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REVIEW ARTICLE

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Teeth-derived stem cells: A source for cell therapy

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Abstract

Cell therapy is one of the important therapeutic approaches in the treatment of many diseases such as cancer, degenerative diseases, and cardiovascular diseases. Among various cell types, which could be used as cell therapies, stem cell therapy has emerged as powerful tools in the treatment of several diseases. Multipotent stem cells are one of the main classes of stem cells that could originate from different parts of the body such as bone marrow, adipose, placenta, and tooth. Among several types of multipotent stem cells, tooth-derived stem cells (TDSCs) are associated with special properties such as accessible, easy isolation, and low invasive, which have introduced them as a good source for using in the treatment of several diseases such as neural injuries, liver fibrosis, and Cohrn's disease. Here, we provided an overview of TDSCs particular stem cells from human exfoliated deciduous teeth and clinical application of them. Moreover, we highlighted molecular mechanisms involved in the regulation of dental stem cells fate.

KEYWORDS

stem cell, therapy, tooth-derived stem cells (TDSCs)

1 | INTRODUCTION

Stem cells are clonogenic cells, which are differentiated from different parts of the body. The capacities of both self-renewal and multilineage differentiation are main stem cell properties. The potential of stem cells is extensively investigated as a novel therapeutic approach that shows great promise in regenerative medicine (Goradel et al., 2018; Mirzaei et al., 2018; Mirzaei et al., 2016; Mirzaei et al., 2018; Pai et al., 2013; Mohammadi et al., 2016; Moradian Tehrani et al., 2017; Tehrani et al., 2018). General properties have been mentioned to delineate the identity of stem cells, including being unspecialized and having the capacity to renew and differentiate to adult specialized cell types. Unspecialized stem cells continually divide to regenerate themselves to maintain their reservoir. In the meantime, some regenerated cells change their phenotype and start differentiation to generate functionally mature cells (Chai & Slavkin, 2003; Telles et al., 2011).

Postnatal stem cells are well-known stem cells resided in adult tissues, which have shown great promise to repair damaged and/or defective tissues. Scientists could isolate postnatal stem cells from a variety of tissues including bone marrow, brain, skin, hair follicles, skeletal muscle, and DP (Gronthos et al., 2003; Jo et al., 2007; Nakashima & Akamine, 2005; Suchánek et al., 2010). Readily accessible TDSCs can be obtained and stored for future use through easy and minimally invasive ways (Arora et al., 2009). DP stem cells have been isolated from permanent, deciduous, and supernumerary teeth (Gronthos et al., 2000; Pierdomenico et al., 2005) and it has been shown that all these populations demonstrate similar features. They present fibroblast-like morphology, high proliferative potential, and high efficiency to form adherent colonies. However, stem cells from the pulp tissue of permanent, deciduous, and supernumerary teeth differ in their specific surface markers and differentiation potential (Gandia et al., 2008; Stevens et al., 2008).

Abbreviations: BDNF, Brain-derived neurotrophic factor; BM-MSCs, Bone marrow mesenchymal stem cells; DP, Dental pulp; DMP-1, Dentin matrix protein 1; DSPP, Dentin sialophosphoprotein; DTSCs, Deciduous teeth–derived stem cells; GDNF, Glial-derived neurotrophic factor; GFAP, Glial fibrillary acidic protein; HATs, Histone acetyltransferases; hDT-MSCs, human dental tissue–derived mesenchymal stem cells; iPSCs, Induced pluripotent stem cells; NCSCs, Neural crest stem cells; NeuN, Neuronal nuclei; NT-3, Neurotrophin-3; SCNs, Stem cell niches; SLE, Systemic lupus erythematosus; SHED, Stem cells from human exfoliated deciduous teeth; TDSCs, Tooth-derived stem cells; TF, Transcription factor; Th17, T helper 17; Tregs, Regulatory T cells; PDLCs, Periodontal ligament cells; VEGF, Vascular endothelial growth factor.

Human postnatal deciduous DP stem cells are categorized as multipotent mesenchymal stem cells (Shi et al., 2017). All DTSCs populations consist of stem cells with ectomesenchymal origin in different proportions. Their embryonic origin, clonogenicity, self-renewal and proliferation capacities, multipotency, and specific markers suggest a comparative equivalent identity for DTSCs and NCSCs. iPSCs can be generated from DTSCs more easily and efficiently in comparison with human fibroblasts.

Following two distinct protocols, different populations of DTSCs were isolated including SHED and human immature dental pulp stem cells (IDPSCs) that opened a new window for obtaining young stem cells (Kerkis et al., 2006; Miura et al., 2003). SHED was introduced as a highly proliferative, clonogenic population of postnatal stem cells with differentiating potency toward a variety of mature cells including neural cells, adipocytes, odontoblasts, chondrocytes, osteoblasts, and mesenchymal stem cells. These features suggest SHED as a promising potential for repairing such as bone regeneration, possible treatment of chronic heart conditions and neural tissue injuries, and degenerative diseases such as Alzheimer's, Parkinson's, and ALS (Arthur et al., 2008; Chotkowski, 2010; Gandia et al., 2008; Gronthos et al., 2000; Kerkis et al., 2008). DTSCs have higher proliferation rate and higher colony forming capacity than DPSCs and therefore are more primitive than their counterparts isolated from permanent teeth (Le Douarin et al., 2004). IDPSCs are multipotent, which could be produced after reprogramming into iPSCs. It has been observed that IDPSCs have the potential to differentiate into multiple cells, among which neurons, adipocytes, odontoblasts, osteoblasts, and endothelial cells present a high proliferation capacity, which offers them an alternative source of stem cells for future clinical applications (Barros et al., 2015). Compared to the other sources, one of the main advantages of using IDPSCs is accessible noninvasive procedures for their isolation. They are generated from naturally exfoliated deciduous teeth that are usually discarded in childhood as medical waste. The use of IDPSCs has almost resolved the ethical concerns about the application of embryonic-derived stem cells (De Souza et al., 2013). Therapeutic potential of IDPSCs has been studied in muscular dystrophy (Kerkis et al., 2008), corneal regeneration (Gomes et al., 2010), and chronic spinal cord injury investigations (Feitosa et al., 2017).

In vitro and in vivo differentiation, developmental potential, immunological compatibility, tissue engineering capacity, and transplantation into animal models of DTSCs populations are focused in the current report (Kerkis & Caplan, 2011).

2 | DECIDUOUS TEETH–DERIVED STEM CELLS (DTSCs)

SCNs in DP of deciduous teeth are established before the birth and will maintain until the permanent teeth erupt. Active growing in deciduous teeth is caused by these active stem cell–rich SCNs, which are not yet deeply affected by genetic and/or environmental factors. Indeed, DP from deciduous teeth provides a source of healthy stem cells for cell therapy, when compared with DP isolated from permanent teeth. DTSCs are isolated from deciduous teeth, which present similar characteristics to both SHED and/or IDPSCs (Kerkis & Caplan, 2011).

Adult stem cells research has been considered as the most advanced sort of medical-scientific research, particularly SHED, which represent an immature stem cell population. This population can be easily harvested by noninvasive procedures, cultured, expanded, and differentiated to multilineage cells. SHED are also able to remain undifferentiated and survive after long-term cryopreservation. Furthermore, few ethical concerns and low immune reactions following SHED transplantation make them the most valuable source for tissue engineering and cell-based medicine therapies (Martinez saez et al., 2016).

3 | IMMUNOMODULATORY PROPERTIES OF STEM CELLS FROM HUMAN EXFOLIATED DECIDUOUS TEETH

Immunomodulatory properties of these cells have been studied in vitro, and it has been shown that SHED significantly inhibits Th17 cells. Transplantation of SHED demonstrated a high efficiency in reversing SLE into MRL/lpr mice. The raised ratio of Tregs to Th17 cells suggests that SHED can alleviate immune disorders through their immunomodulatory abilities. SHED express the mesenchymal surface molecules such as STRO-1, CD146, SSEA4, CD73, CD105, and CD166. Moreover, they have adipogenic and osteogenic differentiating capacity and also, similar to BM-MSCs, activate multiple signaling pathways including TGF, ERK, Akt, Wnt, and platelet-derived growth factor (PDGF). New research has demonstrated that immunomodulatory properties of BM-MSCs help them to treat immune diseases successfully (Yamaza et al., 2010).

4 | MOLECULAR MECHANISMS IN THE REGULATION OF CELLULAR DIFFERENTIATION OF TDSCs

Stem cells are one of the attractive tools in modern medicine, which are associated with specific properties including self-renewal and differentiate into several specialized cell types (Mirzaei et al., 2018). These properties led to introduce them as a new therapeutic option for treating various diseases such as cancer, regenerative diseases, and cardiovascular diseases (Mirzaei et al., 2018). Stem cells could be isolated from many sources. Organs and tissues are one of the main sources for multipotent stem cells. Among various organs and tissues, DTSCs have emerged as an effective source for isolation of various types of stem cells (Liu et al., 2015). It has been shown that DTSCs could be isolated from primary teeth that are naturally replaced, third molars, or other dental tissues (Liu et al., 2015). The identification molecular mechanisms involved in lineage specification could contribute to better understanding of TDSCs behavior. Increasing evidence indicated that a variety of cellular and molecular mechanisms could affect the stem cells fate (Rodas-Junco et al.,

2017). These mechanisms control stem cells fate behaviors during development. Among many factors involved in the regulation of TDSCs, epigenetics mechanisms play critical roles in stem cells fate (Rodas-Junco et al., 2017). Multiple lines of evidence indicated that a variety of epigenetics mechanisms including chromatin and histone modifications, and the regulation of many genes involved in TDSCs fate via expression of microRNAs (miRNAs) are associated with TDSCs fate (Rodas-Junco et al., 2017).

HATs are one of the important epigenetics players in TDSCs fate. In a study, Wang et al indicated that p300, which is as one well-known HATs, plays a critical role in maintaining the stemness of dental pulp *cells* (*DPCs*) (Wang et al., 2014). Their results indicated that upregulation of p300 could increase the transcript levels of *NANOG* and *SOX2*, which could lead to the low expression levels of odontoblastic differentiation markers including *DMP-1*, dentin sialophosphoprotein (*DSPP*), *DSP*, *OPN*, and *OSTEOCALCIN* (*OCN*). These results proposed that p300 plays a key role and interacts with stemness markers under noninductive conditions. Moreover, they showed that there was an increase in H3K9 acetylation levels in the promoter regions of the *OCN* and *DSPP* genes when p300 is upregulated. These results suggested that p300 could act as a co-activator to regulate the odontogenic potential of DPCs (Wang et al., 2014).

MiRNAs are other factors that could be involved in dental stem cells fate (Rodas-Junco et al., 2017). miRNAs are small noncoding RNAs that act as epigenetic regulators (Gholamin et al., 2018; Golabchi et al., 2018; Keshavarzi et al., 2017; Mirzaei et al., 2016; Mirzaei et al., 2018). It has been shown that miRNAs could be involved in a variety of biological processes such as growth, differentiation, angiogenesis, and development (Banikazemi et al., 2018; Hashemi Goradel et al., 2018; Jamali et al., 2018; Masoudi et al., 2018; Mashreghi et al., 2018; Rashidi et al., 2017; Rashidi et al., 2017; Saeedi Borujeni et al., 2018). Increasing evidence revealed that deregulation of miRNAs is associated with initiation and progression of many diseases such as cancer, stroke, cardiovascular diseases, depression, and regenerative diseases (Gholamin et al., 2016; Hoseini et al., 2018; Jafari et al., 2017; Keshavarzi et al., 2017; Khanmohammadi et al., 2018; Mirzaei et al., 2017; Mirzaei, 2017; Moridikia et al., 2018; Mirzaei et al., 2018; Mirzaei et al., 2018; Rabieian et al., 2018; Tavakolizadeh et al., 2017). MiRNAs could be involved in the regulation of several genes related to dental stem cells fate (Wang et al., 2014). Hence, identification of them could help to better understand the underlying mechanisms involved in dental stem cell fate. Several studies revealed that miRNAs play a key role in activation or inactivation of many genes related to cell differentiation of dental tissue stem cells such as angiogenic differentiation, osteogenic, and odontogenic (Wang et al., 2014). MiRNAs have different expressions in various cell populations (Fathullahzadeh et al., 2016; Mohammadi et al., 2016; Mirzaei et al., 2016; Mirzaei et al., 2016; Salarinia et al., 2016; Saadatpour et al., 2016). These differential expressions could lead to the maintenance of the stem cell phenotype or differentiation capacity. The expression profiles of miRNA DPSCs, GSCs, and human periodontal ligament stem cells (PDLSCs) miRNAs showed important alters between differentiated and dedifferentiated cell types (Gay et al., 2014). It has been shown that various miRNAs such as miR-218, miR-210, and miR-99a are involved in the regulation of differentiation in the dental tissues. In a study, Gay et al. (2014) indicated that miR-218 has a critical role in regulating of *RUNX2* expression, which is known as a TF for osteogenic differentiation. They showed that there was a high correlation between lower levels of miR-218 and higher levels of *RUNX2*, which suggested miR-218 could regulate the osteogenic pathway in hDT-MSCs via targeting the *RUNX2* (Gay et al., 2014). In another study, Li et al. (2012) indicated that the expression of miR-101 and miR-21 is associated with osteogenic differentiation in PDLCs. They showed that miR-21 and miR-101 could modulate *periodontal ligament-associated protein 1* expression via enhancing the mineralization capacity of PDLCs (Li et al., 2012).

It has been shown that DPSCs seeded on a titanium implant surface could contribute to enhancing of osteogenic differentiation (Gardin et al., 2016). The titanium implants are able to upregulate miR-196a, which is involved in the inhibition of cell proliferation and the transcriptional activity of *HOMEOBOX C8* and inducing of osteogenic differentiation in DPSCs (Gardin et al., 2016). This result suggested that the interaction between DPSCs and the implant surface could affect stem cell fate via upregulating/downregulating miRNAs, which are related to osseointegration (Gardin et al., 2016).

5 | CLINICAL APPLICATION OF DECIDUOUS TEETH–DERIVED STEM CELLS

Discovery of stem cell technology is considered an important progress in regenerative medicine, which created a new field of experimentation to treat various diseases. A comprehensive list of diseases including stem cell disorders, acute and chronic leukemias, myelo-proliferative disorders, myelodysplastic syndromes, lympho-proliferative disorders, inherited erythrocyte abnormalities, liposomal storage diseases, histiocytic disorders, phagocyte disorders, congenital immune system disorders, inherited platelet abnormalities, plasma cell disorders, and malignancies is currently being treated using stem cells (Arthur et al., 2008; Mao et al., 2006; Reznick & Provider, 2008).

Deciduous teeth DP contained cell populations with mesenchymal stem cell–like features, with a high proliferation, and trilineage differentiation potential could be suitable for further in vitro evaluation of cell-based therapies (Table 1).

6 | SHED CAN BE USED IN DENTAL PULP TISSUE ENGINEERING

The ability of SHED in the regeneration of a functional DP by depositing a mineralized and organized matrix using clinically approachable techniques is a great interest in this area. The SHED-regenerated tissues express odontoblastic differentiating markers such as DMP-1 and DSPP (Sakai et al., 2010). Transplanted SHED into full-length root canals with injectable scaffolds were capable of proliferating within the root canal and expressing putative markers of odontoblasts (DSPP, DMP-1, and

TABLE 1 Various applications of TDSCs

Disease	Outcomes	Model	Injection route	Type of stem cell	Ref
Myocardial infarction (MI)	Improving the function of left ventricular, inducing angiogenesis and decreasing infarct size in a rat model of acute myocardial infarction	In vivo (rat)	Intramyocardial	DPSC	Gandia et al. (2008)
Acute kidney injury (AKI)	Improving the kidney function by attenuation of inflammatory cytokines expression	In vivo (mice)	Subrenal capsule	SHED	Hattori et al. (2015)
Calvarial defects	Repairing critical-size calvarial defects	In vivo (mice)	Subrenal capsule	SHED	Seo et al. (2008)
Alzheimer's disease	Suppression of proinflammatory cytokines, iNOS and 3-nitrotyrosine and improving cognitive function	In vivo (mice)	Intranasally	SHED	Mita et al. (2014)
Focal cerebral ischemia	Enhancing the migration and differentiation of endogenous NPCs and inducing vasculogenesis, leading to ischemic brain injury amelioration	In vivo (rat)	Intranasally	SHED	Inoue et al. (2012)
Stroke (Middle cerebral artery occlusion)	Significant restoration of neurologic dysfunctions	In vivo (rat)	The right dorsolateral striatum	tNSC (DPSC)	Yang et al. (2009)
Hypoxic-ischemic brain injury	Remarkable pathophysiological and neurological recovery through proinflammatory cytokines downregulation, anti-inflammatory cytokines upregulation, and significant apoptosis reduction	In vivo (mice)	Intravenous	SHED	Yamagata et al. (2013)
Cardiac injury	Suppressing inflammation and apoptosis, protecting the heart from acute ischemic injury	In vivo (mice)	Intravenous	SHED-CM	Yamaguchi et al. (2015)
Rheumatoid arthritis	The ED-Siglec-9-dependent induction of M2 macrophage polarization and osteoclastogenesis inhibition	In vivo (mice)	Intravenous	SHED-CM	Ishikawa et al. (2016)
Diabetes	Reversing STZ-induced diabetes	In vivo (mice)	Intravenous	SHED, DPSCs	Kanafi et al. (2013)
Acute lung injury	A strong M2-inducing activity	In vivo (mice) In vitro	Intravenous	SHED	Wakayama et al. (2015)
Wound	Accelerating wound healing	In vivo (mice)	Intravenous	SHED	Nishino et al. (2011)
Acute liver failure (ALF)	anti-apoptosis/hepatocyte protection, angiogenesis, macrophage differentiation and proliferation/differentiation of liver progenitor cells	In vivo (rat)	Intravenous	SHED	Matsushita et al. (2015)
Liver fibrosis	Repairing hepatic dysfunction	In vivo (mice)	Transplantation	SHED	Yamaza et al. (2015)
Multiple sclerosis (MS)	Decreasing the axonal demyelination, inflammatory cell infiltration and proinflammatory cytokines levels in the spinal cord Inhibiting the proliferation of myelin oligodendrocyte glycoprotein–specific CD4 + T cells	In vivo (mice)	Intraperitoneal	SHED-CM	Shimojima et al. (2016)
Parkinson's disease	Neuroprotection against 6-OHDA-induced neurodegeneration and to nigrostriatal tract restoration	In vivo (rat)	Intracerebral transplantation	SHED	Fujii et al. (2015)

(Continues)

TABLE 1 (Continued)

Disease	Outcomes	Model	Injection route	Type of stem cell	Ref
Autoimmune encephalomyelitis	able to suppress EAE clinical score modulates peripherally the $CD4^+$ T cell responses decreasing $CD4^+$ and $CD8^+$ T cell infiltrates in CNS	In vivo (mice)	Intraperitoneal	SHED	Rossato et al. (2017)
Mandibular defect	Proliferation and osteogenesis	In vivo (dog)	Directly implantation or injection to the damaged tissue	SHED	Behnia et al. (2014)
Spinal cord injury (SCI)	Neuroprotection and inhibiting early neuronal apoptosis	In vivo (rat)	Intravenous	SHED	Nicola et al. (2017)
Focal cerebral ischemia	Improving ischemic brain injury by inducing vasculogenesis and promoting the migration and differentiation of endogenous NPCs	In vivo (rat)	Intravenous	SHED	Sugiyama et al. (2014)
Calvarial bone defects	Mitigating bone regeneration process	In vivo (rat)	Intraperitoneal	DPSCs	Annibali et al. (2014)
Liver fibrosis	Suppression of liver fibrosis and restoration of AST, ALT, and ammonia levels	In vivo (mice)	Transplantation	DPSCs + melatonin	Cho et al. (2015)
Muscle defect	Muscle regeneration by expressing human dystrophin and myosin heavy chain.	In vivo (mice)	Intramuscular	DPSCs	Yang et al. (2010)
Hindlimb ischemia	Successful cell engraftment and high capillary formation resulting in blood flow elevation	In vivo (mice)	Intramuscular	DPSCs	Iohara et al. (2008)
Corneal stromal	Generating corneal stromal extracellular matrix without inducing immunological rejection or affecting corneal transparency	In vivo (mice)	Injection into corneal stroma	DPSCs	Syed-Picard et al. (2015)
Optic nerve injury	Promotion of neurotrophin-mediated retinal ganglion cell survival and axon regeneration	In vivo (mice)	Intravitreal transplantation	DPSCs	Mead et al. (2013)
Alzheimer's disease	Increasing Bcl-2 level (endogenous survival factor) and decreasing the apoptotic regulator Bax	In vitro	-	DPSCs secretome	Ahmed et al. (2016)

Note. AST: aspartate aminotransferase; ALT: alanine aminotransferase; CNS: central nervous system; EAE: experimental autoimmune encephalomyelitis; iNOS: inducible nitric oxide synthase; NPC: neural precursor cell; OHDA: oxidopamine; SHED: stem cells from human exfoliated deciduous teeth; SHED-CM: stem cells from human exfoliated deciduous teeth-conditioned medium; STZ: streptozotocin; TDSC: tooth-derived stem cells; tNSC: neuronal stem cells from human wisdom teeth.

matrix extracellular phosphoglycoprotein [MEPE]). SHED differentiated into functional odontoblasts that generated new dentin. More investigation must be done to evaluate the ability of SHED in developing functional DP tissue in oral environment (Rosa et al., 2013). In addition, these cells differentiated to vascular endothelial cells. In vitro, VEGF induced SHED to express the endothelial markers vascular endothelial growth factor receptor type 2 (VEGR2), platelet endothelial cell adhesion molecule (CD31), and VE-cadherin (VEC) adherin molecules and organize capillary-like sprouts (Ferrara et al., 2003).

7 | SHED POTENTIAL FOR NEURON TISSUE ENGINEERING

Neurodegenerative disorders such as ALS, Parkinson's, and Alzheimer's disease are characterized by degeneration of neurons, leading to functional impairments (Orange & Ryan, 2000). The fact that the DP tissue is originated from neural crest cells make SHED an interesting cell source for treating neurodegenerative disorders (Nakamura et al., 2009). Under the non-neuronal induction condition, these cells have expressed variant neural markers such as nestin, NeuN, doublecortin, and GFAP at both gene and protein levels (Chai et al., 2000; Majumdar et al., 2016; Sakai et al., 2012). In addition, differentiated cells are also positive for intermediate filament peripherin, Brn3a, and apolipoprotein E, which is expressed within the glia in the peripheral nervous system (Jarmalavičiūtė et al., 2013).

8 | DIFFERENTIATION CAPACITY OF SHED FOR DEVELOPING HORMONE-SECRETING CELLS

SHED have presented potential to treat diabetes and hepatic diseases. Under proper stimulation, SHED express a set of hepatic markers such as hepatic nuclear ?-fetoprotein, factor-4?, and insulin-like growth factor-1 indicating that SHED can differentiate into hepatic lineage cells (Ishkitiev et al., 2012). Transplantation of SHED into the mice following carbon tetrachloride–induced liver fibrosis showed that these cells can help regenerate damaged liver through both direct (tissue replacement) and indirect (antifibrotic and anti-inflammatory effects) mechanisms. Moreover, in vitro studies revealed the potential of SHED to develop islet-like cell aggregates. Therefore, they can introduce an alternative for cell replacement therapy in diabetes (Govindasamy et al., 2011). Transplantation of SHED-derived islet-like cells into streptozotocin (STZ)-induced diabetic mice reversed the diabetes condition and restored the normoglycemia after three to four weeks (Kanafi et al., 2013).

9 | SHED ABILITY FOR SYSTEMIC LUPUS ERYTHEMATOSUS TREATMENT

SLE disease provokes the destruction of target tissues and accumulates the autoreactive lymphocytes and immune complexes. The physiopathology of disease presents conflicting immune modulations, including both deficiency and hyperactivity of the immune system. SHED have shown immunomodulatory abilities as these cells significantly inhibited Th17 cells in vitro and after transplantation in MRL/lpr mice, SHED exhibited a high efficiency in reversing SLE. SHED provided an enhanced therapeutic effect when compared with BM-MSCs. The raised ratio of Tregs to Th17 cells suggests that SHED can provide a treatment of immune disorders via improved immunomodulatory properties (Yamaza et al., 2010).

10 | OSTEOGENIC DIFFERENTIATING POTENTIAL OF SHED

Even though SHED cannot differentiate directly into osteoblasts but they induce new bone formation by forming an osteoinductive template to recruit murine host osteogenic cells. These data imply that deciduous teeth may not only provide guidance for the eruption of permanent teeth, as generally assumed, but may also be involved in inducing bone formation during the eruption of permanent teeth (Miura et al., 2003).

Bone formation ability of SHED was further investigated using porcine cells. The efficacy of porcine autologous SHED in regenerating orthofacial bone defects was recently tested in a miniature pig, where the critical-size bone defects were produced in the mandible. Six months after transplantation, the porcine SHED were able to regenerate bone and to repair critical-size mandibular defect (Zheng et al., 2009).

11 | IDPSCs FOR BONE FORMATION

Human IDPSCs were utilized to reconstruct critical-size cranial bone defects in rats. Bone formation was evaluated two months after transplantation of IDPSC. The results revealed a well-formed mature bone on the side of CM with IDPSCs, whereas less-mature tissue was detected in the control side.

Human IDPSCs transplantation was used for bone tissue recovery in an ovine model of induced osteonecrosis in the femoral head. Cell delivery resulted in the proliferation of IDPSCs within the injured site, which provided bone tissue fabrication (Chadipiralla et al., 2010).

12 | IDPSCs FOR OCULAR SURFACE RECONSTRUCTION

Some studies have disclosed similar properties between IDPSCs and limbal stem cells (LSCs). Research showed that IDPSCs express a set of LSC-specific markers, such as integrin b-1 (CD29), Delta Np63 (tumor expressing protein p63), vimentin, ATP-binding cassette, subfamily G, member 2, cytokeratin-12, and connexin 43 (gap junction protein) (Kerkis & Caplan, 2011).

In a rabbit model, IDPSCs were utilized to reverse total LSC deficiency after the chemically induced corneal surface injury. The study showed that, similar to LSCs, IDPSCs have the capacity to reconstruct the entire corneal epithelium as they formed a new corneal surface expressing specific human proteins in an appropriate and functional manner (Gomes et al., 2010).

13 | IDPSCs AND MUSCULAR DYSTROPHY

Because they have exhibited robust in vitro muscle differentiation, the safety, efficiency, and capacity of human IDPSCs to restore dystrophin expression were evaluate in a golden retriever muscular dystrophy (GRMD) dog's model (Kerkis et al., 2008).

14 | IDPSCs AND NEURONAL INJURY

IDPSCs have been used to enhance spinal cord regeneration after trauma. In vitro cultivated IDPSCs were seen to express mRNA transcripts of several neurotrophic factors such as nerve growth factor, GDNF, BDNF, NT-3, and NT-4/5. Besides, IDPSCs were also able to express Schwann cell marker S-100 and astrocyte marker GFAP after homing in the recipient tissue. Taking these findings together, IDPSCs can be used in repairing the spinal cord injury (de Almeida et al., 2011).

15 | CONCLUSION

The utilization of stem cells has emerged in effective therapeutic approaches as a good source for transplantation and treatment of various diseases. To date, many studies indicated that various types of stem cells including multipotent stem cells and induced pluripotent stem could be used for a therapeutic source in the treatment of several diseases such as cancer, inflammatory diseases, cardiovascular diseases, and degenerative diseases. Multipotent stem cells, which are known as adult stem cells, have good properties, which led to many applications of them in clinical. Among various types of multipotent stem cells, TDSCs could be used as a new source for clinical applications. Multiple lines of evidence indicated that TDSCs have particular properties such as accessiblilty, fast and easy isolation, and lower invasiveness than other types of stem cells. These properties have led to introducing TDSCs as effective tools for treatment of several diseases. Hence, it seems that more assessment of the therapeutic potential of TDSCs could contribute to the identification of various obstacles in using them and help to find more clinical applications of them.

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