAP makes this population of cells suitable for cell-based regeneration and preferentially for forming roots. They are capable of forming odontoblast-like cells and produce dentin in vivo and are likely to be the cell source of primary odontoblasts for the root dentin formation (131).

SCAPs (stem cells from apical papilla) demonstrated positive results in the formation of dentin pulp-like complex and were able to form a root-like structure when seeded onto hydroxyapatite-based scaffolds and

implanted in pig jaws (9,137,138).

Also, Yagyuu et al. 2010 found that SCAPs obtained from human wisdom teeth could form hard tissue both in vivo and in vitro, and the extensive proliferative ability and hard tissue-forming potential of these cells after freezing (139).

7- Tooth germ stem cells (TGSCs):

Tooth germs form during embryonic development as a result of ecto-mesodermal interactions that give rise to neural crest cells (79). These progenitor cells differentiate into the dental organ, dental papilla, and dental follicle (140).

In humans, tooth germ tissues derived from third molars are unique as they undergo organo-genesis to give rise to dental structures at around age 6. It means that until this time, embryonic tissues remain quiescent and undifferentiated. In other words, organo-genesis occurs in third molars (wisdom teeth) well after birth (79).

Ikeda et al. 2008 identified a novel stem cell, which named tooth germ progenitor cells (TGPCs), from discarded third molar, and demonstrated the characterization and distinctiveness of the TGSCs, and found that these cells showed high proliferation activity and capability to differentiate in vitro into cells of three germ layers including osteoblasts, neural cells, and hepatocytes (67). Also, Yalvac et al. 2010 found that under specific culture conditions, TGSCs differentiated into osteogenic, adipogenic, and neurogenic cells, as well as formed tube-like structures in Matrigel assay (141). Recently, Ercala et al. 2017 demonstrated a high osteogenic differentiation capacity of TGPCs for bone tissue engineering applications (142).

So these multipotential TGSCs could be important stem cell sources for autologous transplantation (141).

8- Gingiva-derived mesenchymal stem cells (GMSCs):

Wound healing within the gingiva and oral mucosa are characterized by markedly reduced inflammation, rapid re-epithelialization, and fetal-like scarless healing, contrary to the common scar formation present in the skin (143-145). Such differences in wound healing between gingival/oral mucosa and skin may be attributed to the unique tolerogenic properties of the oral mucosal/gingival immune network (146).

Zhang et al. 2009 have isolated and characterized a new population of precursor cells from human gingival tissues, termed GMSC, which exhibit several unique stem cell-like properties as MSCs derived from bone marrow and other postnatal tissues (68).

GMSCs showed multipotency with high proliferation and characteristics of mesenchymal stem cells (147). Compared with MSCs derived from several other adult dental tissues GMSCs express a similar profile of cell surface molecules, a high proliferative rate, and an increased population doubling, and thus can be easily expanded ex vivo for several cell-based clinical applications (68).

GMSCs exhibited the potential to differentiate into osteogenic, adipogenic, and chondrogenic lineages, and they possessed the capacity to generate new bone following ectopic transplantation (148).

Recently, Jauregui et al. 2018 demonstrated that GMSCs can be isolated from healthy and periodontally diseased tissues, and found that GMSCs preserve of 'stemness' and osteogenic potential of GMSC even in the presence of disease (diseased gingival), opening up the possibility of using routinely discarded, diseased gingival tissue as an alternate source of adult MSCs (149).

MSCs isolated from human gingiva are an attractive option in stem cell-based therapies because of their relative abundance, ease of isolation from the oral cavity with minimal discomfort, and rapid ex vivo expansion (150,151).

CONCLUSION

The easy accessibility to obtain dental MSCs made them an attractive alternative to bone marrow-derived mesenchymal stem cells (BMMSCs) for use in clinical trials to evaluate their safety and efficacy.

MSCs derived from human dental tissues keep a promising role in the future regenerative medicine because of their ease of collection, and their capacity to undergo self-renewal and multilineage differentiation.

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