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Review Article

Immunobiology of Dental Tissue-Derived Stem Cells; As a Potentiated Candidate for Cell Therapy

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Abstract: *Background and aims:* Mesenchymal stem cells (MSCs) are non-hematopoietic, undifferentiated, heterogeneous and multipotential stem cells population with immunosuppressive capacities in innate and acquired immune systems. During last decade, they have glisten in regenerative medicine. They can differentiate into various cell types and secrete soluble growth factors that impact on host immune system. One of these newly introduced stem cells, are Dental tissue derived Stem Cells (D-SCs). They are able to hold immunomodulatory and anti-inflammatory effects through cell-cell contact. Some of them are seen to be full of promising therapeutic applications. The aim of this study is to emphasize immune markers and biological effectiveness of these cells. *Search method:* Data of this study is collected from PubMed, Scopus, Science Direct databases and Google Scholar search engine by using 6 keywords (as: Dental derived Stem Cells, Immunomodulation, Immune markers, Cell therapy, Tissue reconstruction, Therapeutic applications) ultimately from 60 articles of 2000 up to 2016. *Results:* Some recent studies demonstrate that D-SCs render their immunomodulatory functions through soluble factors such as Prostaglandin E2 (PGE2), Indoleamine 2, 3-Dioxygenase (IDO), Transforming Growth Factor-β (TGF- β) and Human Leukocyte Antigen G5 (HLA-G5). Also, others do it by interactions between DSCs and immune cells such as T cells, B cells, macrophages, and dendritic cells. *Conclusion:* It appears that the immunomodulatory properties of dental MSCs is a promising window to cell-based therapy of immune and inflammation-related diseases.

Keywords: Dental Derived Stem Cells, Immunomodulation, Immune Markers, Cell Therapy, Tissue Reconstruction, Therapeutic Applications

1. Introduction

Nowadays, finding a strategy for reconstruction of missing damaged tissues and restoring organ function, are of particular importance. Meantime, in recent years, exponential growth of stem cells research has opened a window to novel clinical applications. There are different types of stem cells regenerating too many parts of the body tissues. Mesenchymal Stem Cells (MSCs) are not only self-renewable, but also are capable to differentiate into cell lineages leading to mesenchymal and connective tissues induction [1, 2]. These cells have mainly high cell turnover and can differentiate into mesodermal cells, like chondrocytes, adipocytes and osteocytes (Fig. 1) [3, 4]. These cells are capable in injury repairing and tissue regeneration. Their resources are present in many tissues like bone marrow, placenta, adipocyte, umbilical cord blood and mouth cavity. Their considerable growth potency and differentiation properties, specifies them as a precious tool for certain mentioned purposes toward advancement of medicine. One of the stem cells sources that have been recently isolated and identified, are human Dental tissue-derived Stem Cells (D-SCs) [5].

For D-SCs, Characteristics such as easy access and differentiation into other cell types with the aim of autogenic or allogenic cell therapy, has made them a novel choice for various cell-based therapies. In this systematic review, it has been focused on six types of D-SCs (Fig 1): DPSCs (Dental Pulp Stem Cells), SHEDs (Stem cells from Human Exfoliated Deciduous teeth), DFPCs (*Dental Follicle Precursor Cells*), SCAPs (Stem Cells from the Apical Papilla), PDLSCs (Periodontal Ligament Stem Cells) and *GMSCs (Gingival Mesenchymal Stem Cells). Then it is decided to outline the properties of these dental MSCs-like population as a glimmer of hope for some immune and neurodegenerative disorders which are known as major challenges of Health System* [6-11].

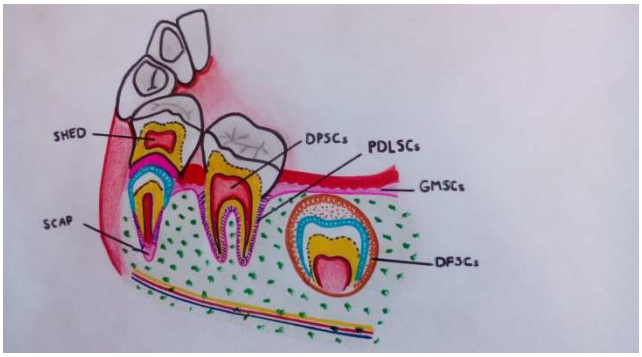

Figure 1. *Dental tissue-derived Stem Cells.*

Several studies demonstrated that these cells have the advantage of multiple differentiation potential rate. Aside from these, they have some immunomodulatory features that places them as a more accessible cell source than bone marrow-derived MSCs for cell-based therapy of immune and inflammation-related diseases [12-16]. So, On the other hand, with the aim of clinical applications vision, it is tried to highlight special immunobiomarkers by which, appropriate stem cells are chosen properly to the research and therapeutic purposes [10, 17].

2. Dental Stem Cells

2.1. DPSCs (Dental Pulp Stem Cells)

Among D-SCs, DPSCs is a well-known accessible source which can be found in pulp tissue of healthy permanent teeth [1, 18]. The first time that DPSCs were isolated was in 2000 by *Gronthos et al*. through enzymatic digestion from dental pulp tissues of primary incisors, exfoliated deciduous and permanent third molar teeth. DPSCs are originally formed from both epithelial and mesenchymal stem cell progenitors, the epithelial-derived ameloblasts and the mesenchymal-derived dentin/bone/soft tissues of the periodontium (Table 1). Culture media and storage associated factors influence on the isolation quality for these cells. These cells represent an interesting source due to the high content of cells and low-invasive procedures required for cell isolation [19-22].

Table 1. *"An updated overview to Stem cell types in dental pulps"[38].*

Properties / stem cells	**DPSCs**	**SHEDs**	**DFPCs**	**SCAPs**	**PDLSCs**	***GMSCs***
Proliferation rate	Moderate	High	High	High	High	High
Heterogeneity	Yes	Yes	Yes	Yes	Yes	Yes
Multipotency	Odontoblast Osteoblast Chondrocyte Neurocyte Adipocyte iPS Corneal Epithelial cell Myocyte	Odontoblast Osteoblast Neurocyte Adipocyte iPS Myocyte	Odontoblast Osteoblast Neurocyte	Odontoblast Osteoblast Neurocyte Adipocyte iPS	Odontoblast Osteoblast Chondrocyte Neurocyte	Odontoblast Osteoblast
Tissue Repair	Bone regeneration, Myogenic regeneration	Dentin-pulp regeneration,	Neuroregeneration,	Periodontal regeneration,	Periodontal regeneration, Root regeneration Teeth nutrition and homeostasis.	Bone reconstruction

They are multipotent stromal stem cells that can differentiate into many types of lineages, like dentin-producing odontoblasts, osteoblasts, adipocytes, chondrocyte, skeletal and smooth muscle cells, elastic cartilage cells, endothelial and neural cells both *in vivo* and *in vitro* under certain stimuli conditions [23, 24]. They have immunosuppressive effects [25-27], easy eradication and access features with less morbidity, so are operative in clinical trials [3, 10, 28, 29].

Many studies showed that, DPSCs express surface antigens like CD105, CD90, CD44 and CD73, CD166 that are known on mesenchymal lineages [9, 30]. In addition, DPSCs show higher internal heterogenecity than DFPCs and PDLSCs with significant differences in expression of Runx2 and osteocalcin (OC) [6].

DPSCs are positive for STRO-1, c-Kit, CD146 and CD34 (not always), but negative for CD45 (Table 2). This confirms it`s application for osteo/odontogenic differentiation in stem cells-based clinical therapies [31, 32]. The clinical applications of DPSCs has been investigated in reconstruction or amelioration of myocardial infarction, neurodegenerative disorders, cerebral ischemia and damaged corneal epithelium

[33-37]. DPSCs can suppress T cell proliferation and might be suitable for preventing or treating T cell alloreactivity associated with hematopoietic or solid-organ allogeneic transplantation [10, 27]. In addition, Toll-like receptors (TLRs), were shown to trigger the immunosuppression of DPSCs by up-regulating the expression of transforming growth factor (TGF) -β and interleukin (IL) -6. DPSCs are able to induce activated T cell apoptosis *in vitro* and recovery of inflammation-related tissue injuries in mice with colitis, which was associated with the expression of the Fas Ligand (FasL) [10]. Most recently, *Kerakis et al*, in a Duchenne Muscular Dystrophy (DMD) dog by using human immature DPSCs, exerted relief symptoms [10, 27].

2.2. SHEDs (Stem Cells from Human Exfoliated Deciduous Teeth)

In 2003 *Miura et al*. isolated these cells from naturally coronal pulp of exfoliated deciduous teeth (Table 1). They observed high proliferation and clonogenic capacity of SHEDs. These cells formed sphere-like cell-cluster formation, which could be separated and grown as individual fibroblast [4, 39].

This source of stem cells represent more immature multipotent SCs compared with the other Dental-derived SCs [40]. These cells may be an attractive vast reservoir of MSCs for their readily accessible and some immunomodulatory properties [41]. These cells have been identified as a population of postnatal stem cells which are able to differentiate into functional odontoblasts that secrete mineralized dentin matrices. SHEDs have capacity of differentiation into various cell types like endothelioid, neural, adipocytes, osteoblasts, chondrocytes and MSCs. It has been observed that SHEDs have the potential of differentiation into functional vascular endothelial cells in a vasculogenesis-like process. Researches demonstrated that they could differentiate into functional blood vessels in immune deficient mice [41, 42]. In addition, SHEDs have matchless ability in response to neurogenic markers. Deciduous teeth have been considered as a unique source of SCs to induce bone regeneration and as an ideal source for repairing damaged tooth structures [33, 34, 43, 44].

Ali Behnia et al. (2014) used SHEDs which were isolated and characterized 5 years ago and stored them at cryopreservation banking. They were capable of proliferation and osteogenesis after 5 years, and fortunately, no immune response was observed after three months of seeded SHEDs. Recently, *in-vivo* studies have shown that using human DPSCs won`t lead to any tissue rejection [33, 35, 43].

SHEDs derived from autologous cells exhibit higher proliferation rates compared to DPSCs and Bone Marrow-derived Mesenchymal Stem Cells (BM-MSCs). Due to their association with upper hair follicle epithelium, they can induce new end bulb formation and hair growth. Also, SHEDs were reported to enhance wound healing in an excisional wound-splinting mouse model [41].

Because of neurotrophic factors secretion, SHEDs are beneficial for neurodegenerative diseases treatment and repairing of motor neurons after stroke or injury. In addition, they can utilize in alleviating Parkinson's disease, Alzheimer's disease and cerebral palsy. It is worth noting that they are known as biological wastes, so we have no ethical concerns about using SHEDs. Moreover, obtaining stem cells from SHEDs is easier than BM-MSCs and other adult stem cell [37, 44].

SHEDs are positive for STRO-1 and CD146, CD73, CD129, CD166 and CD105 (Table 2). Also, they activate TGFβ, ERK and PDGF signaling pathways. In fact, STRO-1, CD146 positive cells around blood vessels approve that possible SHED's origin is perivascular environment [39]. Also, Nanog, Nestin, OCT-4 (pluripotency marker) and specific embryonic antigens-3, 4 (SSEA-3, SSEA-4) expression has been investigated [41, 45, 46]. The immunomodulatory properties of SHEDs has been compared with BM-MSCs. SHEDs, *in vitro*, have significant effects on inhibiting Th17 and in fact, on up regulation of Treg/Th17 ratio. SHED infusion in MRL/*lpr* mice reduces serum levels of anti-double stranded DNA (dsDNA) IgG/IgM and anti-nuclear antibodies (ANA). Ultimately, it appears that SHED transplantation is capable of reserving Systemic Lupus Erythematous (SLE) associated disorders [10, 41].

2.3. SCAPs (Stem Cells from the Apical Papilla)

SCAP was discovered in the apical papilla of human immature permanent teeth. In 2006, *Sonoyama et al.* isolated SCAPs as a new population of D-SCs [4, 47].

As we know, there is a zone between pulp and apical papilla that is described as an" apical cell-rich zone" which includes more blood vessels and cells. During development of tooth morphogenesis from the bud to the cap stage, odontogenic ectomesenchymal gives rise to two distinct cell lineages: I: Dental papilla cells, which are surrounded by the dental epithelial organ (enamel epithelium), and II: Dental follicle cells, which form the investing cell layers around the whole tooth germ (Table 1) [10, 48].

SCAPs show a higher proliferation rate and mineralization potential than DPSCs. They inhibit T cell proliferation and show minimum immunogenicity *in vitro*. SCAPs possess low immunogenicity and can inhibit T cell proliferation *in vitro* through an apoptosis-independent mechanism. Also, they suppress mixed-lymphocyte reaction (MLR) and their immune properties are not endured cryopreservation [10, 47].

According to *Sonoyama* study, SCAPs at passage 1 expressed many surface markers including STRO-1, ALP, CD24, CD29, CD73, CD90, CD105, CD106, CD146, CD166, and ALP; but were negative for CD34, CD45, CD18, and CD150. STRO-1 and CD146 have been identified as early mesenchymal stem cell markers present on both BMSCs and DPSCs. According to the researches, CD24 appears to be a specific marker for SCAPs, not detectable in other mesenchymal stem cells including DPSCs and BMSCs [49].

2.4. DFPCs (Dental Follicle Precursor Cells)

Progenitor cells have typically been isolated from the dental follicle of human third molars with an extended proliferation

ability. DFPCs are positive for CD73, CD44 and CD90, but negative for CD33, CD34 and CD45 (Table2) [4]. Studies demonstrate that DFPCs have cementoblasts and periodontal ligament cells, because they express periodontal ligament-associated protein-1 (PLAP-1), fibroblast growth factor-2 (FGF-2) and cementum protein-1 (CEMP-1) [10].

In 2015, *S. Sowmya et al*. [50] showed Osteoblastic differentiation (Table 1), by demonstrating of Runt-related transcription factor 2 (RUNX-2), alkaline phosphatase (ALKP) activity, alizarin staining, calcium quantification, collagen type-1 (Col-1) and osteopontin (OPN) expression.

Via TGF-β secretion, DFPCs suppress the proliferation of PBMCs. For accelerating this suppression and potentiating TGF-β and IL-6 secretion, TLR3 and TLR4 agonist are needed. These mentioned features, illustrates them as a desirable tool for the treatment of chronic inflammatory diseases which are accompanied by tissue injury (Table 2) [10].

Table 2. *Immunobiomarkers profile of different Mesenchymal stem cell populations in vitro.*

DFPCs human*Dental Follicle Precursor Cells*	TGF-β TLR3 TLR4 IL-6 CD9 CD10	Suppress proliferation of PBMCs. Suitable for the treatment of chronic inflammatory diseases and tissue injury. Formation of Granulomatous tissue induction when transplanted to xenogeneic host, nevertheless needs to more research [10, 27].
SCAPs Stem Cells from the Apical Papilla	STRO-1 CD146 CD34 CD24	Tcell proliferation inhibition and minimum immunogenicity, *in vitro*, Immune properties are not effected by cryopreservation. Suppression of MLR, Soluble factors show immune suppression [10, 27].
PDLSCs Periodontal Ligament Stem Cells	STRO-1 CD73 CD90 CD105 CD9 CD44 CD106* CD146	Bone Sialo protein Scleraxis TGF-β HGF ID0 CD10	Low immunogenicity and marked immunomodulation via PGE2-induced T-cell anergy, Inhibitory effects on the proliferation of allogeneic and xenogeneic PBMCs through suppressing the cell division of PBMCs by secretion of TGF-β, HGF, and IDO [10, 27].
GMSCs *Human Gingival Mesenchymal Stem Cells*	IFNγ ID0 IL10 COX-2 iNOS IL6 Induction of Th17 cell expansion	Elicit M_2 polarization of macrophage (MR;CD206), Potent inhibitory effect on T-cell proliferation, Anti-inflammatory effect, partly via IFN-induced stimulation of IDO, IL-10, COX-2, and inducible nitric oxide synthase (iNOS) expression, eventually colitis attenuation, Alleviation of Contact Dermatitis [10, 27].
SHEDs	CD44 CD106* CD146 STRO-1 Collagen type I/II ALP	More remarkable inhibitory effect on IL-17 levels, SLE improvement [10, 27].
DPSCs	CD44 CD106 CD146 STRO-1 ALP	Inhibition the stimulated T cell proliferation, Suppression of T-cell-mediated reaction in the allogeneic bone marrow transplantation, Suppression the proliferation of PBMCs through the secretion of TGF-β [10, 27].

*: positive but not always.

2.5. DLSCs (Periodontal Ligament Stem Cells)

Periodontal ligament derived from dental follicle with origin of neural crest. These cells are postnatal multipotent stem cells that have potential to differentiate into adipocytes, odontoblasts and oligodendrocyte-like cells (Table 1) [4, 20, 26, 38].

PDLSCs are positive for STRO-1, CD146, CD29, CD13, CD44, CD90, CD105 and CD166 that approves their capacity of being stromal and endothelial cells, but negative for CD40, CD80 (B7-1) and CD86 (B7-2), that are hematopoietic cells surface markers [51, 52]. These cells due to secretion of soluble factors, such as TGFβ, HGF and Indoleamine 2, 3-Dioxygenase (IDO), suppress Peripheral Blood Mononuclear Cells (PBMCs) proliferation. PDLSCs were discovered to possess immunosuppressive activity via prostaglandin E2 (PGE2)-induced T cell anergy and reduction of Treg induction [10]. In an *in vitro* co-culture experiment, PDLSCs displayed inhibitory effects on the proliferation of allogeneic and xenogeneic PBMCs through suppressing PBMCs division and less induction of IL-10/ Treg $CD4^+$ $CD25^+$ $Foxp3^+$ secretion [27].

2.6. GMSCs (Gingiva-derived Mesenchymal Stem Cells)

Human Gingival Mesenchymal Stem Cells known as multipotent postnatal stem cells were isolated by *Zhang et al* In 2009. GMSCs express CDs and display positive signals for

Oct4, Sox2, Nanog, Nestin, SSEA-4, are positive for STRO-1, CD29, CD105, CD90 and negative for CD34 and CD45 [27]. Expression of collagen type I, alkaline phosphatase, osteocalcin and Cbfa1 that are osteoblast genes was confirmed. Also, GMSCs have potential of differentiation to osteoblasts, chondrocytes and adipocytes. These cells display their anti-inflammatory properties by inducible Nitric Oxide Synthase (iNOS) and CycloOxygenase-2 (COX-2) which could attenuate colitis in Inflammatory Bowel Diseases (IBD). Moreover, these cells through shifting to M2 macrophage phenotype, can speed wound healing up. In 2011, *Fang Wang et al*. [10, 53] for the first time introduced GMSCs as a novel approach in bone reconstruction [54].

3. Conclusion

Up to now, uncompensatable damaged tissues remained as a great challenge in Health System. Recently, MSCs based therapy strategies appear a promising window for tissue reconstruction and organ function improvement. Among these newly introduced cells, D-SCs glitter as a precious tool for coming true this goal. So, using their specific immunobiomarkers and secretory factors, is recommended for selection of favorable stem cells suitable to research and therapeutic purposes. According to the contradiction and clinical interactions, it's important to know which source of stem cells in appropriate dose of administration should be used.

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