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**Multidifferentiation potential of dental-derived stem cells**

Yin JY *et al*. Multidifferentiation potential of DMSCs

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**Abstract**

Tooth-related diseases and tooth loss are widespread and are a major public health issue. The loss of teeth can affect chewing, speech, appearance and even psychology. Therefore, the science of tooth regeneration has emerged, and attention has focused on tooth regeneration based on the principles of tooth development and stem cells combined with tissue engineering technology. As undifferentiated stem cells in normal tooth tissues, dental mesenchymal stem cells (DMSCs), which are a desirable source of autologous stem cells, play a significant role in tooth regeneration. Researchers hope to reconstruct the complete tooth tissues with normal functions and vascularization by utilizing the odontogenic differentiation potential of DMSCs. Moreover, DMSCs also have the ability to differentiate towards cells of other tissue types due to their multipotency. This review focuses on the multipotential capacity of DMSCs to differentiate into various tissues, such as bone, cartilage, tendon, vessels, neural tissues, muscle-like tissues, hepatic-like tissues, eye tissues and glands and the influence of various regulatory factors, such as non-coding RNAs, signaling pathways, inflammation, aging and exosomes, on the odontogenic/osteogenic differentiation of DMSCs in tooth regeneration. The application of DMSCs in regenerative medicine and tissue engineering will be improved if the differentiation characteristics of DMSCs can be fully utilized, and the factors that regulate their differentiation can be well controlled.

**Key Words:** Dental mesenchymal stem cells; Regenerative medicine; Tissue engineering; Multipotency; Odontogenic differentiation; Osteogenic differentiation

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**Core Tip:** Dental mesenchymal stem cells have been widely used in tissue engineering and regenerative medicine due to their multipotential differentiation ability. We herein discuss the multipotency of dental mesenchymal stem cells and some related factors influencing the odontogenic/osteogenic differentiation, which provide guidance for fully utilizing the multipotency of dental mesenchymal stem cells.

**INTRODUCTION**

Over the past three decades, in the search for treatments for a variety of degenerative diseases and irreversible forms of tissue and organ damage, the emerging field of tissue engineering and regenerative medicine (TERM) has attracted a lot of interest, and great efforts have been made to realize the regeneration of different types of tissues and organs to restore normal physiology and body function. As one of the important aspects of regenerative medicine, tissue engineering mainly takes advantages of the following three methods: (1) cell/biomaterial complex systems with cell-seeded biomaterials implanted into the body to restore and regenerate tissues/organs; (2) cell systems, such as stem cell transplantation; and (3) biomaterial systems implanted into the body and integrated into tissues[1]. As a vital part of TERM, a suitable source of stem cells is a significant initial requirement. Since the 1990s, the field of stem cell biology has gradually developed and rapidly become a main research trend in regenerative medicine. Induced pluripotent stem cells, progenitor cells from various tissues, human embryonic stem cells and adult stem cells are all potential seed cells for TERM[2]. Cells derived from induced pluripotent stem cells or differentiated from human embryonic stem cells can be used to build related tissue cell models. Progenitor cells and adult stem cells from various tissues can differentiate into mature tissues.

As adult stem cells, dental mesenchymal stem cells (DMSCs), including dental pulp stem cells (DPSCs), periodontal ligament stem cells (PDLSCs), stem cells from apical papilla (SCAPs), gingival mesenchymal stem cells (GMSCs), stem cells from human exfoliated deciduous teeth (SHED) and dental follicle stem cells (DFSCs) have been widely studied because of their ready availability, easy accessibility and lack of complex ethical issues. DMSCs have multiple differentiation potential and can differentiate into a variety of tissue-like cells under specific induction conditions, providing potential seed cells for TERM. For example, SHED are capable of inhibiting bone loss, decreasing neuronal apoptosis and forming pancreatic islet-like clusters[3-5]. DPSCs can differentiate into myogenic lineage and corneal stromal-like constructs[6,7] and can also reduce bone loss in an osteoporosis mouse model, prevent retinal ganglion cell loss and repair spinal cord injury[8-10].

DMSCs, in particular, have great potential for application in engineering regeneration of dental tissues. In 2006, Sonoyama *et al*[11] transplanted a hydroxyapatite/SCAP-Gelfoam/PDLSC structure into a swine alveolar socket, which regenerated mineralized root-like tissue and formed periodontal ligament space[11]. In 2012, Guo *et al*[12] identified a method of combining DFSCs with treated dentin matrix scaffolds in the alveolar fossa that proved to be a promising strategy for tooth root regeneration[12]. In 2013, Iohara *et al*[13] transplanted autologous DPSCs with granulocyte-colony stimulating factor into a dog pulpectomized tooth and found that newly formed pulp tissue, including innervation and vasculature, fully filled in the root canal[13].

Efforts have been made to promote tooth regeneration by DMSCs, but many factors affect this complex regeneration process, such as correlative non-coding RNAs, signaling pathways, inflammation, aging and exosomes. In the process of induced differentiation of DMSCs, many non-coding RNAs, including microRNAs and long noncoding RNAs (lncRNAs) and related signaling pathways are involved to regulate the expression of odontogenic/osteogenic differentiation genes. In addition, donor age, cell senescence and the complex oral inflammatory microenvironment also pose great challenges to tooth regeneration by DMSCs. Moreover, the hot topic of research in recent years, exosomes, which carry a variety of contents, have also captured the attention of researchers in inducing the differentiation of DMSCs. If we can regulate these factors well, it will enable a big step forward in the application of DMSCs in the field of tooth regeneration. This review focuses on the multidirectional differentiation potential of DMSCs and the effect of the above-mentioned factors on the odontogenic/osteogenic differentiation of DMSCs in the field of tooth regeneration, hoping to provide a reference for the efficient use of DMSCs.

**DIVERSE DIFFERENTIATION OF DMSCs**

In addition to the odontogenic differentiation ability of DMSCs, in recent years the research on the differentiation of DMSCs into other tissue-like cells, such as osteogenesis, chondrogenesis, angiogenesis, neurogenesis and differentiation potential toward tendon-like cells, insulin-producing cells, hepatic-like cells, corneal stromal-like cells, *etc*. has become popular (Figure 1). To explore the diverse differentiation ability of DMSCs is an issue worth exploring.

***DPSCs***

In 2000, Gronthos *et al*[14]identified that DPSCs can form alizarin red-positive condensed nodules with high levels of calcium cultivated by L-ascorbate-2-phosphate, glucocorticoid, dexamethasone and inorganic phosphate[14]. As a seed cell for bone regeneration, DPSCs usually attached to some materials for bone defect models. For example, Wongsupa *et al*[15]fabricated a scaffold combination of poly-ɛ-caprolactone–biphasic calcium phosphate with the modified melt stretching and multilayer deposition technique seeded with human DPSCs (hDPSCs), which increased the newly formed bone in calvarial defects rabbit models[15]. However, Jin *et al*[16] showed that adipose tissue-derived stem cells exhibited greater osteogenic differentiation potential compared to DPSCs[16].

*In vitro*, DPSCs can differentiate into chondroblasts, which suggests that it can be useful for cartilage injuries[17]. CD146 marked DPSCs can express the chondrogenic inducing factor transforming growth factor (TGF)-β3 and form three-dimensional cartilage constructs when seeded on poly-L-lactic acid/polyethylene glycol electrospun fiber scaffolds[18]. Costal chondrocytes are able to supply a chondro-inductive niche that promote the DPSCs to undergo chondrogenic differentiation and enhance the formation of cartilage[19]. Xenotransplantation of DPSCs in platelet-rich plasma and 3% alginate hydrogels significantly regenerated cartilage in rabbit models of cartilage damage[20,21].

In 2016, Chen *et al*[22] first identified expression of tendon-related markers such as scleraxis, tenascin-C, tenomodulin, eye absent homologue 2, collagen I and collagen VI in dental pulp tissues. Also, DPSCs seeded in aligned polyglycolic acid fiber scaffolds can promote the expression of tendon-related markers under mechanical stimulation and form mature tendon-like tissue in a mouse model[22]. As neural crest-derived cells, DPSCs can be induced to differentiate into neuron-like cells with the use of growth factors, including basic fibroblast growth factor and epidermal growth factor, which are preferable to the chemical-induction method[23-25]. DPSCs transplanted into a rat model of middle cerebral artery occlusion, peripheral nerve injuries and retinal injury expressed related neuronal markers[26-28].

Three-dimensional culture promoted the differentiation of hDPSCs into insulin-producing cells[29], and pancreatic islets were also generated from DPSCs[30]. The potential toward insulin-producing cells of hDPSCs was superior to human PDLSCs (hPDLSCs)[31]. DPSCs also exhibited angiogenic potential when implanted into mouse brain and into a rat model of acute myocardial infarction by promoting neovasculogenesis[32,33]. Furthermore, DPSCs differentiated into bladder smooth muscle cells in a particular culture medium[34], while the Wnt-GSK3β/β-catenin pathway played an important role in this process[35]. DPSCs had the potential to form a high-purity hepatic lineage when cultured in serum-free medium[36], and DPSCs derived from cryopreserved dental pulp tissue of vital extracted diseased teeth also showed the potential to differentiate into hepatic-like cells[37]. Additionally, DPSCs had the capacity to differentiate into melanocyte-like cells when cultured in a specific melanocyte differentiating medium[38].

***PDLSCs and GMSCs***

PDLSCs have great osteogenic differentiation potential. Kato *et al*[39] observed that PDLSCs have the highest levels of some bone differentiation markers without osteogenic differentiation among mesenchymal stromal cells derived from bone marrow and adipose-derived mesenchymal stem cells[39]. Seeded on nanohydroxyapatite-coated genipin-chitosan conjunction scaffold, PDLSCs exhibited significantly greater viability and alkaline phosphatase activity and promoted calvarial bone repair[40]. Moshaverinia *et al*[41,42]reported that PDLSCs and GMSCs capsulated in an injectable arginine-glycine-aspartic acid tripeptide-coupled alginate microsphere delivery system promoted bone regeneration and chondrogenesis, respectively, for a calvarial defect animal and subcutaneous implantation of nude mice, and PDLSCs showed significantly higher osteogenic and chondrogenic differentiation capability compared with GMSCs.

In 2021, Shen *et al*[43]showed that 6-bromoindir-ubin-3’-oxime promoted mineralized nodule formation in PDLSCs[43]. PDLSCs from beagle dogs and humans can both be induced to differentiate into neural-like cells by various protocols[44,45], and the Wnt/β-catenin signaling pathway has been implicated in this process[46]. Bueno *et al*[47]found that the nuclear shape of hPDLSC-derived neural-like cells was similar to cells in neurogenic niches from adult mouse brain, and no cell proliferation occurred in the course of neurogenesis. The potential for neurogenesis is improved by the addition of specific short peptides or phytocompounds[48-50]. As another stem cell type derived from periodontal tissue, GMSCs also have neurogenic differentiation potential and displayed action potential capacity when tested by a neurosphere-mediated induction method[51], while hypoxia preconditioning activated more genes associated with neuronal development[52]. In addition, over prolonged passages, human GMSCs have been found to spontaneously differentiate into neural precursor cells[53].

Encapsulated PDLSCs and GMSCs in an alginate/hyaluronic acid three-dimensional scaffold promoted the regeneration of neurogenic tissue[54]. Besides, PDLSCs had the ability to differentiate into corneal stromal keratocyte-like cells[55] and constructed a multilamellar human corneal stromal-like tissue *in vitro* when seeded onto orthogonally aligned, multilayered silk membranes and supplemented with the neuropeptide substance P[56]. PDLSCs also could be directed to develop into retinal progenitors and islet-like cell clusters with competence for photoreceptor differentiation and secretion of insulin[57,58]. Moreover, both PDLSCs and GMSCs differentiated into tendon-like cells using an injectable and biodegradable arginine-glycine-aspartic acid tripeptide-coupled alginate hydrogel scaffold[59]. The GMSCs could also be induced to differentiate into functional keratinocytes when treated with *Acalypha indica* in a three-dimensional microenvironment[60].

***DFSCs***

Human DFSCs can differentiate to osteogenic lineage cellsin osteogenic induction medium without dexamethasone, and BMP6 is a key gene in the osteogenic differentiation[61]. Plasma rich in growth factors and soluble silica can promote osteogenic differentiation of DFSCs[62,63]. Lucaciu *et al*[64] indicated that DFSCs could be used for promoting bone regeneration on titanium implant surfaces[64]. DFSCs were loaded into poly-ɛ-caprolactone scaffold and implanted into skulls defects of Sprague Dawley rats, and bone regeneration was observed[65]. Undifferentiated DFSCs expressed some neural markers, such as nestin, β-III-tubulin and S100β and exhibited a spindle-like morphology[66]. Using a two-step strategy for neuronal differentiation, DFSCs could be differentiated into neurosphere-like cell clusters, and finally developed a cellular morphology with small bodies and long cellular extrusions while exhibiting increased expression of neural cell markers[67].

It has been suggested that human DFSCs may have the potential to differentiation toward the glial lineage rather than the neuronal lineage[66]. Induced cardiomyocytes derived from DFSCs, which were cultured in medium with suberoylanilide hydroxamic acid, could be intraperitoneally injected into experimental mice and exhibited homing capacity into the heart muscle[68]. Comparing the differentiation potential toward pancreatic β cell-like cells among the stem cells from dental pulp, papilla and follicle, the DFSCs demonstrated higher potency and secreted more insulin upon glucose challenge[69]. Furthermore, epithelial stem-like cells from the human dental follicle were able to differentiate into salivary gland acinar and duct cells[70].

***SHED***

SHED represent a promising cell source for bone regeneration, which are usually combined with many biomaterials. Combined hydroxyapatite scaffold and SHED can promote alveolar bone regeneration, and interleukin-17A can enhance osteogenic differentiation of SHED, both due to increasing osteoprotegerin/receptor activator of nuclear factor κB ligand ratio[71,72]. FGF-2 pretreated SHED represent a faster formation of intramembranous bone after implanted in craniofacial bone defects than hypoxia pretreated[73]. A carbon nanomaterial named graphene oxide quantum dots promotes osteogenic differentiation of SHED *via* the Wnt/β-catenin signaling pathway[74]. In addition, SHED have the chondrogenic differentiation ability. After transplantation into the subcutaneous space on the back of nude mice, SHED recombined with β-TCP scaffolds were able to produce new cartilage-like tissues[75].

In 2011, SHED were successfully induced to differentiate into neural-like cells by a simple short-term growth factor-mediated induction protocol[76], and then in 2013, a novel three-stage method was established[77]. Yang *et al*[78]found that Noggin overexpression combined with the Rho kinase inhibitor Y-27632 exhibited a synergistic effect in promoting differentiation of SHED into neuron-like cells[78]. The lncRNA C21orf121 promotes SHED differentiation into neuronal cells by upregulating the expression of BMP2, acting as a competing endogenous RNA to compete with BMP2 binding to miR-140-5p[79]. SHED in polyglycolic acid tubes combined with autografting can regenerate the mandibular branch of the rat facial nerve[80]. Also, SHED have been used to repair a Parkinsonian rat model, an acute contused spinal cord injury model and a model of diabetic peripheral neuropathy[81-83].

In addition, SHED can differentiate into angiogenic endothelial cells, and when cultured with decellularized extracellular matrix of human umbilical vein endothelial cells can improve endothelial differentiation[84,85]. Using shear stress *via* the downstream pathway of vascular endothelial-derived growth factor-Notch signaling or by inhibiting TGF-β signaling in SHED can enhance endothelial differentiation[86,87]. SHED transplanted into immunodeficient mice using Matrigel with human umbilical vein endothelial cells form extensive vessel-like structures[88].

SHED also have the potential for hepatic differentiation, which can be improved by using liquorice or angelica extracts in the culture medium[89]. CD117+ SHED hepatically differentiated *in vitro* were used to repair either acute liver injury or induced secondary biliary cirrhosis in a rat model[90]. Meanwhile SHED or SHED-converted hepatocyte-like cell-based spheroids transplanted into a CCl4-induced chronic liver fibrosis mouse model improved hepatic dysfunction[91,92].

Furthermore, SHED can differentiate into epidermal cells and accelerate wound repair when seeded onto polyvinyl alcohol/silk fibroin nanofiber dressings[93]. CD117+ SHED also have the potential to differentiate toward all functional endocrine and exocrine subsets of pancreatic cells in serum-free conditions[94]. When cocultured with immortal corneal epithelium cells *in vitro*, SHED display the potential for transdifferentiation to corneal epithelium-like cells[95]. Li *et al*[96]indicated that SHED can transdifferentiate into retinal photoreceptor-like cells *in vitro* and retain good viability *in vivo* after transplantation into mice with a normal immune system[96]. Moreover, functional smooth muscle cells can be differentiated from SHED by TGF-β1 induction, while the ALK5 signaling pathway may regulate this process[97].

***SCAPs***

In 2020, Deng *et al*[98]reported that platelet derived growth factor BB promoted SCAPs osteogenic differentiation and enhanced bone formation in calvarial defects combined with a thermosensitive hydrogel[98]. Both conditioned culture medium containing traditional Chinese herbal remedy, Yunnan Baiyao, and high glucose α-Minimal Essential Medium can promote the odonto/osteogenic differentiation of SCAPs through the nuclear factor κB signaling pathway[99,100]. Depletion of lysine-specific demethylase 2A enhanced the adipogenic and chondrogenic differentiation potentials of SCAPs[101]. In 2020, Yang *et al*[102] reported that DLX5 and HOXC8 enhanced the expression of chondrogenic markers including type II collagen, type V collagen and sex-determining region Y box protein 9[102].

In 2017, Kim *et al*[103]first formed a three-dimensional cell-based nerve-like tissue with axons and myelin structures using SCAPs through a three-dimensional organotypic culture method[103]. The secreted frizzled-related protein 2, a Wnt signaling modulator, and insulin-like growth factor (IGF)-2 improved the neurogenic differentiation potential of SCAPs[104,105]. Adding graphene dispersion and water-soluble single-walled carbon nanotubes to the neuroinductive medium enhanced the neural differentiation of SCAPs[106].

SCAPs show angiogenic potential, and SCAPs and/or DPSCs transplanted in three-dimensional-printed hydroxyapatite scaffolds can form vascularized dentin/pulp-like tissue[107]. Coculture of human umbilical vein endothelial cells and SCAPs under hypoxic conditions promotes the construction of vessel-like structures *in vitro*, and ephrinB2 may play an important role in stabilizing the vascular-like structures[108,109]. Furthermore, erythropoietin enhances the endothelial differentiation of SCAPs[110]. In addition, SCAPs also have hepatogenic potential[111], and mesenchymal stem cells derived from dental papilla can also be differentiated into pancreatic β cell-like cells[69].

**MULTIPLE FACTORS INFLUENCING THE ODONTOGENIC/OSTEOGENIC DIFFERENTIATION OF DMSCs**

***MicroRNAs***

MicroRNAs (miRNAs) play important roles in regulating the tooth regeneration process (Table 1). Downregulation of miR-143-5p and miR-143-3p promotes the odontoblastic differentiation of DPSCs through the osteoprotegerin/receptor activator of nuclear factor κB ligand signaling pathway[112,113]. Acting *via* the p38 mitogen-activated protein kinases (MAPK) signaling pathway, downregulated miR-143-5p and miR-488 are capable of inducing DPSCs to differentiate into odontoblast-like cells by targeting MAPK14 and MAPK1, respectively[114,115]. Wang *et al*[116]found that miR-125a-3p regulates odontoblastic differentiation of DPSCs in an inflammation model by targeting Fyn, a member of the protein tyrosine kinase Src family[116].

Meanwhile miR-let-7c-5p can restore the osteogenic differentiation of inflamed DPSCs by suppressing the lipopolysaccharide (LPS)-induced inflammatory phenomena[117]. In inflamed pulp tissues, miR-223-3p is remarkably upregulated, and overexpression of miR-223-3p in DPSCs can increase the protein levels of dentine sialophosphoprotein (DSPP) and dentine matrix protein 1[118]. Sun *et al*[119]found that during LPS-mediated odontoblastic differentiation of DPSCs, the expression of miR-140-5p is markedly decreased, while when miR-140-5p is expressed in DPSCs after LPS treatment, the odontoblastic differentiation ability is inhibited[119].

Additionally, during odontogenesis of hDPSCs, the expression of miR-508-5p decreases gradually, while significant inhibition of odontogenesis is observed after overexpression of miR-508-5p, which targets glycoprotein nonmetastatic melanomal protein B[120]. Xu *et al*[121]reported that during odontoblast differentiation of DPSCs, the expression of miR-21 can be regulated by treating with TNF-α, while downregulation of miR-21 causes a decrease in the expression of dentine matrix protein 1 and DSPP by interacting with STAT3[121]. Moreover, miR-146a-5p promotes odontogenic/osteogenic differentiation of STRO-1+ DPSCs[122]. miR-143 suppresses the osteogenic differentiation of DPSCs by regulating the TNF-α/nuclear factor κB pathway[123], while miR-215 and miR-219a-1-3p inhibit the osteogenic differentiation capability of DPSCs by downregulation of heat shock protein B8[124].

During osteogenic differentiation of PDLSCs, the expression of miR-21 and miR-24-3p decrease, and their downregulation markedly inhibits osteogenesis of hPDLSCs by targeting SMAD family member 5 (Smad5)[125,126]. miR-21 also performs a positive function in mediating the stretch-induced osteogenic differentiation of hPDLSCs by regulating the expression of activin receptor type IIB[127]. Inhibition of miR-214 in PDLSCs can decrease osteogenic differentiation by targeting activating transcription factor 4 and regulating the Wnt/β-catenin signaling pathway[128,129]. Downregulation of miR-148a in PDLSCs rescues the inhibition of osteogenesis triggered by LPS stimulation[130]. miR-22 and miR-17 promote osteogenesis of PDLSCs by inhibiting HDAC6 and HDAC9 expression, respectively, the latter under inflammatory conditions[131,132]. In addition, in osteogenic differentiation of PDLSCs, miR-132 decreases, and overexpression of miR-132 inhibits osteogenesis by targeting growth differentiation factor 5 and activating the nuclear factor κB signaling pathway[133]. Meanwhile miR-31 plays a role in the high glucose-suppressed osteogenic differentiation of PDLSCs by targeting Satb2[134].

Upregulation of miR-34a in human fetal dental papilla cells increases the expression of DSPP and decreases the expression of alkaline phosphatase (ALP)[135]. In addition, miR-34a mimic transfection in SCAPs significantly upregulates odontogenic/osteogenic markers[136]. miR-hsa-let-7b suppresses the odontogenic/osteogenic differentiation of SCAPs partly by targeting matrix metalloproteinase 1[137]. Moreover, overexpression of miR-450a-5p or miR-28-5p in SHED supports osteogenesis[138]. miR-101 enhances osteogenic differentiation in human DFSCs[139], and miR-3940-5p promotes the osteo/dentinogenic differentiation of GMSCs[140].

***LncRNAs***

LncRNAs significantly regulate the multiple differentiations of mesenchymal stem cells, and there are several reports of the regulatory effect of lncRNAs in regenerative engineering of dental-tissue-derived stem cells (Table 2). In 2020, Liu *et al*[141] identified a total of 89 lncRNAs differentially expressed after osteo/odontogenic induction of hDPSCs, and downregulation of lncRNA SNHG7 was found to inhibit the differentiation of DPSCs, upregulating the expression of miR-1226-3p and miR-210-5p at the same time[141]. In 2020, Chen *et al*[142] reported that 132 lncRNAs were differentially expressed between the odontoblastic-differentiated and undifferentiated hDPSCs and that lncRNA-G043225 exerted a positive regulatory effect through miR-588 and fibrillin 1[142]. Additionally, 47 lncRNAs were differentially expressed in hDPSCs between normoxic and hypoxic induction conditions, and 561 lncRNAs were differentially expressed between young and old donors in hDPSCs after osteoinduction[143,144]. Overexpression of lncRNAs CCAT1 and lncRNA H19 promotes odontogenic differentiation of hDPSCs by inhibiting expression of miR-218 and regulating expression of the *DLX3* gene, respectively[145,146]. Knockdown of lncRNA STL and lncRNA X-inactive specific transcript inhibits the osteogenic potential of DPSCs, and the latter is essential for efficient osteogenic differentiation induced by TNF-α[143,147].

In 2016, Qu *et al*[148] demonstrated that 2171 lncRNAs were differentially expressed between osteogenic-differentiated and undifferentiated PDLSCs, and 393 lncRNAs were strongly associated with osteogenesis-related mRNAs[148]. Zheng *et al*[149] indicated that downregulation of lncRNA maternally-expressed 8 and lncRNA MIR22HG markedly suppressed the osteogenic differentiation of PDLSCs[149]. Knockdown of lncRNA maternally-expressed 3 inhibits the osteogenesis of PDLSCs in periodontitis *via* the miR-27a-3p/IGF1 axis, while it plays a positive role in human DFSCs by activating the Wnt/β-catenin signaling pathway[150,151]. In 2016, Wang *et al*[152] identified a novel lncRNA named lncRNA-POIR, while Xu *et al*[153] first named lncRNA-TWIST1 in 2019; both are osteogenesis impairment-related lncRNAs of PDLSCs from periodontitis patients and can enhance the osteogenic differentiation of PDLSCs from healthy individuals and periodontitis patients by interacting with miR-182 and inhibiting TWIST1 expression, respectively[152,153]. Prostate cancer-associated ncRNA transcript-1 upregulation reverses the suppression effect of osteogenic differentiation in PDLSCs caused by miR-106a-5p overexpression[154].

LncRNA FER1L4 and lncRNA X-inactive specific transcript can promote the osteogenesis of PDLSCs by sponging miR-874-3p and miR-214-3p, respectively[155,156]. In addition, downregulation of antidifferentiation noncoding RNA can facilitate the osteogenic differentiation of DPSCs, PDLSCs and SCAPs[157], while this regulatory effect on PDLSCs is related to the canonical Wnt signaling pathway[158]. The antidifferentiation noncoding RNA/miR-758/Notch2 axis may also participate[159]. Furthermore, lncRNA TUG1 improves osteogenic differentiation of PDLSCs by regulating the expression of lin-28 homolog A[160]. Knockdown of lncRNA differentiation antagonizing nonprotein coding RNA positively regulates the osteogenic differentiation of PDLSCs[161]. Moreover, lncRNA H19 overexpression promotes the osteo/odontogenesis of SCAPs *via* the lncRNA-H19/miR-141/SPAG9/MAPK positive feedback loop[162].

***Signaling pathways***

**Wnt signaling pathway:** The Wnt/β-catenin signaling pathway plays an important role in regulating DMSC differentiation, which is a key signaling pathway. For odontoblastic differentiation, activating the Wnt/β-catenin signaling pathway partially reverses the vacuolar protein sorting 4B knockdown-driven suppression of odontoblastic differentiation of hDPSCs[163] and rescues the osteoblastic/odontoblastic differentiation of stathmin-deletion hDPSCs[164]. These studies revealed that activation of the Wnt signaling pathway promotes osteogenic/odontoblastic differentiation of DPSCs. However, Scheller *et al*[165] first reported that Wnt/β-catenin inhibits odontoblastic differentiation of DPSCs in 2008[165]. The reason for the conflicting effects of Wnt signaling on odontoblastic differentiation in these studies is undefined and needs to be further explored. For osteoblastic differentiation, Rolph *et al*[166] confirmed that ferutinin promoted osteoblastic differentiation of DPSCs by modulating the Wnt/β-catenin signaling pathway[166] when Wnt5a was reported to inhibit osteoblastic differentiation of human periodontal ligament stem cell-like cells[167].

***MAPK signaling pathway***

The MAPK signaling pathway includes the ERK signaling pathway and the p38/MAPK signaling pathway[168]. In odontoblastic differentiation, one study showed that a combination of mineral trioxide aggregate and propolis significantly promoted the expression of DSPP and Dentine matrix protein 1 as well as mineralized nodule formation through activating the ERK signaling pathway in hDPSCs[169]. Kong *et al*[170] confirmed that a magnesium-enriched microenvironment enhanced the odontoblastic differentiation of hDPSCs by activating the ERK/BMP2/Smad signaling pathway[170]. In osteoblastic differentiation, berberine was reported to bind to epidermal growth factor receptor in hPDLSCs to activate the ERK signaling pathway and upregulate the nuclear-related gene FOS, thus promoting osteoblastic differentiation of PDLSCs[171]. In addition, mineral trioxide aggregate was confirmed to promote osteo/odontoblastic differentiation of SCAP through activation of the p38 and ERK signaling pathway. Another study showed that parathyroid hormone promoted the osteo/odontoblastic differentiation of DPSCs by activating the ERK and p38 signaling pathway[172].

***Mechanistic target of rapamycin signaling pathway***

Mechanistic target of rapamycin (mTOR), a highly conserved serine/threonine protein kinase, is involved in regulating interactions between proteins[173]. The mTOR signaling pathway has been confirmed to play a significant role in the osteo/odontoblastic differentiation of DMSCs. Tanaka *et al*[174] confirmed that inhibiting mTOR signaling promoted osteo/odontoblastic differentiation of SCAPs[174]. However, activation of the mTOR signaling pathway promoted osteogenic differentiation of hDPSCs in the process regulated by IGF-1 in which rapamycin blocked osteogenic differentiation induced by IGF-1[175] while inhibiting mTORC1 limited mineralized nodule formation by SHED[176]. Taken together, these data suggest that the mTOR signaling pathway plays different roles in different cell types of DMSCs.

***AKT signaling pathway***

The AKT signaling pathway is critical for cell proliferation, growth, metabolism and differentiation, especially in differentiation of DMSCs. Recent studies have shown that metformin and miR-let-7c-5p enhance the osteogenic differentiation of PDLSCs by activation of the AKT signaling pathway[117,177]. Another study reported that activation of the AKT signaling pathway could enhance the osteogenic differentiation of DPSCs in LPS-induced inflammation. In short, the AKT signaling pathway may play a positive role in odontogenic/osteogenic differentiation of DMSCs.

***Notch and shh signaling pathway***

The Notch signaling pathway is critical for development and cell differentiation. Notch signaling has been confirmed to inhibit odontoblastic differentiation of hDPSCs[178]. Interestingly, another study showed that overexpression of CCN3 activated the Notch signaling pathway to promote odontoblastic differentiation of DPSCs, which suggested that Notch signaling pathway activation promotes odontoblastic differentiation of DPSCs[179]. The reasons for these contradictory effects in odontoblastic differentiation of DPSCs remain undefined and need to be explored.

It is worth noting that the Shh signaling pathway is also involved in odontogenic/osteogenic differentiation of DMSCs. A recent study has shown that stathmin regulates odontogenic/osteogenic differentiation of DPSCs *via* the Shh signaling pathway[180].

***Inflammation***

In an inflammatory microenvironment, DMSCs from inflamed tissue contact and interact closely with extrinsic irritants, local cells or their components, immune cells and multiple soluble regulatory molecules[181]. For example, dental caries are one such gram-negative microbial infection that is primarily responsible for pulpal inflammation. LPS was used to create *in vitro* inflammatory conditions that initiate infection-stem cell interaction, which has been used widely to induce an inflammatory microenvironment[182].

Immunophenotyping of cell surface antigens by flow cytometry showed that DMSCs and inflamed DMSCs have similar expression patterns of surface markers[181,183]. The cells are positive for STRO-1, CD105, CD73, CD90, CD29 and CD44[184] and negative for CD45, CD34, CD14 and HLA-DR, indicating a mesenchymal stem cell phenotype[183,185-187]. In addition, inflamed DMSCs have the potential to differentiate into multiple lineages. Mesenchymal stem cells isolated from inflamed pulp possess stemness and multidifferentiation potential similar to DPSCs from healthy pulp[185]. Like DPSCs, inflamed DPSCs are capable of adipogenic and osteo/dentinogenic differentiation under the corresponding *in vitro* induction conditions. However, chronic inflammation impairs differentiation of DPSCs[188]. On the other hand, inflamed DPSCs show increased ALP and osteocalcin. In the inflammatory microenvironment, PDLSCs from inflamed periodontal tissue show higher proliferation rates but express lower levels of osteogenic differentiation markers[189-191]. Both inflamed hPDLSCs and hPDLSCs have been successfully differentiated under osteogenic and adipogenic conditions[192]. Because of evident similarities in their immunomodulatory properties, inflamed PDLSCs can provide a promising alternative to PDLSCs[193]. Cells isolated from human periapical cysts demonstrate a strong osteogenic but weak adipogenic capacity[184,194]. Osteogenic differentiation of inflamed DFSCs results in decreased ALP activity and alizarin red S staining compared to normal DFSCs[195]. Similarly, the osteogenic differentiation of LPS-treated DFSCs is suppressed, and the cells display low levels of TGF-β1 and high levels of TGF-β2.

***Aging***

Aging is an intricate degenerative process during which the regenerative capacity of MSCs progressively declines[196]. Unavoidably, DMSCs also undergo physiological age-related changes with declines in proliferation and osteo/odontogenic differentiation potentials with increased age[197,198]. Improving the performance of aging DMSCs is important for tissue regeneration engineering. Yi *et al*[144] demonstrated that the osteogenic potential of DPSCs from young donors was superior to that of those from old donors, and 304 mRNAs and 561 LncRNAs were differentially expressed between age-groups[144]. Wang *et al*[199] found that miR-433 may be one of the important senescence-related miRNAs of human dental pulp cells, which inhibits mineralization of human dental pulp cells by negatively regulating GRB2 and the RAS–MAPK signaling pathway[199]. SHED and DPSCs undergo senescence, including declines in the proliferation rate and osteogenic differentiation capability, following serial expansion from P4 to P20. SHED exhibit a better performance than DPSCs, which indicates that mineralization capacity is related to replicative senescence *in vitro* and to donor age[200].

As a significant factor regulating the function of differentiated odontoblasts[201], sclerostin advances the aging process of human dental pulp cells through the Wnt/β-catenin pathway and reduces the proliferation and odontoblastic differentiation capability of senescent human dental pulp cells[202]. The Wnt/β-catenin signaling pathway is one of the important pathways that regulates cell differentiation, increasing the osteogenic/dentinogenic differentiation potential of DPSCs[203]. It has been reported that the rate of dentin deposition and neurogenic differentiation potential declines with advanced age, which may be related to a decrease in endogenous Wnt/β-catenin signaling[204,205].

In 2014, Feng *et al*[206] compared the characteristics of DPSCs from five different age groups (5–12 years, 12–20 years, 20–35 years, 35–50 years and > 50 years) and found that the expression of p16INK4A markedly increased with age and inhibited osteogenic/odontogenic differentiation when upregulated[206]. Then in 2017, Mas-Bargues *et al*[207] indicated that p16INK4A also played a part in oxidative stress-related premature senescence of DPSCs caused by long-term culture in 21% ambient oxygen tension compared with 3%-6% physiological oxygen tension[207]. Replicative senescence of DPSCs resulted in decreases of B-lymphoma Mo-MLV insertion region 1, organic carbon, DSP and bone sialoprotein compared with rapidly proliferating cells and increases of p16INK4A, while B-lymphoma Mo-MLV insertion region 1 transduction promoted the expression of organic carbon and DSP, ALP activity and mineralized nodule formation. Therefore, this may indicate that the odontogenic differentiation potential of DPSCs weakens during senescence, partly due to decreased B-lymphoma Mo-MLV insertion region 1 expression[208].

In contrast, Ma *et al*[209] reported that adult DPSCs cultured in juvenile dental pulp cell-conditioned medium demonstrated decreased osteogenic differentiation capability, whereas juvenile DPSCs induced by adult dental pulp cell-conditioned medium showed improved osteogenic differentiation capability, indicating that the activity of DPSCs can be modulated by the extrinsic microenvironment[209]. A certain degree of inflammatory stimulation promoted the proliferation and mineralization of both adult and juvenile rat DPSCs, but this effect declined with age[210]. Furthermore, Horibe *et al*[211] isolated a type of mobilized dental pulp stem cells induced by granulocyte colony-stimulating factor from young and old donors, which showed minimal characteristic changes with aging, suggesting that mobilized dental pulp stem cells act as an advantaged source in dental pulp regeneration[211].

***Exosomes***

Exosomes are vesicles secreted by different cells with a diameter of 30–100 nm. They can function as carriers for different components to impact intercellular communication, including various miRNAs, lncRNAs and proteins. Exosomes play an important role in mediating some signaling pathways to influence the physiological function of cells. In recent years, increasing research into the effect of exosomes on the odontoblastic/osteogenic differentiation of DMSCs has been proposed (Figure 2).

In 2016, Huang *et al*[212] indicated that the exosomes derived from hDPSCs cultured with growth (DPSC-Exo) or odontogenic differentiation media (DPSC-OD-Exo) enhanced the odontogenic differentiation of DPSCs *in vitro*, and DPSC-OD-Exo showed stronger induction differentiation-inducing ability than exosomes derived from hDPSCs cultured with growth media in a three-dimensional environment consisting of type I collagen hydrogels and a tooth root-slice regeneration model[212]. In 2019, Hu *et al*[213]further identified the miRNA profile of human exosomes derived from hDPSCs cultured with growth media and DPSC-OD-Exo by miRNA sequencing, and the results indicated that miR-27a-5p was highly expressed in DPSC-OD-Exo, promoting odontogenic differentiation of DPSCs through the TGF-β1/Smad signaling pathway[213].

In 2019, Chew *et al*[214] reported that human MSC exosome-loaded collagen sponge used in an immunocompetent rat model with periodontal intrabony defects significantly repaired the defects by regenerating newly formed bone and periodontal ligament as a result of periodontal ligament cell migration and proliferation[214]. Meanwhile in 2020, Wang *et al*[215] reported that conditioned SHED-Exos derived from a 3 d osteogenic supernatant improved the osteogenic ability of PDLSCs by activating the BMP/Smad and Wnt/β-catenin signaling pathways and that BMP2 and Wnt3a carried by SHED-Exos played a pivotal part in this process[215].

Moreover, extracellular vesicles (EVs) are a type of mixed vesicles, consisting of endosome-derived exosomes and cell membrane-derived ectosomes. In 2017, Li *et al*[216] demonstrated that the EVs derived from Schwann cells promoted the osteogenic differentiation of hDPSCs[216]. In 2019, Čebatariūnienė *et al*[217] indicated that hPDLSC EVs did not influence osteogenic mineralization of PDLSCs but reversed the inhibitory effect on PDLSC osteogenic differentiation of an anti-TLR4 blocking Ab. They also revealed that the EVs may have a potential regulatory ability of genes related to osteogenesis and interfere with TLR4 signaling[217]. Additionally, Pizzicannella *et al*[218] reported that EVs derived from human GMSCs combined with a three-dimensional polylactide biomaterial enhanced the osteogenic differentiation of human GMSCs *in vitro*[218].

**CONCLUSION**

At present, most studies of the multidirectional differentiation of DMSCs focus on the following areas: the regeneration of teeth, bone, cartilage, tendon and blood vessels; the repair of nerve injury; the formation of retina and cornea; and the secretion of insulin. Different types of DMSCs have different abilities towards differentiation into diverse lineages. It is significant to explore the potential of DMSCs to differentiate into various tissues. In addition to the application of oral tissue regeneration, these studies are helpful to the future application of DMSCs in neurovascular injury-related diseases, retinal and corneal injury-related diseases and endocrine diseases such as diabetes. The induction of DMSCs to differentiate insulin-producing cells and neuron-like cells *in vitro* requires the conditioned-culture medium with a variety of auxiliary inducing factors, like some growth factors and peptides, and sometimes it needs to be induced in several steps, which takes a long time and is relatively complex. The cells induced by the conditioned culture medium express the specific molecules of related tissue-like cells. Researchers detect the specific expression molecules to determine whether the cells differentiate into specific tissue-like cells. Such *in vitro* differentiation is often limited and may not represent the true differentiation of the cell itself. It is of great significance to improve the induction mode and shorten the induction time for the application of DMSCs in the future. IN addition, combining DMSCs with materials possessing good biological compatibility may provide a better approach to tissue regeneration.

Making full use of the odontogenic/osteogenic differentiation ability of DMSCs is of great significance to the application of DMSCs in dental tissue regeneration engineering. In this review, some factors related to the regulation of DMSCs in odontogenic/osteogenic differentiation are reviewed. The regulation process of DMSC odontogenic/osteogenic differentiation is complex. A variety of non-coding RNAs and multiple signaling pathways participate in the differentiation process of DMSCs. The application of DMSCs should consider the donor age and cell aging. With increasing donor age and number of cell passages, differentiation ability may decrease accordingly. At the same time, the future clinical application of DMSCs should account for the impact of the inflammatory microenvironment. How to increase the anti-inflammatory ability of DMSCs is a difficult problem for clinical application of DMSCs in the future. In addition, exosomes, as a crucial medium for communication and transmission of information between cells, have become a hotspot in recent years. In the process of normal tooth development, exosomes also seem to play an important role in regulating gene expression of target cells through their rich and varied contents. Utilizing the characteristics of exosomes endocytosed by cells, discovering other exosomes or transforming contents to promote DMSC odontogenic/osteogenic differentiation will be a future research direction. If we can positively regulate the related factors that advance the odontogenic/osteogenic differentiation of DMSCs and make full use of their differentiation potential, there will be great progress in the application of DMSCs in dental tissue regeneration engineering. Future research should emphasize effectively combining the various types of DMSCs with odontogenic/osteogenic, neurogenic, vascularization and other multipotencies to provide a potential scheme for dental tissue regeneration with normal functions.

**REFERENCES**

1 **Han F**, Wang J, Ding L, Hu Y, Li W, Yuan Z, Guo Q, Zhu C, Yu L, Wang H, Zhao Z, Jia L, Li J, Yu Y, Zhang W, Chu G, Chen S, Li B. Tissue Engineering and Regenerative Medicine: Achievements, Future, and Sustainability in Asia. *Front Bioeng Biotechnol* 2020; **8**: 83 [PMID: 32266221 DOI: 10.3389/fbioe.2020.00083]

2 **Badylak SF**, Nerem RM. Progress in tissue engineering and regenerative medicine. *Proc Natl Acad Sci U S A* 2010; **107**: 3285-3286 [PMID: 20181571 DOI: 10.1073/pnas.1000256107]

3 **Ma L**, Makino Y, Yamaza H, Akiyama K, Hoshino Y, Song G, Kukita T, Nonaka K, Shi S, Yamaza T. Cryopreserved dental pulp tissues of exfoliated deciduous teeth is a feasible stem cell resource for regenerative medicine. *PLoS One* 2012; **7**: e51777 [PMID: 23251621 DOI: 10.1371/journal.pone.0051777]

4 **Nicola FDC**, Marques MR, Odorcyk F, Arcego DM, Petenuzzo L, Aristimunha D, Vizuete A, Sanches EF, Pereira DP, Maurmann N, Dalmaz C, Pranke P, Netto CA. Neuroprotector effect of stem cells from human exfoliated deciduous teeth transplanted after traumatic spinal cord injury involves inhibition of early neuronal apoptosis. *Brain Res* 2017; **1663**: 95-105 [PMID: 28322752 DOI: 10.1016/j.brainres.2017.03.015]

5 **Kanafi MM**, Rajeshwari YB, Gupta S, Dadheech N, Nair PD, Gupta PK, Bhonde RR. Transplantation of islet-like cell clusters derived from human dental pulp stem cells restores normoglycemia in diabetic mice. *Cytotherapy* 2013; **15**: 1228-1236 [PMID: 23845187 DOI: 10.1016/j.jcyt.2013.05.008]

6 **Pisciotta A**, Riccio M, Carnevale G, Lu A, De Biasi S, Gibellini L, La Sala GB, Bruzzesi G, Ferrari A, Huard J, De Pol A. Stem cells isolated from human dental pulp and amniotic fluid improve skeletal muscle histopathology in mdx/SCID mice. *Stem Cell Res Ther* 2015; **6**: 156 [PMID: 26316011 DOI: 10.1186/s13287-015-0141-y]

7 **Syed-Picard FN**, Du Y, Lathrop KL, Mann MM, Funderburgh ML, Funderburgh JL. Dental pulp stem cells: a new cellular resource for corneal stromal regeneration. *Stem Cells Transl Med* 2015; **4**: 276-285 [PMID: 25713466 DOI: 10.5966/sctm.2014-0115]

8 **Kong F**, Shi X, Xiao F, Yang Y, Zhang X, Wang LS, Wu CT, Wang H. Transplantation of Hepatocyte Growth Factor-Modified Dental Pulp Stem Cells Prevents Bone Loss in the Early Phase of Ovariectomy-Induced Osteoporosis. *Hum Gene Ther* 2018; **29**: 271-282 [PMID: 28950723 DOI: 10.1089/hum.2017.091]

9 **Mead B**, Hill LJ, Blanch RJ, Ward K, Logan A, Berry M, Leadbeater W, Scheven BA. Mesenchymal stromal cell-mediated neuroprotection and functional preservation of retinal ganglion cells in a rodent model of glaucoma. *Cytotherapy* 2016; **18**: 487-496 [PMID: 26897559 DOI: 10.1016/j.jcyt.2015.12.002]

10 **Yang C**, Li X, Sun L, Guo W, Tian W. Potential of human dental stem cells in repairing the complete transection of rat spinal cord. *J Neural Eng* 2017; **14**: 026005 [PMID: 28085005 DOI: 10.1088/1741-2552/aa596b]

11 **Sonoyama W**, Liu Y, Fang D, Yamaza T, Seo BM, Zhang C, Liu H, Gronthos S, Wang CY, Wang S, Shi S. Mesenchymal stem cell-mediated functional tooth regeneration in swine. *PLoS One* 2006; **1**: e79 [PMID: 17183711 DOI: 10.1371/journal.pone.0000079]

12 **Guo W**, Gong K, Shi H, Zhu G, He Y, Ding B, Wen L, Jin Y. Dental follicle cells and treated dentin matrix scaffold for tissue engineering the tooth root. *Biomaterials* 2012; **33**: 1291-1302 [PMID: 22088889 DOI: 10.1016/j.biomaterials.2011.09.068]

13 **Iohara K**, Murakami M, Takeuchi N, Osako Y, Ito M, Ishizaka R, Utunomiya S, Nakamura H, Matsushita K, Nakashima M. A Novel Combinatorial Therapy With Pulp Stem Cells and Granulocyte Colony-Stimulating Factor for Total Pulp Regeneration. *Stem Cells Transl Med* 2013; **2**: 818 [PMID: 28945010 DOI: 10.5966/sctm.2012-0132erratum]

14 **Gronthos S**, Mankani M, Brahim J, Robey PG, Shi S. Postnatal human dental pulp stem cells (DPSCs) *in vitro* and in vivo. *Proc Natl Acad Sci U S A* 2000; **97**: 13625-13630 [PMID: 11087820 DOI: 10.1073/pnas.240309797]

15 **Wongsupa N**, Nuntanaranont T, Kamolmattayakul S, Thuaksuban N. Assessment of bone regeneration of a tissue-engineered bone complex using human dental pulp stem cells/poly(ε-caprolactone)-biphasic calcium phosphate scaffold constructs in rabbit calvarial defects. *J Mater Sci Mater Med* 2017; **28**: 77 [PMID: 28386853 DOI: 10.1007/s10856-017-5883-x]

16 **Jin Q**, Yuan K, Lin W, Niu C, Ma R, Huang Z. Comparative characterization of mesenchymal stem cells from human dental pulp and adipose tissue for bone regeneration potential. *Artif Cells Nanomed Biotechnol* 2019; **47**: 1577-1584 [PMID: 31027424 DOI: 10.1080/21691401.2019.1594861]

17 **Hilkens P**, Gervois P, Fanton Y, Vanormelingen J, Martens W, Struys T, Politis C, Lambrichts I, Bronckaers A. Effect of isolation methodology on stem cell properties and multilineage differentiation potential of human dental pulp stem cells. *Cell Tissue Res* 2013; **353**: 65-78 [PMID: 23715720 DOI: 10.1007/s00441-013-1630-x]

18 **Rizk A**, Rabie AB. Human dental pulp stem cells expressing transforming growth factor β3 transgene for cartilage-like tissue engineering. *Cytotherapy* 2013; **15**: 712-725 [PMID: 23474328 DOI: 10.1016/j.jcyt.2013.01.012]

19 **Dai J**, Wang J, Lu J, Zou D, Sun H, Dong Y, Yu H, Zhang L, Yang T, Zhang X, Wang X, Shen G. The effect of co-culturing costal chondrocytes and dental pulp stem cells combined with exogenous FGF9 protein on chondrogenesis and ossification in engineered cartilage. *Biomaterials* 2012; **33**: 7699-7711 [PMID: 22841919 DOI: 10.1016/j.biomaterials.2012.07.020]

20 **Yanasse RH**, De Lábio RW, Marques L, Fukasawa JT, Segato R, Kinoshita A, Matsumoto MA, Felisbino SL, Solano B, Dos Santos RR, Payão SLM. Xenotransplantation of human dental pulp stem cells in platelet-rich plasma for the treatment of full-thickness articular cartilage defects in a rabbit model. *Exp Ther Med* 2019; **17**: 4344-4356 [PMID: 31186677 DOI: 10.3892/etm.2019.7499]

21 **Mata M**, Milian L, Oliver M, Zurriaga J, Sancho-Tello M, de Llano JJM, Carda C. *In Vivo* Articular Cartilage Regeneration Using Human Dental Pulp Stem Cells Cultured in an Alginate Scaffold: A Preliminary Study. *Stem Cells Int* 2017; **2017**: 8309256 [PMID: 28951745 DOI: 10.1155/2017/8309256]

22 **Chen YY**, He ST, Yan FH, Zhou PF, Luo K, Zhang YD, Xiao Y, Lin MK. Dental pulp stem cells express tendon markers under mechanical loading and are a potential cell source for tissue engineering of tendon-like tissue. *Int J Oral Sci* 2016; **8**: 213-222 [PMID: 27811845 DOI: 10.1038/ijos.2016.33]

23 **Luke AM**, Patnaik R, Kuriadom S, Abu-Fanas S, Mathew S, Shetty KP. Human dental pulp stem cells differentiation to neural cells, osteocytes and adipocytes-An *in vitro* study. *Heliyon* 2020; **6**: e03054 [PMID: 32042932 DOI: 10.1016/j.heliyon.2019.e03054]

24 **Rafiee F**, Pourteymourfard-Tabrizi Z, Mahmoudian-Sani MR, Mehri-Ghahfarrokhi A, Soltani A, Hashemzadeh-Chaleshtori M, Jami MS. Differentiation of dental pulp stem cells into neuron-like cells. *Int J Neurosci* 2020; **130**: 107-116 [PMID: 31599165 DOI: 10.1080/00207454.2019.1664518]

25 **Osathanon T**, Sawangmake C, Nowwarote N, Pavasant P. Neurogenic differentiation of human dental pulp stem cells using different induction protocols. *Oral Dis* 2014; **20**: 352-358 [PMID: 23651465 DOI: 10.1111/odi.12119]

26 **Zhang X**, Zhou Y, Li H, Wang R, Yang D, Li B, Cao X, Fu J. Transplanted Dental Pulp Stem Cells Migrate to Injured Area and Express Neural Markers in a Rat Model of Cerebral Ischemia. *Cell Physiol Biochem* 2018; **45**: 258-266 [PMID: 29402798 DOI: 10.1159/000486772]

27 **Sanen K**, Martens W, Georgiou M, Ameloot M, Lambrichts I, Phillips J. Engineered neural tissue with Schwann cell differentiated human dental pulp stem cells: potential for peripheral nerve repair? *J Tissue Eng Regen Med* 2017; **11**: 3362-3372 [PMID: 28052540 DOI: 10.1002/term.2249]

28 **Bray AF**, Cevallos RR, Gazarian K, Lamas M. Human dental pulp stem cells respond to cues from the rat retina and differentiate to express the retinal neuronal marker rhodopsin. *Neuroscience* 2014; **280**: 142-155 [PMID: 25242642 DOI: 10.1016/j.neuroscience.2014.09.023]

29 **Xu B**, Fan D, Zhao Y, Li J, Wang Z, Wang J, Wang X, Guan Z, Niu B. Three-Dimensional Culture Promotes the Differentiation of Human Dental Pulp Mesenchymal Stem Cells Into Insulin-Producing Cells for Improving the Diabetes Therapy. *Front Pharmacol* 2019; **10**: 1576 [PMID: 32038250 DOI: 10.3389/fphar.2019.01576]

30 **Yagi Mendoza H**, Yokoyama T, Tanaka T, Ii H, Yaegaki K. Regeneration of insulin-producing islets from dental pulp stem cells using a 3D culture system. *Regen Med* 2018; **13**: 673-687 [PMID: 30028236 DOI: 10.2217/rme-2018-0074]

31 **Sawangmake C**, Nowwarote N, Pavasant P, Chansiripornchai P, Osathanon T. A feasibility study of an *in vitro* differentiation potential toward insulin-producing cells by dental tissue-derived mesenchymal stem cells. *Biochem Biophys Res Commun* 2014; **452**: 581-587 [PMID: 25181343 DOI: 10.1016/j.bbrc.2014.08.121]

32 **Luzuriaga J**, Pastor-Alonso O, Encinas JM, Unda F, Ibarretxe G, Pineda JR. Human Dental Pulp Stem Cells Grown in Neurogenic Media Differentiate Into Endothelial Cells and Promote Neovasculogenesis in the Mouse Brain. *Front Physiol* 2019; **10**: 347 [PMID: 30984027 DOI: 10.3389/fphys.2019.00347]

33 **Gandia C**, Armiñan A, García-Verdugo JM, Lledó E, Ruiz A, Miñana MD, Sanchez-Torrijos J, Payá R, Mirabet V, Carbonell-Uberos F, Llop M, Montero JA, Sepúlveda P. Human dental pulp stem cells improve left ventricular function, induce angiogenesis, and reduce infarct size in rats with acute myocardial infarction. *Stem Cells* 2008; **26**: 638-645 [PMID: 18079433 DOI: 10.1634/stemcells.2007-0484]

34 **Song B**, Jiang W, Alraies A, Liu Q, Gudla V, Oni J, Wei X, Sloan A, Ni L, Agarwal M. Bladder Smooth Muscle Cells Differentiation from Dental Pulp Stem Cells: Future Potential for Bladder Tissue Engineering. *Stem Cells Int* 2016; **2016**: 6979368 [PMID: 26880982 DOI: 10.1155/2016/6979368]

35 **Jiang W**, Wang D, Alraies A, Liu Q, Zhu B, Sloan AJ, Ni L, Song B. Wnt-GSK3*β*/*β*-Catenin Regulates the Differentiation of Dental Pulp Stem Cells into Bladder Smooth Muscle Cells. *Stem Cells Int* 2019; **2019**: 8907570 [PMID: 30809265 DOI: 10.1155/2019/8907570]

36 **Ishkitiev N**, Yaegaki K, Imai T, Tanaka T, Nakahara T, Ishikawa H, Mitev V, Haapasalo M. High-purity hepatic lineage differentiated from dental pulp stem cells in serum-free medium. *J Endod* 2012; **38**: 475-480 [PMID: 22414832 DOI: 10.1016/j.joen.2011.12.011]

37 **Chen YK**, Huang AH, Chan AW, Lin LM. Human dental pulp stem cells derived from cryopreserved dental pulp tissues of vital extracted teeth with disease demonstrate hepatic-like differentiation. *J Tissue Eng Regen Med* 2016; **10**: 475-485 [PMID: 23950016 DOI: 10.1002/term.1763]

38 **Paino F**, Ricci G, De Rosa A, D'Aquino R, Laino L, Pirozzi G, Tirino V, Papaccio G. Ecto-mesenchymal stem cells from dental pulp are committed to differentiate into active melanocytes. *Eur Cell Mater* 2010; **20**: 295-305 [PMID: 20931491 DOI: 10.22203/ecm.v020a24]

39 **Kato T**, Hattori K, Deguchi T, Katsube Y, Matsumoto T, Ohgushi H, Numabe Y. Osteogenic potential of rat stromal cells derived from periodontal ligament. *J Tissue Eng Regen Med* 2011; **5**: 798-805 [PMID: 22002923 DOI: 10.1002/term.379]

40 **Ge S**, Zhao N, Wang L, Yu M, Liu H, Song A, Huang J, Wang G, Yang P. Bone repair by periodontal ligament stem cellseeded nanohydroxyapatite-chitosan scaffold. *Int J Nanomedicine* 2012; **7**: 5405-5414 [PMID: 23091383 DOI: 10.2147/IJN.S36714]

41 **Moshaverinia A**, Chen C, Xu X, Akiyama K, Ansari S, Zadeh HH, Shi S. Bone regeneration potential of stem cells derived from periodontal ligament or gingival tissue sources encapsulated in RGD-modified alginate scaffold. *Tissue Eng Part A* 2014; **20**: 611-621 [PMID: 24070211 DOI: 10.1089/ten.TEA.2013.0229]

42 **Moshaverinia A**, Xu X, Chen C, Akiyama K, Snead ML, Shi S. Dental mesenchymal stem cells encapsulated in an alginate hydrogel co-delivery microencapsulation system for cartilage regeneration. *Acta Biomater* 2013; **9**: 9343-9350 [PMID: 23891740 DOI: 10.1016/j.actbio.2013.07.023]

43 **Shen S**, Zhang Y, Zhang S, Wang B, Shang L, Shao J, Lin M, Cui Y, Sun S, Ge S. 6-Bromoindirubin-3'-oxime Promotes Osteogenic Differentiation of Periodontal Ligament Stem Cells and Facilitates Bone Regeneration in a Mouse Periodontitis Model. *ACS Biomater Sci Eng* 2021; **7**: 232-241 [PMID: 33320531 DOI: 10.1021/acsbiomaterials.0c01078]

44 **Li X**, Gong P, Liao D. In vitro neural/glial differentiation potential of periodontal ligament stem cells. *Arch Med Sci* 2010; **6**: 678-685 [PMID: 22419924 DOI: 10.5114/aoms.2010.17080]

45 **Fortino VR**, Chen RS, Pelaez D, Cheung HS. Neurogenesis of neural crest-derived periodontal ligament stem cells by EGF and bFGF. *J Cell Physiol* 2014; **229**: 479-488 [PMID: 24105823 DOI: 10.1002/jcp.24468]

46 **Liao D**, Li X, Dong Y, Sun G. The Role of Wnt/β-Catenin Signaling Pathway in the Transdifferentiation from Periodontal Ligament Stem Cells to Schwann Cells. *Cell Reprogram* 2017; **19**: 384-388 [PMID: 29215941 DOI: 10.1089/cell.2017.0017]

47 **Bueno C**, Martínez-Morga M, Martínez S. Non-proliferative neurogenesis in human periodontal ligament stem cells. *Sci Rep* 2019; **9**: 18038 [PMID: 31792338 DOI: 10.1038/s41598-019-54745-3]

48 **Caputi S**, Trubiani O, Sinjari B, Trofimova S, Diomede F, Linkova N, Diatlova A, Khavinson V. Effect of short peptides on neuronal differentiation of stem cells. *Int J Immunopathol Pharmacol* 2019; **33**: 2058738419828613 [PMID: 30791821 DOI: 10.1177/2058738419828613]

49 **Lanza Cariccio V**, Scionti D, Raffa A, Iori R, Pollastro F, Diomede F, Bramanti P, Trubiani O, Mazzon E. Treatment of Periodontal Ligament Stem Cells with MOR and CBD Promotes Cell Survival and Neuronal Differentiation *via* the PI3K/Akt/mTOR Pathway. *Int J Mol Sci* 2018; **19** [PMID: 30096889 DOI: 10.3390/ijms19082341]

50 **Romeo L**, Diomede F, Gugliandolo A, Scionti D, Lo Giudice F, Lanza Cariccio V, Iori R, Bramanti P, Trubiani O, Mazzon E. Moringin Induces Neural Differentiation in the Stem Cell of the Human Periodontal Ligament. *Sci Rep* 2018; **8**: 9153 [PMID: 29904155 DOI: 10.1038/s41598-018-27492-0]

51 **Li D**, Zou XY, El-Ayachi I, Romero LO, Yu Z, Iglesias-Linares A, Cordero-Morales JF, Huang GT. Human Dental Pulp Stem Cells and Gingival Mesenchymal Stem Cells Display Action Potential Capacity In Vitro after Neuronogenic Differentiation. *Stem Cell Rev Rep* 2019; **15**: 67-81 [PMID: 30324358 DOI: 10.1007/s12015-018-9854-5]

52 **Gugliandolo A**, Diomede F, Scionti D, Bramanti P, Trubiani O, Mazzon E. The Role of Hypoxia on the Neuronal Differentiation of Gingival Mesenchymal Stem Cells: A Transcriptional Study. *Cell Transplant* 2019; **28**: 538-552 [PMID: 30642188 DOI: 10.1177/0963689718814470]

53 **Rajan TS**, Scionti D, Diomede F, Piattelli A, Bramanti P, Mazzon E, Trubiani O. Prolonged Expansion Induces Spontaneous Neural Progenitor Differentiation from Human Gingiva-Derived Mesenchymal Stem Cells. *Cell Reprogram* 2017; **19**: 389-401 [PMID: 29058474 DOI: 10.1089/cell.2017.0012]

54 **Ansari S**, Diniz IM, Chen C, Sarrion P, Tamayol A, Wu BM, Moshaverinia A. Human Periodontal Ligament- and Gingiva-derived Mesenchymal Stem Cells Promote Nerve Regeneration When Encapsulated in Alginate/Hyaluronic Acid 3D Scaffold. *Adv Healthc Mater* 2017; **6** [PMID: 29076281 DOI: 10.1002/adhm.201700670]

55 **Yam GH**, Teo EP, Setiawan M, Lovatt MJ, Yusoff NZBM, Fuest M, Goh BT, Mehta JS. Postnatal periodontal ligament as a novel adult stem cell source for regenerative corneal cell therapy. *J Cell Mol Med* 2018; **22**: 3119-3132 [PMID: 29536619 DOI: 10.1111/jcmm.13589]

56 **Chen J**, Zhang W, Kelk P, Backman LJ, Danielson P. Substance P and patterned silk biomaterial stimulate periodontal ligament stem cells to form corneal stroma in a bioengineered three-dimensional model. *Stem Cell Res Ther* 2017; **8**: 260 [PMID: 29132420 DOI: 10.1186/s13287-017-0715-y]

57 **Huang L**, Liang J, Geng Y, Tsang WM, Yao X, Jhanji V, Zhang M, Cheung HS, Pang CP, Yam GH. Directing adult human periodontal ligament-derived stem cells to retinal fate. *Invest Ophthalmol Vis Sci* 2013; **54**: 3965-3974 [PMID: 23661377 DOI: 10.1167/iovs.13-11910]

58 **Lee JS**, An SY, Kwon IK, Heo JS. Transdifferentiation of human periodontal ligament stem cells into pancreatic cell lineage. *Cell Biochem Funct* 2014; **32**: 605-611 [PMID: 25187163 DOI: 10.1002/cbf.3057]

59 **Moshaverinia A**, Xu X, Chen C, Ansari S, Zadeh HH, Snead ML, Shi S. Application of stem cells derived from the periodontal ligament or gingival tissue sources for tendon tissue regeneration. *Biomaterials* 2014; **35**: 2642-2650 [PMID: 24397989 DOI: 10.1016/j.biomaterials.2013.12.053]

60 **Murugan Girija D**, Kalachaveedu M, Ranga Rao S, Subbarayan R. Transdifferentiation of human gingival mesenchymal stem cells into functional keratinocytes by Acalypha indica in three-dimensional microenvironment. *J Cell Physiol* 2018; **233**: 8450-8457 [PMID: 29923273 DOI: 10.1002/jcp.26807]

61 **Takahashi K**, Ogura N, Aonuma H, Ito K, Ishigami D, Kamino Y, Kondoh T. Bone morphogenetic protein 6 stimulates mineralization in human dental follicle cells without dexamethasone. *Arch Oral Biol* 2013; **58**: 690-698 [PMID: 23317773 DOI: 10.1016/j.archoralbio.2012.10.018]

62 **Okada H**, Takahashi K, Ogura N, Tomoki R, Ito K, Kondoh T. Plasma rich in growth factors stimulates proliferation, migration, and gene expression associated with bone formation in human dental follicle cells. *J Dent Sci* 2016; **11**: 245-252 [PMID: 30894980 DOI: 10.1016/j.jds.2015.12.001]

63 **Uribe P**, Johansson A, Jugdaohsingh R, Powell JJ, Magnusson C, Davila M, Westerlund A, Ransjö M. Soluble silica stimulates osteogenic differentiation and gap junction communication in human dental follicle cells. *Sci Rep* 2020; **10**: 9923 [PMID: 32555274 DOI: 10.1038/s41598-020-66939-1]

64 **Lucaciu O**, Soriţău O, Gheban D, Ciuca DR, Virtic O, Vulpoi A, Dirzu N, Câmpian R, Băciuţ G, Popa C, Simon S, Berce P, Băciuţ M, Crisan B. Dental follicle stem cells in bone regeneration on titanium implants. *BMC Biotechnol* 2015; **15**: 114 [PMID: 26718927 DOI: 10.1186/s12896-015-0229-6]

65 **Rezai-Rad M**, Bova JF, Orooji M, Pepping J, Qureshi A, Del Piero F, Hayes D, Yao S. Evaluation of bone regeneration potential of dental follicle stem cells for treatment of craniofacial defects. *Cytotherapy* 2015; **17**: 1572-1581 [PMID: 26342992 DOI: 10.1016/j.jcyt.2015.07.013]

66 **Kanao S**, Ogura N, Takahashi K, Ito K, Suemitsu M, Kuyama K, Kondoh T. Capacity of Human Dental Follicle Cells to Differentiate into Neural Cells *In Vitro*. *Stem Cells Int* 2017; **2017**: 8371326 [PMID: 28261273 DOI: 10.1155/2017/8371326]

67 **Völlner F**, Ernst W, Driemel O, Morsczeck C. A two-step strategy for neuronal differentiation *in vitro* of human dental follicle cells. *Differentiation* 2009; **77**: 433-441 [PMID: 19394129 DOI: 10.1016/j.diff.2009.03.002]

68 **Sung IY**, Son HN, Ullah I, Bharti D, Park JM, Cho YC, Byun JH, Kang YH, Sung SJ, Kim JW, Rho GJ, Park BW. Cardiomyogenic Differentiation of Human Dental Follicle-derived Stem Cells by Suberoylanilide Hydroxamic Acid and Their *In Vivo* Homing Property. *Int J Med Sci* 2016; **13**: 841-852 [PMID: 27877076 DOI: 10.7150/ijms.16573]

69 **Shivakumar SB**, Lee HJ, Son YB, Bharti D, Ock SA, Lee SL, Kang YH, Park BW, Rho GJ. *In vitro* differentiation of single donor derived human dental mesenchymal stem cells into pancreatic β cell-like cells. *Biosci Rep* 2019; **39** [PMID: 31015367 DOI: 10.1042/BSR20182051]

70 **Xu QL**, Furuhashi A, Zhang QZ, Jiang CM, Chang TH, Le AD. Induction of Salivary Gland-Like Cells from Dental Follicle Epithelial Cells. *J Dent Res* 2017; **96**: 1035-1043 [PMID: 28541773 DOI: 10.1177/0022034517711146]

71 **Prahasanti C**, Subrata LH, Saskianti T, Suardita K, Ernawati DS. Combined Hydroxyapatite Scaffold and Stem Cell from Human Exfoliated Deciduous Teeth Modulating Alveolar Bone Regeneration *via* Regulating Receptor Activator of Nuclear Factor-Κb and Osteoprotegerin System. *Iran J Med Sci* 2019; **44**: 415-421 [PMID: 31582866 DOI: 10.30476/IJMS.2019.44962]

72 **Sebastian AA**, Kannan TP, Norazmi MN, Nurul AA. Interleukin-17A promotes osteogenic differentiation by increasing OPG/RANKL ratio in stem cells from human exfoliated deciduous teeth (SHED). *J Tissue Eng Regen Med* 2018; **12**: 1856-1866 [PMID: 29774992 DOI: 10.1002/term.2706]

73 **Novais A**, Lesieur J, Sadoine J, Slimani L, Baroukh B, Saubaméa B, Schmitt A, Vital S, Poliard A, Hélary C, Rochefort GY, Chaussain C, Gorin C. Priming Dental Pulp Stem Cells from Human Exfoliated Deciduous Teeth with Fibroblast Growth Factor-2 Enhances Mineralization Within Tissue-Engineered Constructs Implanted in Craniofacial Bone Defects. *Stem Cells Transl Med* 2019; **8**: 844-857 [PMID: 31016898 DOI: 10.1002/sctm.18-0182]

74 **Yang X**, Zhao Q, Chen J, Liu J, Lin J, Lu J, Li W, Yu D, Zhao W. Graphene Oxide Quantum Dots Promote Osteogenic Differentiation of Stem Cells from Human Exfoliated Deciduous Teeth *via* the Wnt/*β*-Catenin Signaling Pathway. *Stem Cells Int* 2021; **2021**: 8876745 [PMID: 33628273 DOI: 10.1155/2021/8876745]

75 **Chen K**, Xiong H, Xu N, Shen Y, Huang Y, Liu C. Chondrogenic potential of stem cells from human exfoliated deciduous teeth *in vitro* and in vivo. *Acta Odontol Scand* 2014; **72**: 664-672 [PMID: 24580092 DOI: 10.3109/00016357.2014.888756]

76 **Nourbakhsh N**, Soleimani M, Taghipour Z, Karbalaie K, Mousavi SB, Talebi A, Nadali F, Tanhaei S, Kiyani GA, Nematollahi M, Rabiei F, Mardani M, Bahramiyan H, Torabinejad M, Nasr-Esfahani MH, Baharvand H. Induced *in vitro* differentiation of neural-like cells from human exfoliated deciduous teeth-derived stem cells. *Int J Dev Biol* 2011; **55**: 189-195 [PMID: 21671222 DOI: 10.1387/ijdb.103090nn]

77 **Jarmalavičiūtė A**, Tunaitis V, Strainienė E, Aldonytė R, Ramanavičius A, Venalis A, Magnusson KE, Pivoriūnas A. A New Experimental Model for Neuronal and Glial Differentiation Using Stem Cells Derived from Human Exfoliated Deciduous Teeth. *J Mol Neurosci* 2013 [PMID: 23797732 DOI: 10.1007/s12031-013-0046-0]

78 **Yang S**, Xin C, Zhang B, Zhang H, Hao Y. Synergistic effects of Rho kinase inhibitor Y-27632 and Noggin overexpression on the proliferation and neuron-like cell differentiation of stem cells derived from human exfoliated deciduous teeth. *IUBMB Life* 2020; **72**: 665-676 [PMID: 31889420 DOI: 10.1002/iub.2208]

79 **Liu J**, Zhang ZY, Yu H, Yang AP, Hu PF, Liu Z, Wang M. Long noncoding RNA C21orf121/bone morphogenetic protein 2/microRNA-140-5p gene network promotes directed differentiation of stem cells from human exfoliated deciduous teeth to neuronal cells. *J Cell Biochem* 2018 [PMID: 30317665 DOI: 10.1002/jcb.27313]

80 **Pereira LV**, Bento RF, Cruz DB, Marchi C, Salomone R, Oiticicca J, Costa MP, Haddad LA, Mingroni-Netto RC, Costa HJZR. Stem Cells from Human Exfoliated Deciduous Teeth (SHED) Differentiate *in vivo* and Promote Facial Nerve Regeneration. *Cell Transplant* 2019; **28**: 55-64 [PMID: 30380914 DOI: 10.1177/0963689718809090]

81 **Zhang N**, Lu X, Wu S, Li X, Duan J, Chen C, Wang W, Song H, Tong J, Li S, Liu Y, Kang X, Wang X, Han F. Intrastriatal transplantation of stem cells from human exfoliated deciduous teeth reduces motor defects in Parkinsonian rats. *Cytotherapy* 2018; **20**: 670-686 [PMID: 29576501 DOI: 10.1016/j.jcyt.2018.02.371]

82 **Taghipour Z**, Karbalaie K, Kiani A, Niapour A, Bahramian H, Nasr-Esfahani MH, Baharvand H. Transplantation of undifferentiated and induced human exfoliated deciduous teeth-derived stem cells promote functional recovery of rat spinal cord contusion injury model. *Stem Cells Dev* 2012; **21**: 1794-1802 [PMID: 21970342 DOI: 10.1089/scd.2011.0408]

83 **Xie J**, Rao N, Zhai Y, Li J, Zhao Y, Ge L, Wang Y. Therapeutic effects of stem cells from human exfoliated deciduous teeth on diabetic peripheral neuropathy. *Diabetol Metab Syndr* 2019; **11**: 38 [PMID: 31131042 DOI: 10.1186/s13098-019-0433-y]

84 **Sakai VT**, Zhang Z, Dong Z, Neiva KG, Machado MA, Shi S, Santos CF, Nör JE. SHED differentiate into functional odontoblasts and endothelium. *J Dent Res* 2010; **89**: 791-796 [PMID: 20395410 DOI: 10.1177/0022034510368647]

85 **Gong T**, Heng BC, Xu J, Zhu S, Yuan C, Lo EC, Zhang C. Decellularized extracellular matrix of human umbilical vein endothelial cells promotes endothelial differentiation of stem cells from exfoliated deciduous teeth. *J Biomed Mater Res A* 2017; **105**: 1083-1093 [PMID: 28076902 DOI: 10.1002/jbm.a.36003]

86 **Wang P**, Zhu S, Yuan C, Wang L, Xu J, Liu Z. Shear stress promotes differentiation of stem cells from human exfoliated deciduous teeth into endothelial cells *via* the downstream pathway of VEGF-Notch signaling. *Int J Mol Med* 2018; **42**: 1827-1836 [PMID: 30015843 DOI: 10.3892/ijmm.2018.3761]

87 **Xu JG**, Gong T, Wang YY, Zou T, Heng BC, Yang YQ, Zhang CF. Inhibition of TGF-β Signaling in SHED Enhances Endothelial Differentiation. *J Dent Res* 2018; **97**: 218-225 [PMID: 28972822 DOI: 10.1177/0022034517733741]

88 **Kim JH**, Kim GH, Kim JW, Pyeon HJ, Lee JC, Lee G, Nam H. *In Vivo* Angiogenic Capacity of Stem Cells from Human Exfoliated Deciduous Teeth with Human Umbilical Vein Endothelial Cells. *Mol Cells* 2016; **39**: 790-796 [PMID: 27871176 DOI: 10.14348/molcells.2016.0131]

89 **Su WT**, Chen XW. Stem cells from human exfoliated deciduous teeth differentiate into functional hepatocyte-like cells by herbal medicine. *Biomed Mater Eng* 2014; **24**: 2243-2247 [PMID: 25226923 DOI: 10.3233/BME-141036]

90 **Ishkitiev N**, Yaegaki K, Imai T, Tanaka T, Fushimi N, Mitev V, Okada M, Tominaga N, Ono S, Ishikawa H. Novel management of acute or secondary biliary liver conditions using hepatically differentiated human dental pulp cells. *Tissue Eng Part A* 2015; **21**: 586-593 [PMID: 25234861 DOI: 10.1089/ten.TEA.2014.0162]

91 **Yamaza T**, Alatas FS, Yuniartha R, Yamaza H, Fujiyoshi JK, Yanagi Y, Yoshimaru K, Hayashida M, Matsuura T, Aijima R, Ihara K, Ohga S, Shi S, Nonaka K, Taguchi T. In vivo hepatogenic capacity and therapeutic potential of stem cells from human exfoliated deciduous teeth in liver fibrosis in mice. *Stem Cell Res Ther* 2015; **6**: 171 [PMID: 26358689 DOI: 10.1186/s13287-015-0154-6]

92 **Takahashi Y**, Yuniartha R, Yamaza T, Sonoda S, Yamaza H, Kirino K, Yoshimaru K, Matsuura T, Taguchi T. Therapeutic potential of spheroids of stem cells from human exfoliated deciduous teeth for chronic liver fibrosis and hemophilia A. *Pediatr Surg Int* 2019; **35**: 1379-1388 [PMID: 31552493 DOI: 10.1007/s00383-019-04564-4]

93 **Huang TY**, Wang GS, Tseng CC, Su WT. Epidermal cells differentiated from stem cells from human exfoliated deciduous teeth and seeded onto polyvinyl alcohol/silk fibroin nanofiber dressings accelerate wound repair. *Mater Sci Eng C Mater Biol Appl* 2019; **104**: 109986 [PMID: 31499995 DOI: 10.1016/j.msec.2019.109986]

94 **Ishkitiev N**, Yaegaki K, Kozhuharova A, Tanaka T, Okada M, Mitev V, Fukuda M, Imai T. Pancreatic differentiation of human dental pulp CD117⁺ stem cells. *Regen Med* 2013; **8**: 597-612 [PMID: 23998753 DOI: 10.2217/rme.13.42]

95 **Tsai CL**, Chuang PC, Kuo HK, Chen YH, Su WH, Wu PC. Differentiation of Stem Cells From Human Exfoliated Deciduous Teeth Toward a Phenotype of Corneal Epithelium In Vitro. *Cornea* 2015; **34**: 1471-1477 [PMID: 26165791 DOI: 10.1097/ICO.0000000000000532]

96 **Li X**, Xie J, Zhai Y, Fang T, Rao N, Hu S, Yang L, Zhao Y, Wang Y, Ge L. Differentiation of Stem Cells from Human Exfoliated Deciduous Teeth into Retinal Photoreceptor-Like Cells and Their Sustainability *In Vivo*. *Stem Cells Int* 2019; **2019**: 2562981 [PMID: 30906327 DOI: 10.1155/2019/2562981]

97 **Xu JG**, Zhu SY, Heng BC, Dissanayaka WL, Zhang CF. TGF-β1-induced differentiation of SHED into functional smooth muscle cells. *Stem Cell Res Ther* 2017; **8**: 10 [PMID: 28114966 DOI: 10.1186/s13287-016-0459-0]

98 **Deng J**, Pan J, Han X, Yu L, Chen J, Zhang W, Zhu L, Huang W, Liu S, You Z, Liu Y. PDGFBB-modified stem cells from apical papilla and thermosensitive hydrogel scaffolds induced bone regeneration. *Chem Biol Interact* 2020; **316**: 108931 [PMID: 31874163 DOI: 10.1016/j.cbi.2019.108931]

99 **Pang X**, Wang Y, Wu J, Zhou Z, Xu T, Jin L, Yu Y, Li Z, Gobin R, Xue C, Yu J. Yunnan Baiyao Conditioned Medium Promotes the Odonto/Osteogenic Capacity of Stem Cells from Apical Papilla *via* Nuclear Factor Kappa B Signaling Pathway. *Biomed Res Int* 2019; **2019**: 9327386 [PMID: 31179335 DOI: 10.1155/2019/9327386]

100 **Wang Y**, Wang Y, Lu Y, Yu J. High Glucose Enhances the Odonto/Osteogenic Differentiation of Stem Cells from Apical Papilla *via* NF-KappaB Signaling Pathway. *Biomed Res Int* 2019; **2019**: 5068258 [PMID: 31080819 DOI: 10.1155/2019/5068258]

101 **Dong R**, Yao R, Du J, Wang S, Fan Z. Depletion of histone demethylase KDM2A enhanced the adipogenic and chondrogenic differentiation potentials of stem cells from apical papilla. *Exp Cell Res* 2013; **319**: 2874-2882 [PMID: 23872478 DOI: 10.1016/j.yexcr.2013.07.008]

102 **Yang H**, Cao Y, Zhang J, Liang Y, Su X, Zhang C, Liu H, Han X, Ge L, Fan Z. DLX5 and HOXC8 enhance the chondrogenic differentiation potential of stem cells from apical papilla *via* LINC01013. *Stem Cell Res Ther* 2020; **11**: 271 [PMID: 32631410 DOI: 10.1186/s13287-020-01791-8]

103 **Kim BC**, Jun SM, Kim SY, Kwon YD, Choe SC, Kim EC, Lee JH, Kim J, Suh JF, Hwang YS. Engineering three dimensional micro nerve tissue using postnatal stem cells from human dental apical papilla. *Biotechnol Bioeng* 2017; **114**: 903-914 [PMID: 27775170 DOI: 10.1002/bit.26205]

104 **Lin X**, Dong R, Diao S, Yu G, Wang L, Li J, Fan Z. SFRP2 enhanced the adipogenic and neuronal differentiation potentials of stem cells from apical papilla. *Cell Biol Int* 2017; **41**: 534-543 [PMID: 28244619 DOI: 10.1002/cbin.10757]

105 **Diao S**, Yang H, Cao Y, Yang D, Fan Z. IGF2 enhanced the osteo-/dentinogenic and neurogenic differentiation potentials of stem cells from apical papilla. *J Oral Rehabil* 2020; **47 Suppl 1**: 55-65 [PMID: 31291686 DOI: 10.1111/joor.12859]

106 **Simonovic J**, Toljic B, Nikolic N, Peric M, Vujin J, Panajotovic R, Gajic R, Bekyarova E, Cataldi A, Parpura V, Milasin J. Differentiation of stem cells from apical papilla into neural lineage using graphene dispersion and single walled carbon nanotubes. *J Biomed Mater Res A* 2018; **106**: 2653-2661 [PMID: 29896770 DOI: 10.1002/jbm.a.36461]

107 **Hilkens P**, Bronckaers A, Ratajczak J, Gervois P, Wolfs E, Lambrichts I. The Angiogenic Potential of DPSCs and SCAPs in an *In Vivo* Model of Dental Pulp Regeneration. *Stem Cells Int* 2017; **2017**: 2582080 [PMID: 29018483 DOI: 10.1155/2017/2582080]

108 **Yuan C**, Wang P, Zhu L, Dissanayaka WL, Green DW, Tong EH, Jin L, Zhang C. Coculture of stem cells from apical papilla and human umbilical vein endothelial cell under hypoxia increases the formation of three-dimensional vessel-like structures in vitro. *Tissue Eng Part A* 2015; **21**: 1163-1172 [PMID: 25380198 DOI: 10.1089/ten.TEA.2014.0058]

109 **Yuan C**, Wang P, Zhu S, Zou T, Wang S, Xu J, Heng BC, Diogenes A, Zhang C. EphrinB2 Stabilizes Vascularlike Structures Generated by Endothelial Cells and Stem Cells from Apical Papilla. *J Endod* 2016; **42**: 1362-1370 [PMID: 27451120 DOI: 10.1016/j.joen.2016.05.012]

110 **Koutsoumparis A**, Vassili A, Bakopoulou A, Ziouta A, Tsiftsoglou AS. Erythropoietin (rhEPOa) promotes endothelial transdifferentiation of stem cells of the apical papilla (SCAP). *Arch Oral Biol* 2018; **96**: 96-103 [PMID: 30205239 DOI: 10.1016/j.archoralbio.2018.09.001]

111 **Kumar A**, Kumar V, Rattan V, Jha V, Pal A, Bhattacharyya S. Molecular spectrum of secretome regulates the relative hepatogenic potential of mesenchymal stem cells from bone marrow and dental tissue. *Sci Rep* 2017; **7**: 15015 [PMID: 29118330 DOI: 10.1038/s41598-017-14358-0]

112 **Zhan FL**, Liu XY, Wang XB. The Role of MicroRNA-143-5p in the Differentiation of Dental Pulp Stem Cells into Odontoblasts by Targeting Runx2 *via* the OPG/RANKL Signaling Pathway. *J Cell Biochem* 2018; **119**: 536-546 [PMID: 28608628 DOI: 10.1002/jcb.26212]

113 **Yang C**, Jia R, Zuo Q, Zheng Y, Wu Q, Luo B, Lin P, Yin L. microRNA-143-3p regulates odontogenic differentiation of human dental pulp stem cells through regulation of the osteoprotegerin-RANK ligand pathway by targeting RANK. *Exp Physiol* 2020; **105**: 876-885 [PMID: 32052500 DOI: 10.1113/EP087992]

114 **Wang BL**, Wang Z, Nan X, Zhang QC, Liu W. Downregulation of microRNA-143-5p is required for the promotion of odontoblasts differentiation of human dental pulp stem cells through the activation of the mitogen-activated protein kinases 14-dependent p38 mitogen-activated protein kinases signaling pathway. *J Cell Physiol* 2019; **234**: 4840-4850 [PMID: 30362514 DOI: 10.1002/jcp.27282]

115 **Yu D**, Zhao X, Cheng JZ, Wang D, Zhang HH, Han GH. Downregulated microRNA-488 enhances odontoblast differentiation of human dental pulp stem cells *via* activation of the p38 MAPK signaling pathway. *J Cell Physiol* 2019; **234**: 1442-1451 [PMID: 30132853 DOI: 10.1002/jcp.26950]

116 **Wang J**, Zheng Y, Bai B, Song Y, Zheng K, Xiao J, Liang Y, Bao L, Zhou Q, Ji L, Feng X. MicroRNA-125a-3p participates in odontoblastic differentiation of dental pulp stem cells by targeting Fyn. *Cytotechnology* 2020; **72**: 69-79 [PMID: 31953701 DOI: 10.1007/s10616-019-00358-7]

117 **Yuan H**, Zhao H, Wang J, Zhang H, Hong L, Li H, Che H, Zhang Z. MicroRNA let-7c-5p promotes osteogenic differentiation of dental pulp stem cells by inhibiting lipopolysaccharide-induced inflammation *via* HMGA2/PI3K/Akt signal blockade. *Clin Exp Pharmacol Physiol* 2019; **46**: 389-397 [PMID: 30575977 DOI: 10.1111/1440-1681.13059]

118 **Huang X**, Liu F, Hou J, Chen K. Inflammation-induced overexpression of microRNA-223-3p regulates odontoblastic differentiation of human dental pulp stem cells by targeting SMAD3. *Int Endod J* 2019; **52**: 491-503 [PMID: 30368846 DOI: 10.1111/iej.13032]

119 **Sun DG**, Xin BC, Wu D, Zhou L, Wu HB, Gong W, Lv J. miR-140-5p-mediated regulation of the proliferation and differentiation of human dental pulp stem cells occurs through the lipopolysaccharide/toll-like receptor 4 signaling pathway. *Eur J Oral Sci* 2017; **125**: 419-425 [PMID: 29130547 DOI: 10.1111/eos.12384]

120 **Liu F**, Wang X, Yang Y, Hu R, Wang W, Wang Y. The suppressive effects of miR-508-5p on the odontogenic differentiation of human dental pulp stem cells by targeting glycoprotein non-metastatic melanomal protein B. *Stem Cell Res Ther* 2019; **10**: 35 [PMID: 30670091 DOI: 10.1186/s13287-019-1146-8]

121 **Xu K**, Xiao J, Zheng K, Feng X, Zhang J, Song D, Wang C, Shen X, Zhao X, Wei C, Huang D, Feng G. MiR-21/STAT3 Signal Is Involved in Odontoblast Differentiation of Human Dental Pulp Stem Cells Mediated by TNF-α. *Cell Reprogram* 2018; **20**: 107-116 [PMID: 29620442 DOI: 10.1089/cell.2017.0042]

122 **Qiu Z**, Lin S, Hu X, Zeng J, Xiao T, Ke Z, Lv H. Involvement of miR-146a-5p/neurogenic locus notch homolog protein 1 in the proliferation and differentiation of STRO-1+ human dental pulp stem cells. *Eur J Oral Sci* 2019; **127**: 294-303 [PMID: 31216106 DOI: 10.1111/eos.12624]

123 **Zhang P**, Yang W, Wang G, Li Y. miR-143 suppresses the osteogenic differentiation of dental pulp stem cells by inactivation of NF-κB signaling pathway *via* targeting TNF-α. *Arch Oral Biol* 2018; **87**: 172-179 [PMID: 29306073 DOI: 10.1016/j.archoralbio.2017.12.031]

124 **Yao S**, Li C, Budenski AM, Li P, Ramos A, Guo S. Expression of microRNAs targeting heat shock protein B8 during *in vitro* expansion of dental pulp stem cells in regulating osteogenic differentiation. *Arch Oral Biol* 2019; **107**: 104485 [PMID: 31376703 DOI: 10.1016/j.archoralbio.2019.104485]

125 **Wei F**, Yang S, Guo Q, Zhang X, Ren D, Lv T, Xu X. MicroRNA-21 regulates Osteogenic Differentiation of Periodontal Ligament Stem Cells by targeting Smad5. *Sci Rep* 2017; **7**: 16608 [PMID: 29192241 DOI: 10.1038/s41598-017-16720-8]

126 **Li Z**, Sun Y, Cao S, Zhang J, Wei J. Downregulation of miR-24-3p promotes osteogenic differentiation of human periodontal ligament stem cells by targeting SMAD family member 5. *J Cell Physiol* 2019; **234**: 7411-7419 [PMID: 30378100 DOI: 10.1002/jcp.27499]

127 **Wei F**, Liu D, Feng C, Zhang F, Yang S, Hu Y, Ding G, Wang S. microRNA-21 mediates stretch-induced osteogenic differentiation in human periodontal ligament stem cells. *Stem Cells Dev* 2015; **24**: 312-319 [PMID: 25203845 DOI: 10.1089/scd.2014.0191]

128 **Yao S**, Zhao W, Ou Q, Liang L, Lin X, Wang Y. MicroRNA-214 Suppresses Osteogenic Differentiation of Human Periodontal Ligament Stem Cells by Targeting ATF4. *Stem Cells Int* 2017; **2017**: 3028647 [PMID: 29213288 DOI: 10.1155/2017/3028647]

129 **Cao F**, Zhan J, Chen X, Zhang K, Lai R, Feng Z. miR-214 promotes periodontal ligament stem cell osteoblastic differentiation by modulating Wnt/β‑catenin signaling. *Mol Med Rep* 2017; **16**: 9301-9308 [PMID: 29152645 DOI: 10.3892/mmr.2017.7821]

130 **Bao L**, Zhang X, Xu Y, Wang M, Song Y, Gu Y, Zheng Y, Xiao J, Wang Y, Zhou Q, Qian J, Liang Y, Ji L, Feng X. Dysfunction of MiR-148a-NRP1 Functional Axis Suppresses Osteogenic Differentiation of Periodontal Ligament Stem Cells Under Inflammatory Microenvironment. *Cell Reprogram* 2019; **21**: 314-322 [PMID: 31809209 DOI: 10.1089/cell.2019.0026]

131 **Yan GQ**, Wang X, Yang F, Yang ML, Zhang GR, Wang GK, Zhou Q. MicroRNA-22 Promoted Osteogenic Differentiation of Human Periodontal Ligament Stem Cells by Targeting HDAC6. *J Cell Biochem* 2017; **118**: 1653-1658 [PMID: 28195408 DOI: 10.1002/jcb.25931]

132 **Li L**, Liu W, Wang H, Yang Q, Zhang L, Jin F, Jin Y. Mutual inhibition between HDAC9 and miR-17 regulates osteogenesis of human periodontal ligament stem cells in inflammatory conditions. *Cell Death Dis* 2018; **9**: 480 [PMID: 29691366 DOI: 10.1038/s41419-018-0480-6]

133 **Xu Y**, Ren C, Zhao X, Wang W, Zhang N. microRNA-132 inhibits osteogenic differentiation of periodontal ligament stem cells *via* GDF5 and the NF-κB signaling pathway. *Pathol Res Pract* 2019; **215**: 152722 [PMID: 31718857 DOI: 10.1016/j.prp.2019.152722]

134 **Zhen L**, Jiang X, Chen Y, Fan D. MiR-31 is involved in the high glucose-suppressed osteogenic differentiation of human periodontal ligament stem cells by targeting Satb2. *Am J Transl Res* 2017; **9**: 2384-2393 [PMID: 28559988]

135 **Wan M**, Gao B, Sun F, Tang Y, Ye L, Fan Y, Klein OD, Zhou X, Zheng L. microRNA miR-34a regulates cytodifferentiation and targets multi-signaling pathways in human dental papilla cells. *PLoS One* 2012; **7**: e50090 [PMID: 23226240 DOI: 10.1371/journal.pone.0050090]

136 **Sun F**, Wan M, Xu X, Gao B, Zhou Y, Sun J, Cheng L, Klein OD, Zhou X, Zheng L. Crosstalk between miR-34a and Notch Signaling Promotes Differentiation in Apical Papilla Stem Cells (SCAPs). *J Dent Res* 2014; **93**: 589-595 [PMID: 24710391 DOI: 10.1177/0022034514531146]

137 **Wang Y**, Pang X, Wu J, Jin L, Yu Y, Gobin R, Yu J. MicroRNA hsa-let-7b suppresses the odonto/osteogenic differentiation capacity of stem cells from apical papilla by targeting MMP1. *J Cell Biochem* 2018; **119**: 6545-6554 [PMID: 29384216 DOI: 10.1002/jcb.26737]

138 **Dernowsek JA**, Pereira MC, Fornari TA, Macedo C, Assis AF, Donate PB, Bombonato-Prado KF, Passos-Bueno MR, Passos GA. Posttranscriptional Interaction Between miR-450a-5p and miR-28-5p and STAT1 mRNA Triggers Osteoblastic Differentiation of Human Mesenchymal Stem Cells. *J Cell Biochem* 2017; **118**: 4045-4062 [PMID: 28407302 DOI: 10.1002/jcb.26060]

139 **Klingelhöffer C**, Codrin C, Ettl T, Reichert T, Morsczeck C. miRNA-101 supports the osteogenic differentiation in human dental follicle cells. *Arch Oral Biol* 2016; **72**: 47-50 [PMID: 27541634 DOI: 10.1016/j.archoralbio.2016.08.005]

140 **Han X**, Yang H, Cao Y, Ge L, Han N, Zhang C, Fan Z, Yao R. The miR-3940-5p inhibits cell proliferation of gingival mesenchymal stem cells. *Oral Dis* 2019; **25**: 1363-1373 [PMID: 30908814 DOI: 10.1111/odi.13092]

141 **Liu Z**, Xu S, Dao J, Gan Z, Zeng X. Differential expression of lncRNA/miRNA/mRNA and their related functional networks during the osteogenic/odontogenic differentiation of dental pulp stem cells. *J Cell Physiol* 2020; **235**: 3350-3361 [PMID: 31549394 DOI: 10.1002/jcp.29223]

142 **Chen Z**, Zhang K, Qiu W, Luo Y, Pan Y, Li J, Yang Y, Wu B, Fang F. Genome-wide identification of long noncoding RNAs and their competing endogenous RNA networks involved in the odontogenic differentiation of human dental pulp stem cells. *Stem Cell Res Ther* 2020; **11**: 114 [PMID: 32169113 DOI: 10.1186/s13287-020-01622-w]

143 **Shi R**, Yang H, Lin X, Cao Y, Zhang C, Fan Z, Hou B. Analysis of the characteristics and expression profiles of coding and noncoding RNAs of human dental pulp stem cells in hypoxic conditions. *Stem Cell Res Ther* 2019; **10**: 89 [PMID: 30867055 DOI: 10.1186/s13287-019-1192-2]

144 **Yi Q**, Liu O, Yan F, Lin X, Diao S, Wang L, Jin L, Wang S, Lu Y, Fan Z. Analysis of Senescence-Related Differentiation Potentials and Gene Expression Profiles in Human Dental Pulp Stem Cells. *Cells Tissues Organs* 2017; **203**: 1-11 [PMID: 27627434 DOI: 10.1159/000448026]

145 **Zhong YX**, Li WS, Liao LS, Liang L. LncRNA CCAT1 promotes cell proliferation and differentiation *via* negative modulation of miRNA-218 in human DPSCs. *Eur Rev Med Pharmacol Sci* 2019; **23**: 3575-3583 [PMID: 31114981 DOI: 10.26355/eurrev\_201905\_17779]

146 **Zeng L**, Sun S, Han D, Liu Y, Liu H, Feng H, Wang Y. Long non-coding RNA H19/SAHH axis epigenetically regulates odontogenic differentiation of human dental pulp stem cells. *Cell Signal* 2018; **52**: 65-73 [PMID: 30165103 DOI: 10.1016/j.cellsig.2018.08.015]

147 **Tao R**, Li YX, Liu YK, Liu F, Zhou ZY. Profiling lncRNA alterations during TNF‑α induced osteogenic differentiation of dental pulp stem cells. *Mol Med Rep* 2019; **19**: 2831-2836 [PMID: 30720070 DOI: 10.3892/mmr.2019.9894]

148 **Qu Q**, Fang F, Wu B, Hu Y, Chen M, Deng Z, Ma D, Chen T, Hao Y, Ge Y. Potential Role of Long Non-Coding RNA in Osteogenic Differentiation of Human Periodontal Ligament Stem Cells. *J Periodontol* 2016; **87**: e127-e137 [PMID: 26991483 DOI: 10.1902/jop.2016.150592]

149 **Zheng Y**, Li X, Huang Y, Jia L, Li W. Time series clustering of mRNA and lncRNA expression during osteogenic differentiation of periodontal ligament stem cells. *PeerJ* 2018; **6**: e5214 [PMID: 30038865 DOI: 10.7717/peerj.5214]

150 **Liu Y**, Liu C, Zhang A, Yin S, Wang T, Wang Y, Wang M, Liu Y, Ying Q, Sun J, Wei F, Liu D, Wang C, Ge S. Down-regulation of long non-coding RNA MEG3 suppresses osteogenic differentiation of periodontal ligament stem cells (PDLSCs) through miR-27a-3p/IGF1 axis in periodontitis. *Aging (Albany NY)* 2019; **11**: 5334-5350 [PMID: 31398715 DOI: 10.18632/aging.102105]

151 **Deng L**, Hong H, Zhang X, Chen D, Chen Z, Ling J, Wu L. Down-regulated lncRNA MEG3 promotes osteogenic differentiation of human dental follicle stem cells by epigenetically regulating Wnt pathway. *Biochem Biophys Res Commun* 2018; **503**: 2061-2067 [PMID: 30103943 DOI: 10.1016/j.bbrc.2018.07.160]

152 **Wang L**, Wu F, Song Y, Li X, Wu Q, Duan Y, Jin Z. Long noncoding RNA related to periodontitis interacts with miR-182 to upregulate osteogenic differentiation in periodontal mesenchymal stem cells of periodontitis patients. *Cell Death Dis* 2016; **7**: e2327 [PMID: 27512949 DOI: 10.1038/cddis.2016.125]

153 **Xu Y**, Qin W, Guo D, Liu J, Zhang M, Jin Z. LncRNA-TWIST1 Promoted Osteogenic Differentiation Both in PPDLSCs and in HPDLSCs by Inhibiting TWIST1 Expression. *Biomed Res Int* 2019; **2019**: 8735952 [PMID: 31341908 DOI: 10.1155/2019/8735952]

154 **Jia B**, Qiu X, Chen J, Sun X, Zheng X, Zhao J, Li Q, Wang Z. A feed-forward regulatory network lncPCAT1/miR-106a-5p/E2F5 regulates the osteogenic differentiation of periodontal ligament stem cells. *J Cell Physiol* 2019; **234**: 19523-19538 [PMID: 30997692 DOI: 10.1002/jcp.28550]

155 **Huang Y**, Han Y, Guo R, Liu H, Li X, Jia L, Zheng Y, Li W. Long non-coding RNA FER1L4 promotes osteogenic differentiation of human periodontal ligament stromal cells *via* miR-874-3p and vascular endothelial growth factor A. *Stem Cell Res Ther* 2020; **11**: 5 [PMID: 31900200 DOI: 10.1186/s13287-019-1519-z]

156 **Feng Y**, Wan P, Yin L. Long Noncoding RNA X-Inactive Specific Transcript (XIST) Promotes Osteogenic Differentiation of Periodontal Ligament Stem Cells by Sponging MicroRNA-214-3p. *Med Sci Monit* 2020; **26**: e918932 [PMID: 32057034 DOI: 10.12659/MSM.918932]

157 **Jia Q**, Chen X, Jiang W, Wang W, Guo B, Ni L. The Regulatory Effects of Long Noncoding RNA-ANCR on Dental Tissue-Derived Stem Cells. *Stem Cells Int* 2016; **2016**: 3146805 [PMID: 27648074 DOI: 10.1155/2016/3146805]

158 **Jia Q**, Jiang W, Ni L. Down-regulated non-coding RNA (lncRNA-ANCR) promotes osteogenic differentiation of periodontal ligament stem cells. *Arch Oral Biol* 2015; **60**: 234-241 [PMID: 25463901 DOI: 10.1016/j.archoralbio.2014.10.007]

159 **Peng W**, Deng W, Zhang J, Pei G, Rong Q, Zhu S. Long noncoding RNA ANCR suppresses bone formation of periodontal ligament stem cells *via* sponging miRNA-758. *Biochem Biophys Res Commun* 2018; **503**: 815-821 [PMID: 29913147 DOI: 10.1016/j.bbrc.2018.06.081]

160 **He Q**, Yang S, Gu X, Li M, Wang C, Wei F. Long noncoding RNA TUG1 facilitates osteogenic differentiation of periodontal ligament stem cells *via* interacting with Lin28A. *Cell Death Dis* 2018; **9**: 455 [PMID: 29674645 DOI: 10.1038/s41419-018-0484-2]

161 **Wang Z**, Huang Y, Tan L. Downregulation of lncRNA DANCR promotes osteogenic differentiation of periodontal ligament stem cells. *BMC Dev Biol* 2020; **20**: 2 [PMID: 31931700 DOI: 10.1186/s12861-019-0206-8]

162 **Li Z**, Yan M, Yu Y, Wang Y, Lei G, Pan Y, Li N, Gobin R, Yu J. LncRNA H19 promotes the committed differentiation of stem cells from apical papilla *via* miR-141/SPAG9 pathway. *Cell Death Dis* 2019; **10**: 130 [PMID: 30755596 DOI: 10.1038/s41419-019-1337-3]

163 **Pan Y**, Lu T, Peng L, Chen Z, Li M, Zhang K, Xiong F, Wu B. Vacuolar protein sorting 4B regulates the proliferation and odontoblastic differentiation of human dental pulp stem cells through the Wnt-β-catenin signalling pathway. *Artif Cells Nanomed Biotechnol* 2019; **47**: 2575-2584 [PMID: 31218890 DOI: 10.1080/21691401.2019.1629950]

164 **Zhang X**, Ning T, Wang H, Xu S, Yu H, Luo X, Hao C, Wu B, Ma D. Stathmin regulates the proliferation and odontoblastic/osteogenic differentiation of human dental pulp stem cells through Wnt/β-catenin signaling pathway. *J Proteomics* 2019; **202**: 103364 [PMID: 31009804 DOI: 10.1016/j.jprot.2019.04.014]

165 **Scheller EL**, Chang J, Wang CY. Wnt/beta-catenin inhibits dental pulp stem cell differentiation. *J Dent Res* 2008; **87**: 126-130 [PMID: 18218837 DOI: 10.1177/154405910808700206]

166 **Rolph DN**, Deb M, Kanji S, Greene CJ, Das M, Joseph M, Aggarwal R, Leblebicioglu B, Das H. Ferutinin directs dental pulp-derived stem cells towards the osteogenic lineage by epigenetically regulating canonical Wnt signaling. *Biochim Biophys Acta Mol Basis Dis* 2020; **1866**: 165314 [PMID: 30412793 DOI: 10.1016/j.bbadis.2018.10.032]

167 **Hasegawa D**, Wada N, Yoshida S, Mitarai H, Arima M, Tomokiyo A, Hamano S, Sugii H, Maeda H. Wnt5a suppresses osteoblastic differentiation of human periodontal ligament stem cell-like cells *via* Ror2/JNK signaling. *J Cell Physiol* 2018; **233**: 1752-1762 [PMID: 28681925 DOI: 10.1002/jcp.26086]

168 **Chen Z**, Gibson TB, Robinson F, Silvestro L, Pearson G, Xu B, Wright A, Vanderbilt C, Cobb MH. MAP kinases. *Chem Rev* 2001; **101**: 2449-2476 [PMID: 11749383 DOI: 10.1021/cr000241p]

169 **Kim JH**, Kim SY, Woo SM, Jeong HN, Jung JY, Kim SM, Lim HS. Combination of mineral trioxide aggregate and propolis promotes odontoblastic differentiation of human dental pulp stem cells through ERK signaling pathway. *Food Sci Biotechnol* 2019; **28**: 1801-1809 [PMID: 31807353 DOI: 10.1007/s10068-019-00609-5]

170 **Kong Y**, Hu X, Zhong Y, Xu K, Wu B, Zheng J. Magnesium-enriched microenvironment promotes odontogenic differentiation in human dental pulp stem cells by activating ERK/BMP2/Smads signaling. *Stem Cell Res Ther* 2019; **10**: 378 [PMID: 31823825 DOI: 10.1186/s13287-019-1493-5]

171 **Liu J**, Zhao X, Pei D, Sun G, Li Y, Zhu C, Qiang C, Sun J, Shi J, Dong Y, Gou J, Wang S, Li A. The promotion function of Berberine for osteogenic differentiation of human periodontal ligament stem cells *via* ERK-FOS pathway mediated by EGFR. *Sci Rep* 2018; **8**: 2848 [PMID: 29434321 DOI: 10.1038/s41598-018-21116-3]

172 **Ge X**, Li Z, Jing S, Wang Y, Li N, Lu J, Yu J. Parathyroid hormone enhances the osteo/odontogenic differentiation of dental pulp stem cells *via* ERK and P38 MAPK pathways. *J Cell Physiol* 2020; **235**: 1209-1221 [PMID: 31276209 DOI: 10.1002/jcp.29034]

173 **Tao Z**, Barker J, Shi SD, Gehring M, Sun S. Steady-state kinetic and inhibition studies of the mammalian target of rapamycin (mTOR) kinase domain and mTOR complexes. *Biochemistry* 2010; **49**: 8488-8498 [PMID: 20804212 DOI: 10.1021/bi100673c]

174 **Tanaka Y**, Sonoda S, Yamaza H, Murata S, Nishida K, Hama S, Kyumoto-Nakamura Y, Uehara N, Nonaka K, Kukita T, Yamaza T. Suppression of AKT-mTOR signal pathway enhances osteogenic/dentinogenic capacity of stem cells from apical papilla. *Stem Cell Res Ther* 2018; **9**: 334 [PMID: 30486861 DOI: 10.1186/s13287-018-1077-9]

175 **Feng X**, Huang D, Lu X, Feng G, Xing J, Lu J, Xu K, Xia W, Meng Y, Tao T, Li L, Gu Z. Insulin-like growth factor 1 can promote proliferation and osteogenic differentiation of human dental pulp stem cells *via* mTOR pathway. *Dev Growth Differ* 2014; **56**: 615-624 [PMID: 25388971 DOI: 10.1111/dgd.12179]

176 **Kim JK**, Baker J, Nor JE, Hill EE. mTor plays an important role in odontoblast differentiation. *J Endod* 2011; **37**: 1081-1085 [PMID: 21763898 DOI: 10.1016/j.joen.2011.03.034]

177 **Jia L**, Xiong Y, Zhang W, Ma X, Xu X. Metformin promotes osteogenic differentiation and protects against oxidative stress-induced damage in periodontal ligament stem cells *via* activation of the Akt/Nrf2 signaling pathway. *Exp Cell Res* 2020; **386**: 111717 [PMID: 31715142 DOI: 10.1016/j.yexcr.2019.111717]

178 **Zhang C**, Chang J, Sonoyama W, Shi S, Wang CY. Inhibition of human dental pulp stem cell differentiation by Notch signaling. *J Dent Res* 2008; **87**: 250-255 [PMID: 18296609 DOI: 10.1177/154405910808700312]

179 **Wang X**, He H, Wu X, Hu J, Tan Y. Promotion of dentin regeneration *via* CCN3 modulation on Notch and BMP signaling pathways. *Biomaterials* 2014; **35**: 2720-2729 [PMID: 24406215 DOI: 10.1016/j.biomaterials.2013.12.029]

180 **Ma D**, Yu H, Xu S, Wang H, Zhang X, Ning T, Wu B. Stathmin inhibits proliferation and differentiation of dental pulp stem cells *via* sonic hedgehog/Gli. *J Cell Mol Med* 2018; **22**: 3442-3451 [PMID: 29655218 DOI: 10.1111/jcmm.13621]

181 **Zhou Y**, Zheng L, Zhou X, Li J, Xu X. Dental Mesenchymal Stem Cells in Inflamed Microenvironment: Potentials and Challenges for Regeneration. *Curr Stem Cell Res Ther* 2015; **10**: 412-421 [PMID: 25764197 DOI: 10.2174/1574888x10666150312102324]

182 **Bindal P**, Ramasamy TS, Kasim NHA, Gnanasegaran N, Chai WL. Immune responses of human dental pulp stem cells in lipopolysaccharide-induced microenvironment. *Cell Biol Int* 2018; **42**: 832-840 [PMID: 29363846 DOI: 10.1002/cbin.10938]

183 **Soancă A**, Lupse M, Moldovan M, Pall E, Cenariu M, Roman A, Tudoran O, Surlin P, Șorițău O. Applications of inflammation-derived gingival stem cells for testing the biocompatibility of dental restorative biomaterials. *Ann Anat* 2018; **218**: 28-39 [PMID: 29604386 DOI: 10.1016/j.aanat.2018.02.009]

184 **Liao J**, Al Shahrani M, Al-Habib M, Tanaka T, Huang GT. Cells isolated from inflamed periapical tissue express mesenchymal stem cell markers and are highly osteogenic. *J Endod* 2011; **37**: 1217-1224 [PMID: 21846537 DOI: 10.1016/j.joen.2011.05.022]

185 **Lee S**, Zhang QZ, Karabucak B, Le AD. DPSCs from Inflamed Pulp Modulate Macrophage Function *via* the TNF-α/IDO Axis. *J Dent Res* 2016; **95**: 1274-1281 [PMID: 27384335 DOI: 10.1177/0022034516657817]

186 **Dokić J**, Tomić S, Cerović S, Todorović V, Rudolf R, Colić M. Characterization and immunosuppressive properties of mesenchymal stem cells from periapical lesions. *J Clin Periodontol* 2012; **39**: 807-816 [PMID: 22775529 DOI: 10.1111/j.1600-051X.2012.01917.x]

187 **Zhai Y**, Wang Y, Rao N, Li J, Li X, Fang T, Zhao Y, Ge L. Activation and Biological Properties of Human β Defensin 4 in Stem Cells Derived From Human Exfoliated Deciduous Teeth. *Front Physiol* 2019; **10**: 1304 [PMID: 31695620 DOI: 10.3389/fphys.2019.01304]

188 **Boyle M**, Chun C, Strojny C, Narayanan R, Bartholomew A, Sundivakkam P, Alapati S. Chronic inflammation and angiogenic signaling axis impairs differentiation of dental-pulp stem cells. *PLoS One* 2014; **9**: e113419 [PMID: 25427002 DOI: 10.1371/journal.pone.0113419]

189 **Xu XY**, He XT, Wang J, Li X, Xia Y, Tan YZ, Chen FM. Role of the P2X7 receptor in inflammation-mediated changes in the osteogenesis of periodontal ligament stem cells. *Cell Death Dis* 2019; **10**: 20 [PMID: 30622236 DOI: 10.1038/s41419-018-1253-y]

190 **Zhai QM**, Li B, Wang ZW, Liu L, Jin Y, Jin F. [Endoplasmic reticulum-mitochondrial contact regulates osteogenic differentiation of periodontal ligament stem cells *via* mitofusion 2 in inflammatory microenvironment]. *Zhonghua Kou Qiang Yi Xue Za Zhi* 2018; **53**: 453-458 [PMID: 29996362 DOI: 10.3760/cma.j.issn.1002-0098.2018.07.005]

191 **Tang HN**, Xia Y, Yu Y, Wu RX, Gao LN, Chen FM. Stem cells derived from "inflamed" and healthy periodontal ligament tissues and their sheet functionalities: a patient-matched comparison. *J Clin Periodontol* 2016; **43**: 72-84 [PMID: 26719165 DOI: 10.1111/jcpe.12501]

192 **Park JC**, Kim JM, Jung IH, Kim JC, Choi SH, Cho KS, Kim CS. Isolation and characterization of human periodontal ligament (PDL) stem cells (PDLSCs) from the inflamed PDL tissue: *in vitro* and *in vivo* evaluations. *J Clin Periodontol* 2011; **38**: 721-731 [PMID: 21449989 DOI: 10.1111/j.1600-051X.2011.01716.x]

193 **Li C**, Wang X, Tan J, Wang T, Wang Q. The immunomodulatory properties of periodontal ligament stem cells isolated from inflamed periodontal granulation. *Cells Tissues Organs* 2014; **199**: 256-265 [PMID: 25471814 DOI: 10.1159/000367986]

194 **Marrelli M**, Paduano F, Tatullo M. Cells isolated from human periapical cysts express mesenchymal stem cell-like properties. *Int J Biol Sci* 2013; **9**: 1070-1078 [PMID: 24250252 DOI: 10.7150/ijbs.6662]

195 **Um S**, Lee JH, Seo BM. TGF-β2 downregulates osteogenesis under inflammatory conditions in dental follicle stem cells. *Int J Oral Sci* 2018; **10**: 29 [PMID: 30297828 DOI: 10.1038/s41368-018-0028-8]

196 **Alt EU**, Senst C, Murthy SN, Slakey DP, Dupin CL, Chaffin AE, Kadowitz PJ, Izadpanah R. Aging alters tissue resident mesenchymal stem cell properties. *Stem Cell Res* 2012; **8**: 215-225 [PMID: 22265741 DOI: 10.1016/j.scr.2011.11.002]

197 **Iezzi I**, Cerqueni G, Licini C, Lucarini G, Mattioli Belmonte M. Dental pulp stem cells senescence and regenerative potential relationship. *J Cell Physiol* 2019; **234**: 7186-7197 [PMID: 30362542 DOI: 10.1002/jcp.27472]

198 **Wu W**, Zhou J, Xu CT, Zhang J, Jin YJ, Sun GL. Derivation and growth characteristics of dental pulp stem cells from patients of different ages. *Mol Med Rep* 2015; **12**: 5127-5134 [PMID: 26239849 DOI: 10.3892/mmr.2015.4106]

199 **Wang K**, Li L, Wu J, Qiu Q, Zhou F, Wu H. The different expression profiles of microRNAs in elderly and young human dental pulp and the role of miR-433 in human dental pulp cells. *Mech Ageing Dev* 2015; **146-148**: 1-11 [PMID: 25778413 DOI: 10.1016/j.mad.2015.03.001]

200 **Wang H**, Zhong Q, Yang T, Qi Y, Fu M, Yang X, Qiao L, Ling Q, Liu S, Zhao Y. Comparative characterization of SHED and DPSCs during extended cultivation in vitro. *Mol Med Rep* 2018; **17**: 6551-6559 [PMID: 29532869 DOI: 10.3892/mmr.2018.8725]

201 **Naka T**, Yokose S. Spatiotemporal expression of sclerostin in odontoblasts during embryonic mouse tooth morphogenesis. *J Endod* 2011; **37**: 340-345 [PMID: 21329818 DOI: 10.1016/j.joen.2010.11.025]

202 **Ou Y**, Zhou Y, Liang S, Wang Y. Sclerostin promotes human dental pulp cells senescence. *PeerJ* 2018; **6**: e5808 [PMID: 30356963 DOI: 10.7717/peerj.5808]

203 **Bakopoulou A**, Leyhausen G, Volk J, Papachristou E, Koidis P, Geurtsen W. Wnt/β-catenin signaling regulates Dental Pulp Stem Cells' responses to pulp injury by resinous monomers. *Dent Mater* 2015; **31**: 542-555 [PMID: 25735758 DOI: 10.1016/j.dental.2015.02.004]

204 **Zhao Y**, Yuan X, Bellido T, Helms JA. A Correlation between Wnt/Beta-catenin Signaling and the Rate of Dentin Secretion. *J Endod* 2019; **45**: 1357-1364.e1 [PMID: 31522810 DOI: 10.1016/j.joen.2019.07.014]

205 **Feng X**, Xing J, Feng G, Sang A, Shen B, Xu Y, Jiang J, Liu S, Tan W, Gu Z, Li L. Age-dependent impaired neurogenic differentiation capacity of dental stem cell is associated with Wnt/β-catenin signaling. *Cell Mol Neurobiol* 2013; **33**: 1023-1031 [PMID: 24043508 DOI: 10.1007/s10571-013-9965-0]

206 **Feng X**, Xing J, Feng G, Huang D, Lu X, Liu S, Tan W, Li L, Gu Z. p16(INK4A) mediates age-related changes in mesenchymal stem cells derived from human dental pulp through the DNA damage and stress response. *Mech Ageing Dev* 2014; **141-142**: 46-55 [PMID: 25304494 DOI: 10.1016/j.mad.2014.09.004]

207 **Mas-Bargues C**, Viña-Almunia J, Inglés M, Sanz-Ros J, Gambini J, Ibáñez-Cabellos JS, García-Giménez JL, Viña J, Borrás C. Role of p16INK4a and BMI-1 in oxidative stress-induced premature senescence in human dental pulp stem cells. *Redox Biol* 2017; **12**: 690-698 [PMID: 28410532 DOI: 10.1016/j.redox.2017.04.002]

208 **Mehrazarin S**, Oh JE, Chung CL, Chen W, Kim RH, Shi S, Park NH, Kang MK. Impaired odontogenic differentiation of senescent dental mesenchymal stem cells is associated with loss of Bmi-1 expression. *J Endod* 2011; **37**: 662-666 [PMID: 21496667 DOI: 10.1016/j.joen.2011.02.009]

209 **Ma D**, Ma Z, Zhang X, Wang W, Yang Z, Zhang M, Wu G, Lu W, Deng Z, Jin Y. Effect of age and extrinsic microenvironment on the proliferation and osteogenic differentiation of rat dental pulp stem cells in vitro. *J Endod* 2009; **35**: 1546-1553 [PMID: 19840645 DOI: 10.1016/j.joen.2009.07.016]

210 **Ning T**, Shao J, Zhang X, Luo X, Huang X, Wu H, Xu S, Wu B, Ma D. Ageing affects the proliferation and mineralization of rat dental pulp stem cells under inflammatory conditions. *Int Endod J* 2020; **53**: 72-83 [PMID: 31419325 DOI: 10.1111/iej.13205]

211 **Horibe H**, Murakami M, Iohara K, Hayashi Y, Takeuchi N, Takei Y, Kurita K, Nakashima M. Isolation of a stable subpopulation of mobilized dental pulp stem cells (MDPSCs) with high proliferation, migration, and regeneration potential is independent of age. *PLoS One* 2014; **9**: e98553 [PMID: 24870376 DOI: 10.1371/journal.pone.0098553]

212 **Huang CC**, Narayanan R, Alapati S, Ravindran S. Exosomes as biomimetic tools for stem cell differentiation: Applications in dental pulp tissue regeneration. *Biomaterials* 2016; **111**: 103-115 [PMID: 27728810 DOI: 10.1016/j.biomaterials.2016.09.029]

213 **Hu X**, Zhong Y, Kong Y, Chen Y, Feng J, Zheng J. Lineage-specific exosomes promote the odontogenic differentiation of human dental pulp stem cells (DPSCs) through TGFβ1/smads signaling pathway *via* transfer of microRNAs. *Stem Cell Res Ther* 2019; **10**: 170 [PMID: 31196201 DOI: 10.1186/s13287-019-1278-x]

214 **Chew JRJ**, Chuah SJ, Teo KYW, Zhang S, Lai RC, Fu JH, Lim LP, Lim SK, Toh WS. Mesenchymal stem cell exosomes enhance periodontal ligament cell functions and promote periodontal regeneration. *Acta Biomater* 2019; **89**: 252-264 [PMID: 30878447 DOI: 10.1016/j.actbio.2019.03.021]

215 **Wang M**, Li J, Ye Y, He S, Song J. SHED-derived conditioned exosomes enhance the osteogenic differentiation of PDLSCs *via* Wnt and BMP signaling in vitro. *Differentiation* 2020; **111**: 1-11 [PMID: 31630077 DOI: 10.1016/j.diff.2019.10.003]

216 **Li Z**, Liang Y, Pan K, Li H, Yu M, Guo W, Chen G, Tian W. Schwann cells secrete extracellular vesicles to promote and maintain the proliferation and multipotency of hDPCs. *Cell Prolif* 2017; **50** [PMID: 28714175 DOI: 10.1111/cpr.12353]

217 **Čebatariūnienė A**, Kriaučiūnaitė K, Prunskaitė J, Tunaitis V, Pivoriūnas A. Extracellular Vesicles Suppress Basal and Lipopolysaccharide-Induced NFκB Activity in Human Periodontal Ligament Stem Cells. *Stem Cells Dev* 2019; **28**: 1037-1049 [PMID: 31017040 DOI: 10.1089/scd.2019.0021]

218 **Pizzicannella J**, Diomede F, Gugliandolo A, Chiricosta L, Bramanti P, Merciaro I, Orsini T, Mazzon E, Trubiani O. 3D Printing PLA/Gingival Stem Cells/ EVs Upregulate miR-2861 and -210 during Osteoangiogenesis Commitment. *Int J Mol Sci* 2019; **20** [PMID: 31269731 DOI: 10.3390/ijms20133256]

**Footnotes**

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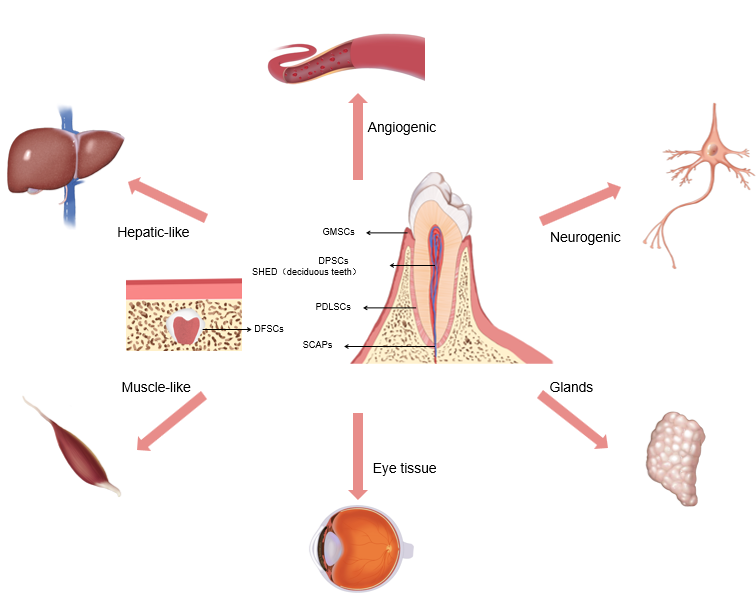
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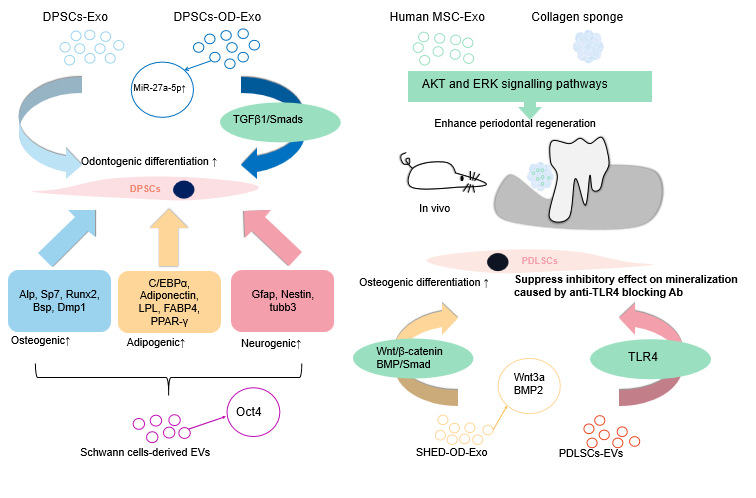
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**Figure Legends**



**Figure 1 Location of dental mesenchymal stem cells and their diverse differentiation potential.** Dental mesenchymal stem cells can be isolated from different tissues of the teeth. Dental mesenchymal stem cells have multidifferentiation ability and can differentiate into many tissue-like cells. DPSCs: Dental pulp stem cells; PDLSCs: Periodontal ligament stem cells; SCAPs: Stem cells from apical papilla; GMSCs: Gingival mesenchymal stem cells; SHED: Stem cells from human exfoliated deciduous teeth; DFSCs: Dental follicle stem cells.



**Figure 2 Reported extracellular vesicles that mainly contributed to the odontogenic/osteogenic differentiation process of dental mesenchymal stem cells.** Extracellular vesicles (EVs) from a variety of cell sources can influence the osteogenic, adipogenic and neurogenic differentiation process of dental mesenchymal stem cells. Exo: Exosomes; DFSCs: Dental follicle stem cells; LPL: Lipoprotein lipase; MSC: Mesenchymal stem cells; PDLSCs: Periodontal ligament stem cells; PPAR-γ: Peroxisome proliferator-activated receptor-γ; SHED: Stem cells from human exfoliated deciduous teeth; TGFβ1: Transforming growth factor β1.

**Table 1 Summary of the microRNAs influencing the odontogenic/osteogenic differentiation of dental mesenchymal stem cells**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ref.** | **MicroRNA** | **Cell type** | **Signaling pathway or targets** | **Outcome** |
| Zhan *et al*[112], 2018 | miR-143-5p | DPSCs | OPG/RANKL | Downregulation promoted odontoblastic differentiation |
| Yang *et al*[113], 2020 | miR-143-3p | DPSCs | OPG/RANKL | Downregulation promoted odontogenic differentiation |
| Wang *et al*[114], 2019 | miR-143-5p | DPSCs | MAPK14 | Downregulation promoted odontoblastic differentiation |
| Yu *et al*[115], 2019 | miR-488 | DPSCs | MAPK1 | Downregulation enhanced odontoblastic differentiation |
| Wang *et al*[116], 2020 | miR-125a-3p | DPSCs | Fyn | Regulated odontoblastic differentiation in an inflammation model |
| Yuan *et al*[117], 2019 | miR-let-7c-5p | Inflamed human DPSCs | - | Restored the osteogenic differentiation |
| Huang *et al*[118], 2019 | miR-223-3p | Inflamed human DPSCs | - | Increased the proteins levels of DSPP and DMP-1 |
| Sun *et al*[119], 2017 | miR-140-5p | DPSCs | - | Inhibited odontoblastic differentiation after LPS treated |
| Liu *et al*[120], 2019 | miR-508-5p | DPSCs | GPNMB | Inhibited odontogenic differentiation |
| Xu *et al*[121], 2018 | miR-21 | DPSCs | STAT3 | Downregulation caused the decreasing expression of DMP-1 and DSPP |
| Qiu *et al*[122], 2019 | miR-146a-5p | STRO-1 + human DPSCs | - | Promoted osteo/odontogenic differentiation |
| Zhang *et al*[123], 2018 | miR-143 | DPSCs | TNF-α/NF-κB | Suppressed the osteogenic differentiation |
| Yao *et al*[124], 2019 | miR-215, miR-219a-1-3p | DPSCs | HspB8 | Inhibited the osteogenic differentiation |
|
| Wei *et al*[125], 2017 | miR-21 | PDLSCs | Smad5 | Inhibited osteogenesis |
| Li *et al*[126], 2019 | miR-24-3p | PDLSCs | Smad5 | Inhibited osteogenic differentiation |
| Wei *et al*[127], 2015 | miR-21 | PDLSCs | ACVR2B | Performed a positive function in mediating the stretch-induced osteogenic differentiation |
| Yao *et al*[128], 2017; Cao *et al*[129], 2017 | miR-214 | PDLSCs | ATF4, Wnt/β-catenin | Downregulation decreased the osteogenic differentiation |
| Bao *et al*[130], 2019 | miR-148a | PDLSCs | - | Downregulation rescued the inhibition of osteogenesis triggered by LPS stimulation |
| Yan *et al*[131], 2017 | miR-22 | PDLSCs | HDAC6 | Promoted osteogenesis |
| Li *et al*[132], 2018 | miR-17 | PDLSCs | HDAC9 | Promoted osteogenesis in an inflammation condition |
| Xu *et al*[133], 2019 | miR-132 | PDLSCs | GDF5, NF-κB | Inhibited the osteogenesis |
| Zhen *et al*[134], 2017 | miR-31 | PDLSCs | Satb2 | Took part in the high glucose-suppressed osteogenic differentiation |
| Wan *et al*[135], 2012 | miR-34a | Human dental papilla cells | - | Increased the expression of DSPP and decreased the expression of ALP |
| Sun *et al*[136], 2014 | miR-34a | SCAPs | - | Upregulated odonto/osteogenic markers |
| Wang *et al*[137], 2018 | miR hsa-let-7b | SCAPs | MMP1 | Suppressed the odonto/osteogenic differentiation |
| Dernowsek *et al*[138], 2017 | miR-450a-5p，miR-28-5p | SHED | - | Supported the osteogenesis |
|
| Klingelhöffer *et al*[139], 2016 | miR-101 | DFSCs | - | Enhanced the osteogenic differentiation |
| Han *et al*[140], 2019 | miR-3940-5p | GMSCs | - | Promoted the osteo/dentinogenic differentiation |

DPSCs: Dental pulp stem cells; PDLSCs: Periodontal ligament stem cells; SCAPs: Stem cells from apical papilla; MAPK: Mitogen-activated protein kinases; OPG/RANKL: Osteoprotegerin/receptor activator of nuclear factor κB ligand; GPNMB: Glycoprotein nonmetastatic melanomal protein B; TNF-α: Tumor necrosis factor-α; NF-κB: Nuclear factor κB; ATF4: Activating transcription factor 4; LPS: Lipopolysaccharide; DSPP: Dentine sialophosphoprotein; ALP: Alkaline phosphatase; SHED: Stem cells from human exfoliated deciduous; GMSCs: Gingival mesenchymal stem cells; DFSCs: Dental follicle stem cells; HspB8: Heat shock protein B8; ACVR2B: Activin receptor type IIB; GDF5: Growth differentiation factor 5; MMP1: Matrix metalloproteinase 1; miR: MicroRNA; DMP-1: Dentine matrix protein 1; Smad5: SMAD family member 5.

**Table 2 Summary of the long noncoding RNAs influencing the odontogenic/osteogenic differentiation of dental mesenchymal stem cells**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ref.** | **LncRNA** | **Cell type** | **Signaling pathway or targets** | **Outcome** |
| Liu *et al*[141], 2020 | lncRNA SNHG7 | DPSCs | miR-1226-3p, miR-210-5p | Downregulation inhibited osteo/odontogenic differentiation |
| Chen *et al*[142], 2020 | lncRNA-G043225 | DPSCs | miR-588, FBN1 | Positively regulated odontoblastic differentiation |
| Zhong *et al*[145], 2019 | lncRNA CCAT1 | DPSCs | miR-218 | Overexpression promoted odontogenic differentiation |
| Zeng *et al*[146], 2018 | lncRNA H19 | DPSCs | DLX3 | Upregulation enhanced odontogenic differentiation |
| Shi *et al*[143], 2019 | lncRNA STL | DPSCs | - | Knockdown inhibited osteogenesis |
| Tao *et al*[147], 2019 | lncRNA XIST | DPSCs | - | Downregulation inhibited osteogenic differentiation |
| Zheng *et al*[149], 2018 | lncRNA MEG8, lncRNA MIR22HG | PDLSCs | - | Downregulation suppressed osteogenic differentiation |
| Liu *et al*[150], 2019; Deng *et al*[151], 2018 | lncRNA MEG3 | PDLSCs | miR-27a-3p/IGF1 axis, Wnt/β-catenin | Knockdown inhibited osteogenesis |
| Wang *et al*[152], 2016 | lncRNA-POIR | PDLSCs | miR-182 | Enhanced osteogenic differentiation |
| Xu *et al*[153], 2019 | lncRNA-TWIST1 | PDLSCs | TWIST1 | Improved osteogenic differentiation |
| Jia *et al*[154], 2019 | lncPCAT1 | PDLSCs | - | Reversed the suppression effect of osteogenesis caused by miR-106a-5p overexpression |
| Huang *et al*[155], 2020 | lncRNA FER1L4 | PDLSCs | miR-874-3p | Promoted osteogenic differentiation |
| Feng *et al*[156], 2020 | lncRNA XIST | PDLSCs | miR-214-3p | Enhanced osteogenic differentiation |
| He *et al*[160], 2018 | lncRNA TUG1 | PDLSCs | lin-28 homolog A | Improved osteogenic differentiation |
| Wang *et al*[161], 2020 | lncRNA DANCR | PDLSCs | - | Positively regulated osteogenic differentiation |
| Li *et al*[162], 2019 | lncRNA H19 | SCAPs | lncRNA-H19/miR-141/SPAG9/MAPK | Promoted the osteo/odontogenesis |
| Jia *et al*[157], 2016; Jia *et al*[158], 2015; Peng *et al*[159], 2018 | lncRNA ANCR | DPSCs, PDLSCs, SCAPs | Wnt, lncRNA-ANCR/miR-758/Notch2 (PDLSCs) | Downregulation facilitated osteogenic differentiation |

DPSCs: Dental pulp stem cells; FBN1: Fibrillin 1; lncRNAs: Long noncoding RNAs; MAPK: Mitogen-activated protein kinases; MEG3/8: Maternally-expressed 3/8; miR: MicroRNA; IGF1: Insulin-like growth factor 1; PDLSCs: Periodontal ligament stem cells; SCAPs: Stem cells from apical papilla; XIST: X-inactive specific transcript.