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Dental-derived cells for regenerative medicine: stem cells, cell reprogramming, and transdifferentiation

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ABSTRACT

Embryonic stem cells have been a popular research topic in regenerative medicine owing to their pluripotency and applicability. However, due to the difficulty in harvesting them and their low yield efficiency, advanced cell reprogramming technology has been introduced as an alternative. Dental stem cells have entered the spotlight due to their regenerative potential and their ability to be obtained from biological waste generated after dental treatment. Cell reprogramming, a process of reverting mature somatic cells into stem cells, and transdifferentiation, a direct conversion between different cell types without induction of a pluripotent state, have helped overcome the shortcomings of stem cells and raised interest in their regenerative potential. Furthermore, the potential of these cells to return to their original cell types due to their epigenetic memory has reinforced the need to control the epigenetic background for successful management of cellular differentiation. Herein, we discuss all available sources of dental stem cells, the procedures used to obtain these cells, and their ability to differentiate into the desired cells. We also introduce the concepts of cell reprogramming and transdifferentiation in terms of genetics and epigenetics, including DNA methylation, histone modification, and non-coding RNA. Finally, we discuss a novel therapeutic avenue for using dental-derived cells as stem cells, and explain cell reprogramming and transdifferentiation, which are used in regenerative medicine and tissue engineering.

Keywords: Cellular reprogramming; Epigenetics; Regenerative medicine; Stem cells; Tissue engineering

INTRODUCTION

Stem cells are undifferentiated cells that have the potential to differentiate into other types of functional cells present in an organism and possess the ability to self-renew. Therefore, stem cell therapy has received attention as a promising tool for regenerative medicine and tissue engineering [1]. Stem cells are classified as totipotent, pluripotent, multipotent, and unipotent based on their differentiation potential [2]. Embryonic stem cells (ESCs) are pluripotent and theoretically capable of differentiating into more than 200 cell types; however, various biological limitations and controversies such as the difficulty of obtaining

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ESCs, ethical aspects related to destruction of the embryo, risks of immune rejection, and teratoma formation have necessitated the search for other alternatives [3]. Somatic stem cells, which originate from autologous cells, have been introduced as alternatives to ESCs. Lineage-specific multipotent stem cells are referred to by their sources of origin, such as skeletal stem cells, muscle stem cells, endothelial stem cells, adipose-derived stem cells, and dental stem cells [4]. Dental stem cells have recently entered the spotlight due to their regenerative potential and their ability to be obtained from biological waste generated after dental treatment [5]. Concepts such as identifying the differentiation potential or "stemness" of cells and cell reprogramming of somatic cells into pluripotent stem cells involving the generation of ESC-like cells through ectopic expression of specific genes have been introduced [6]. Dr. Shinya Yamanaka investigated induced pluripotent stem cells (iPSCs) using 4 transcription factors (Oct4, Klf4, Sox-2, and c-Myc) and demonstrated the conversion of somatic cells into stem cells [7]. However, the generation of iPSCs has limitations such as low efficiency, slow kinetics, and difficulty in the recovery of epigenetic markers. Therefore, transdifferentiation, a direct lineage conversion from one specialized somatic cell to another cell without induction of the pluripotent state, has been introduced most recently. In this review, we outline in detail all available sources of dental stem cells, the procedures used to obtain these cells, their ability to differentiate into the desired cells, and their translational application for tissue regenerations. We also introduce the concepts of cell reprogramming and transdifferentiation in epigenetics, including DNA methylation, histone modification, and non-coding RNA. Finally, we discuss a novel therapeutic avenue for using dental-derived cells as stem cells, iPSCs, and transdifferentiation in regenerative medicine.

CELL-FATE COMMITMENT AND THE WADDINGTON LANDSCAPE MODEL

Conrad Waddington explained cellular differentiation during development using the "epigenetic landscape model" [8]. In the model of Waddington's epigenetic landscape, the impact of epigenetics on cell reprogramming can be easily explained, and this model enables the identification of another route, transdifferentiation, for obtaining desired cells (**Figure 1**). The process of cellular differentiation is depicted by illustrating the concept with the example of hills and marbles. The theory can be explained as "the marble at the top of the hill is the pluripotent stem cell state, and there are several ways for the marble to roll down to the bottom of the hill, and each final destination can be defined as a fully differentiated cell." This model depicts stem cells as differentiating into specialized cells by undergoing epigenetic changes such as DNA methylation and histone modification. It is based on the idea that the normal developmental process is unidirectional and irreversible and demonstrates that stem cells differentiate into specialized mature cells and lose their stemness (**Figure 1A**). Based on this concept, many studies to find stem cell sources have been conducted for tissue regeneration. However, a series of ground-breaking studies, such as the discovery of iPSCs (**Figure 1B**) and direct conversion (**Figure 1C**), have shown that the cell fate could be flexible and reversible, and research trends have changed to modulate cell fates via reprogramming and transdifferentiation using ectopic expression of transcription factors or pharmacological agents. In this model, pluripotent stem cells act as a hub connecting with other cellular lineage paths at the top, and the already differentiated cells at the bottom can switch with each other outside the context of pluripotency [9].

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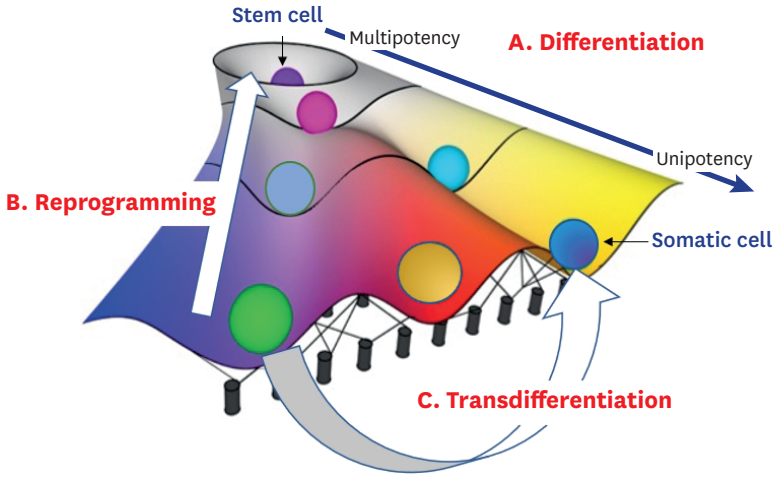

Figure 1. Waddington's epigenetic landscape model. Waddington's epigenetic landscape model represents the process of cell differentiation (A), reprogramming (B), and transdifferentiation (C). The status of stem cells and somatic cells is depicted by rolling marbles from multipotency to unipotency.

DENTAL STEM CELLS

In dentistry, tissue engineering for regenerating oral tissues or replacing missing teeth with various biomaterials has been introduced [10], and various types of adult stem cells in dental tissues have been identified as a source (**Figure 2**).

Dental pulp stem cells (DPSCs)

Dental pulp is the soft connective tissue inside the tooth that contains nerves and blood vessels, which play an important role in tooth development. In 2000, human dental stem cells were first identified in the dental pulp of the third molars and were found to have properties similar to those of bone marrow-derived mesenchymal stem cells (BMSCs) [5]. Subsequently, DPSCs were isolated from exfoliated deciduous teeth [11], permanent teeth [12], and supernumerary teeth [13]. DPSCs have the potential of self-renewal and multi-differentiation,

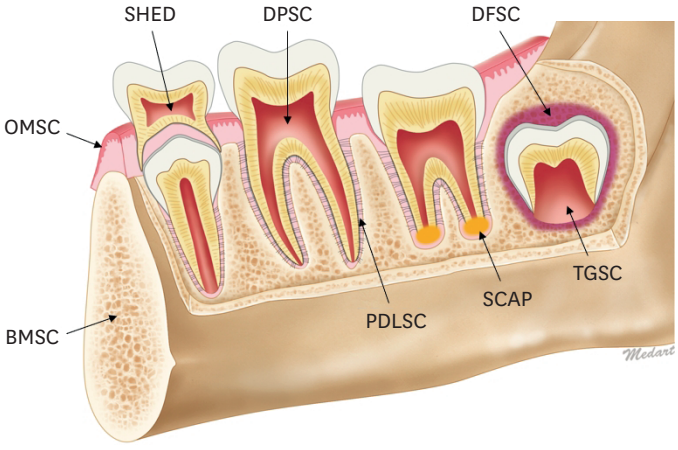

Figure 2. Sources of dental-derived stem cells. Various types of dental tissue-derived stem cells have been identified as sources of tissue regeneration.
OMSC: oral mucosa-derived stem cell, SHED: stem cell from human exfoliated deciduous teeth, DPSC: dental pulp stem cell, DFSC: dental follicle stem cell, BMSC: bone marrow-derived stem cell, PDLSC: periodontal ligament stem cell, SCAP: stem cell from the apical papilla, TGSC: tooth germ stem cell.

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including the odontogenic, osteogenic, neurogenic, chondrogenic, and myogenic lineages [14-18]. DPSCs regenerated the tooth structures forming the dentin-pulp complex when transplanted into immunocompromised mice [5]. DPSCs originate from the embryonic neural crest cells that migrate from the neural tube and produce multiple non-neural or neural cells, including glia and peripheral nervous system neurons [19]. Therefore, it is not surprising that DPSCs represent markers of neural systems; however, their heterogeneous properties can affect the differentiation efficiency [7], and many efforts have been made to obtain a more homogenous cell population than the whole DPSC population. An early marker of multiple MSC-like populations, stromal precursor cell surface marker (STRO-1), has been used to purify DPSCs; however, obtaining sufficient cell numbers was problematic [20]. DPSCs showed the expression of pluripotency markers (SOX2, MYC, and OCT4), and transplanted DPSCs did not form tumors, unlike ESCs and iPSCs [14,21]. These characteristics have made DPSCs a promising candidate for stem cell therapy, especially neurological diseases such as stroke due to their neural crest origin. DPSCs have been reprogrammed to iPSCs, and some studies have shown the conversion of DPSCs into neural stem cells (NSCs) using the neurosphere culture method [22]. DPSCs were differentiated into functional neurons *in vitro* via a 2-stage protocol, comprising stimulation of neurosphere formation, followed by a neuronal maturation [23]. The neurosphere culture technique was demonstrated by Pisciotta et al. [22], who reported prolonged expansion of the spheres while maintaining the properties of the neural crest. In addition, the injected DPSCs in an embryonic model followed the migratory pathway of cranial neural crest cells and differentiated into neuronal cells [24]. Although there is some evidence of the use of the neurosphere system for prolonged culture, the conversion to NSCs via transdifferentiation may be more efficient because DPSCs originate from the neural crest. In addition, Govindasamy et al., demonstrated the differentiation of DPSCs into pancreatic islet-like cells via a 3-step protocol: 1) activin A, sodium butyrate, and b-mercaptoethanol; 2) taurine (0.3 mM); and 3) taurine (3 mM), glucagon-like peptide-1 (100 nM), nicotinamide (1 mM), and non-essential amino acids [25]. The characters of islet-like cells were confirmed by expression of C-peptide, Pdx-1, Pax4, Pax6, Ngn3, and Isl-1, as well as by dithizone-positive staining, and the functionality of islet-like cells was proven by showing glucose-dependent release of insulin and C-peptide.

Periodontal ligament stem cells (PDLSCs)

The periodontal ligament (PDL) is a specialized connective tissue fiber that connects the tooth and alveolar bone. In 2004, PDL stem cells were successfully isolated from impacted third molars, and their differentiation into cementoblast-like cells and collagen-forming cells proved their multipotency [26]. Various subsequent studies have reported the differential potential of PDLSCs according to tissue origin, donor age, culture method, and tooth condition and are still open to controversy [27]. Lee et al. [28] also demonstrated the transdifferentiation of PDLSCs into functional pancreatic islet-like clusters with 3-dimensional cell clustering on Matrigel. PDLSCs have also been applied to regenerate retinal ganglion cells via transdifferentiation. Ng et al. identified the transdifferentiation process of PDLSCs into retinal ganglion-like cells. They induced transdifferentiation with a modified protocol of Noggin-Dkk1-IGF1 induction and determined the miRNA signature of the process. The transdifferentiated cells showed the characteristics of functional neurons, which expressed retinal ganglion cell markers, such as MAP2, TAU, POU4F2, ATOH7, and SIX3, and formed synapses that induced electrical activities; furthermore, VEGF, PTEN, and miR-132 were significantly upregulated during the process [29]. Similarly, several studies have revealed that PDLSCs can differentiate into other functional cells and that both genetic and epigenetic factors are involved in the process of transdifferentiation.

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Stem cells from human exfoliated deciduous teeth (SHEDs)

Deciduous teeth are naturally shed during the eruption of permanent teeth, and the exfoliated deciduous teeth are usually disposed of. The cells from these exfoliated deciduous teeth can differentiate into various useful cells with only a few ethical problems. SHEDs were first identified by Miura et al. [11] in 2003, and they have received attention as stem cell sources in regenerative medicine with high multipotency and proliferative capacities [30]. It has been reported that SHEDs have the ability of multilineage differentiation [31], in addition, they have a distinct property of inducing the formation of a bone-like matrix with a lamellar structure, which was explained by root resorption of deciduous teeth that occurs due to new bone formation around the root [32]. The multilineage differentiation capability of SHEDs was also confirmed in the study of Esmaeili et al. [33]. The neural-like cells derived from SHEDs produced neurotrophic factors, including BDNF, NGF, NT-3, and NT-4.

Tooth germ stem cells (TGSCs)

TGSCs have become a popular cell source with high differentiation potential into multilineage cell types. As a promising cell source for tooth regeneration, mesenchymal cells with endothelial and epithelial cells are strictly needed for tooth morphogenesis. Dogan et al. showed that human TGSCs successfully differentiated into endothelial and epithelial-like cells, which expressed cell-lineage markers for endothelial cells (vWF, VE-cadherin, CD31, and VEGFR2) and epithelial cells (vimentin, EpCaM, and cytokeratin) [34].

Dental follicle stem cells (DFSCs)

Stem cells are also found in the developing dental tissues, including the dental follicle, apical papilla, and tooth germ. The dental follicle is a developing dental sac, which contains loose connective dental tissue. DFSCs were first isolated in 2005 [35], and various studies have shown their multipotent nature, manifesting as an ability to differentiate into various types of cells [36,37]. *In vivo* transplantation of DFSCs into mice resulted in new PDL formation [38], salivary gland-like cells [39], and tooth-root-like tissues [40]. In recent research, DFSCs have been found to exert an immunosuppressive function in both innate and adaptive immune systems and have been applied for the treatment of inflammatory diseases in animal models [41].

Stem cells from the apical papilla (SCAPs)

SCAPs originate from the tooth apical papilla, including the precursor cells of the dental pulp, which are isolated from the wisdom tooth or the open apex of the tooth. In 2006, SCAPs were first isolated from the apical papilla of incompletely developed teeth [42]. Moreover, *in vitro* and *in vivo* studies have demonstrated that SCAPs can differentiate into osteoblasts, and odontoblasts; they have higher stemness due to their potential for tooth formation [43]. Many studies have demonstrated that SCAPs could differentiate into osteoblasts or odontoblasts. Growth factors, such as BMP [44], WNT [45], and IGF [46] promoted the osteogenic and odontogenic differentiation of SCAPs; however, sonic hedgehog [47], homeobox C10 [48], and microRNA hsa-let-7b [49] inhibited SCAP differentiation.

Oral mucosa derived stem cells (OMSCs)

The oral mucosa comprises the epithelium; connective tissue, including the lamina propria; and submucosa. Owing to the ease of obtaining the tissue from oral surgical sites or discarded samples, OMSCs have been the focus of stem cell studies. Various stem cells have been identified in the oral mucosa, namely, OMSCs, oral epithelial stem cells (OESCs), and gingiva-derived MSCs (GMSCs). OMSCs are isolated from the gingiva's lamina propria and can differentiate into other lineage cells [50]. OESCs are isolated from oral keratinocytes,

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which are a small subpopulation of cells but can regenerate the oral mucosa and show an enriched quiescent cell population and long-term proliferative potential [51]. GMSCs have multipotency and high proliferation and self-renewal capacity [52].

BMSCs

The bone marrow is a semi-solid tissue located inside the cancellous bone, where hematopoiesis occurs (i.e., the production of blood cells, such as red blood cells, platelets, and white blood cells). BMSCs in dental tissue can be obtained from the orofacial bones [53,54]. BMSCs are mainly taken from the maxilla or mandible by aspiration during surgical procedures, such as tooth extraction, dental implant surgery, cyst enucleation, and orthognathic surgery [55]. It has been reported that the donor's age does not have a substantial impact on the regenerative potential of BMSCs. Preclinical [56] and clinical [57] studies have shown excellent regenerative properties of orofacial-derived bone grafts in comparison with those of ex-orofacial grafts, such as those derived from the rib or the iliac crest [58]. In addition, Song et al. [59] demonstrated that fully differentiated cells from human BMSCs were capable of transdifferentiation or dedifferentiation into cells of another developmental lineage at the single-cell level. The results showed that fully differentiated osteoblasts from BMSCs helped to transdifferentiate into adipocytes and chondrocytes, and fully differentiated adipocytes and chondrocytes from BMSCs could transdifferentiate into other mesenchymal lineages.

Collectively, the most frequently targeted dental stem cells in previous studies were cells from dental pulp (DPSCs) and periodontal ligament (PDLSCs). SHEDs also have high stemness, but SHEDs are often not isolated and stored in childhood. Although DPSCs and PDLSCs have a lower potential for proliferation than SHEDs, they are obtained relatively easily from teeth selected for extraction or endodontic treatment and have high differentiation potential [60]. In addition, OMSCs have received extensive attention due to their convenient procurement; however, their stemness is lower than that of other cell types. Many *in vitro* pre-clinical and clinical studies have demonstrated promising results regarding dental stem cells for tissue engineering (**Table 1**) [61-72]. However, the first step is to define the differentiation capacity using validated *in vitro* and *in vivo* transplantation assays. More in-depth studies are necessary to establish a strategy for the clinical use of dental stem cells. Several recent studies have been conducted to obtain the desired cells, rather than stem cells, using new technologies.

Table 1. Therapeutic potentials of dental tissue-derived stem cells

Target	Outcome	References
Neural system	Differentiation of DPSCs into immature neuronal-like and oligodendrocyte-like cells.	[61]
Cerebral ischemia	Transplantation of human DPSCs in a rodent model of focal cerebral ischemia resulted in significant improvements in forelimb sensorimotor function.	[62]
Optic nerve regeneration	Intravitreal transplants of DPSCs promoted significant neurotrophin-mediated retinal ganglion cell survival and axon regeneration after optic nerve injury.	[63]
Myocardial infarction	DPSCs improved ventricular function, inducing angiogenesis and reducing infarct size in rat model.	[64]
Muscle regeneration	Clones of DPSCs improved muscle regeneration through dystrophin and myosin heavy chain.	[65]
Bone regeneration	DPSC-containing scaffolds had the potential to ameliorate the bone regeneration process.	[66]
Socket preservation	(Clinical trial) Clinical application of a DPSC-collagen sponge complex restored mandibular bone defects.	[67]
Irreversible pulpitis	(Clinical trial) Transplantation of DPSCs with atelocollagen transplanted regenerated the pulp.	[68]
Periodontal disease	(Clinical trial) Transplantation of PDLSCs into intrabony defect improved periodontal conditions.	[69]
	(Clinical trial) Safety and efficacy of autologous PDL-derived cell sheets were evaluated in a clinical setting.	[70]
Gingival recession	(Clinical trial) The application of autologous fibroblasts resulted in a significant gain of gingiva in terms of root coverage.	[71]
	(Clinical trial) Autologous fibroblasts on a collagen matrix were effective in the treatment of gingival recession.	[72]

DPSC, dental pulp stem cell; PDLSC, periodontal ligament stem cell.

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CELL REPROGRAMMING

Considerable efforts have been devoted to obtaining adult stem cells, and various studies have shown the possibility of cell reprogramming due to advances in genetic engineering. Despite the thought that somatic cells are fully differentiated, have a specific molecular pattern that determines cellular function and physiology, and remain permanent or stable throughout life, somatic cells can also be used for tissue regeneration through their induction into pluripotent stem cells (**Figure 1B**) or direct conversion to another cell type (**Figure 1C**).

iPSCs

iPSCs were first discovered in 2006 by Dr. Shinya Yamanaka, who showed that mouse skin fibroblasts can be reprogrammed to an embryonic stem cell state using defined factors, Oct3/4, Sox2, Klf4, and c-Myc, which were named the Yamanaka factors [73]. In 2007, human iPSCs were produced by Yamanaka's and Thomson's labs from human fibroblast [73,74]. The basis of iPSCs is that dedifferentiation is induced in adult somatic cells to a pluripotent stem cell state and then cells are redifferentiated to the desired cell lineages. With great potential for clinical application, this research program has expanded the scope of regenerative medicine and supported personalized medicine using individual cells. In dentistry, iPSCs have been efficiently generated from gingival fibroblasts, mucosal fibroblasts, and various oral stem/progenitor cells, including those from the PDL and deciduous teeth (**Table 2**) [75-78]. The factors of c-Myc/Klf4/Oct4/Sox2 or Lin28/Nanog/Oct4/Sox2 were used to reprogram dental stem/progenitor cells into iPSCs [75]. Dental pulp cells from extracted teeth and oral mucosa fibroblasts obtained from biopsy effectively established iPSCs [76,77]. Dental tissue-derived cells showed a high reprogramming efficiency [78], and differentiation of iPSCs into ameloblasts and odontogenic mesenchymal cells indicated the possibility of tooth regeneration [79]. This revolutionary discovery has made it possible to obtain pluripotent stem cells as an alternative to ESCs, overcoming the ethical concerns associated with them and bringing forth a novel method of dedifferentiation. In addition, the cell reprogramming technology to produce iPSCs has provided the potential for tissue regeneration for clinical use, and several studies have demonstrated the differentiation of iPSCs into various functional cells, and therapeutic effects of delivered iPSCs in animal disease models (**Table 3**) [80-91].

Although mounting scientific evidence has shown that dental-derived cells are useful somatic cell sources for iPSC generation, a number of problems remain to be solved. The key challenge of iPSCs in clinical application is the risk of carcinogenesis because the Yamanaka factors are protooncogenes and their expression is high in cancers, and incomplete differentiation and reactivation of Yamanaka factors also accelerate carcinogenesis [92]. In addition, further insights are needed to reconsider their capability and characteristics based on the fact that all iPSCs are not equivalent. IPSCs derived from different types of cells may have differential regenerative capacity based on their inherited epigenetic memory. Some studies have demonstrated that iPSCs have epigenetic memory of previous tissue types, which can affect the reprogramming potential of iPSCs [93]. IPSCs from blood cells and

Table 2. Dental tissue-derived iPSCs

Types	Outcome	References
Dental tissue-derived iPSCs	Dental pulp cells were useful for iPSCs.	[75]
	Oral mucosa fibroblasts had high potential for iPSCs.	[76]
	Gingival fibroblast and periodontal ligament were identified as an excellent cell source for iPSCs.	[77]
	Stem cells from dental pulp, apical papilla, and deciduous tooth served as an excellent source for iPSC generation.	[78]

iPSC, induced pluripotent stem cell.

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Table 3. The therapeutic potential of iPSCs for tissue regeneration

Target	Results	References
Cardiomyocytes	Murine iPSCs differentiated into functional cardiomyocytes.	[80]
	Human iPSCs differentiated. into functional cardiomyocytes.	[81]
Endothelial cells	Endothelial cells derived from human iPSCs increased capillary density and improved perfusion in a mouse model of peripheral arterial disease.	[82]
Neural cells	Neurons derived from iPSCs functionally integrated into the fetal brain and improved symptoms of Parkinson's disease in a rat model.	[83]
	Neural differentiation of iPSCs in a mouse model of spinal cord injury.	[84]
	iPSCs from patients with Parkinson's disease differentiated into dopaminergic neuron.	[85]
b-cells	Human iPSCs differentiated into insulin-producing cells in a chemical defined culture system.	[86]
	b-like cells derived from iPSCs secreted insulin in a mouse model of diabetes	[87]
Bone cells	Differentiation of osteoblasts and osteoclasts from human iPSCs.	[88]
	iPSCs could be successfully differentiated to osteoblast lineage cells.	[89]
	Osteoblasts were generated from human pluripotent stem cells under fully defined xeno-free conditions with small-molecule inducers.	[90]
	Lineage-specific differentiation of osteogenic progenitors from human iPSCs revealed the FGF1-RUNX2 association in neural crest-derived osteoprogenitors.	[91]

iPSC, induced pluripotent stem cell.

skin fibroblasts show distinct patterns of differentiation potential; blood cell-derived iPSCs easily transform into hematopoietic colonies, but iPSCs from fibroblasts form osteogenic colonies readily. These studies suggested that some specific features could be acquired during reprogramming, or some remnants of the epigenetic pattern and sequential gene expression could remain from the donor tissue. These residual signatures of epigenetic factors and transcription of the origin cells were termed epigenetic memory [93]. Therefore, the successful formation of iPSCs through reprogramming requires adjustment of the epigenetic landscape to change the epigenetic state.

Epigenetics and epigenetic memory

Epigenetic memory is defined as the inherited modifications of chromatin, which can alter gene expression and affect the phenotypes and properties of cells [94]. This memory could be inherited from ancestor cells by processes such as genomic imprinting and changed by environmental factors [95]. Genetics plays a crucial role in cellular development and physiology; however, epigenetics plays an essential role in the regulation of gene expression. Typical types of epigenetic changes include DNA methylation, histone modification, and production of non-coding RNAs, and these changes affect gene expression in different ways (**Figure 3**) [96].

DNA methylation

DNA methylation mostly occurs at the C-5 position on the cytosine residue in CpG dinucleotides by the addition of a methyl group catalyzed by methyltransferases [97]. In contrast, DNA demethylation is carried out at 5-methylcytosine (5mC) by DNA glycosylase or deaminase. This action of DNA methylation induces a change in the chromatin structure and, along with other epigenetic components, turns gene expression on or off.

Histone modification

Histones are proteins that associate with each other to form the core of nucleosomes, around which chromatin is wrapped and condensed [98]. Histone modifications are an example of post-translational modifications (PTMs), which include acetylation, methylation, ubiquitylation, phosphorylation, and sumoylation. These PTM processes induce the alteration of chromatin structure, which affects diverse biological processes such as transcriptional activation and repression. Among PTMs, acetylation and methylation are

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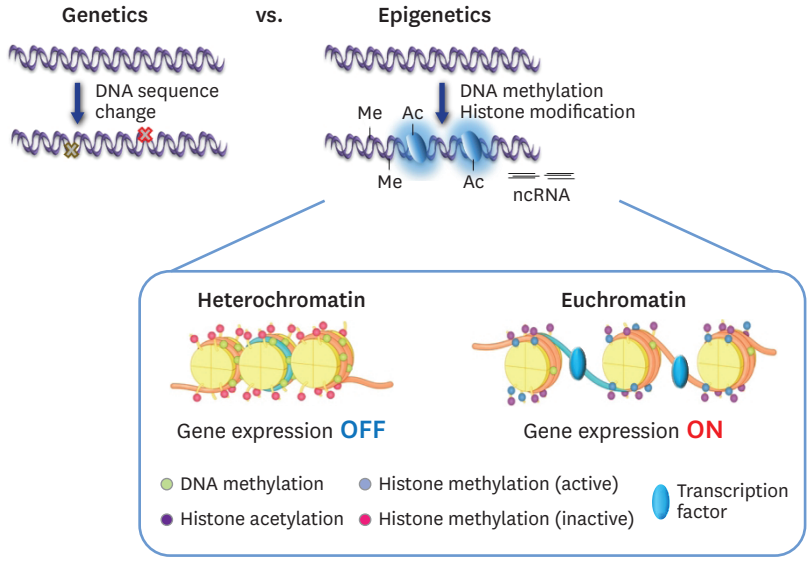

Figure 3. The mechanism of epigenetics. Unlike genetic changes, epigenetic changes do not involve changes in DNA sequences; rather, they change how transcription factors read these DNA sequences. The main epigenetic mechanisms are DNA methylation, histone modification, and regulation by ncRNA. DNA methylation induces a compact structure of DNA and histone proteins; therefore, transcription factors are unable to bind to the promoter region, and gene expression is suppressed. In contrast, histone acetylation induces a loose structure of the DNA and histone complex, and transcription factors bind to the promoter, activating gene expression. ncRNA: non-coding RNA.

tightly involved in chromatin dynamics catalyzed by histone acetyltransferases (HATs), deacetylases (HDACs), and methyltransferases (HMTs) at certain lysine residues.

Non-coding RNAs (ncRNA)

Unlike coding RNA, which encodes proteins, ncRNA does not encode functional proteins and regulates gene expression at the post-transcriptional level. The category of ncRNA is divided into two groups: short-chain ncRNAs—including microRNA (miRNA), small-interfering RNA, and piwi-interacting RNA—and long non-coding RNA (lncRNA) [99]. As previous studies did not elucidate the mechanism of alteration of gene expression without changes in the DNA sequence, epigenetics has emerged as an active research field to shed light on this phenomenon. Epigenetic changes may be induced as a response to our living environment, foods we eat, exposure to pollutants, and even our social interactions. Moreover, epigenetic changes may be caused by the use of long-term medication, nutrient intake, and other environmental factors, and may affect susceptibility to diseases, response to treatment, and prognosis [100].

TRANSDIFFERENTIATION

Transdifferentiation is the direct conversion between different cell types without induction of the pluripotent cell state (**Figure 1C**). It is known to occur naturally by cell injury or artificially under experimental conditions. The fundamental difference between cell reprogramming and transdifferentiation is that in cell reprogramming, full reversal into the pluripotent state occurs, whereas, in transdifferentiation, it does not. Eguchi [101] reported a natural transdifferentiation phenomenon during Wolffian lens regeneration from iris-pigmented epithelial cells in newts. Cartilage regeneration from fibroblasts during urodele amphibian

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Table 4. Trials of transdifferentiation using dental-derived cells

Target	Outcome	References
Cardiac muscle	Co-culture of dental pulp cells with cardiomyocytes induced the nuclear translocation of cardiac-specific transcription factors (NKX2.5 and GATA4) that regulate the appearance of cardiac markers.	[103]
Skeletal muscle	5-Aza-2′-deoxycytidine treatment induced skeletal myogenic differentiation in dental pulp stem cells.	[105]
Endothelial cells	DPSCs transplanted in mice with Matrigel enhanced angiogenesis by secreting VEGF ligands and associating with vessels resembling pericyte-like cells.	[106]
Neuronal cells	DPSCs cultured under neuroinductive conditions differentiated into immature neuronal-like networks.	[104]
Pancreatic cells	PDLSCs cultured in Matrigel with differentiation-inducing agents could transdifferentiate into functional pancreatic islet-like cells.	[28]

DPSC, dental pulp stem cell; PDLSC, periodontal ligament stem cell.

limb regeneration also showed transdifferentiation [102]. In addition, a number of studies have reported that dental-derived cells may have the capacity to differentiate into desired cells such as cardiac cells, neuronal cells, and pancreatic cells [28,103-105], and various experimental studies have indicated the potential of transdifferentiation (**Table 4**) [28,103-106]. By forced ectopic expression of specific genes using transfection of transcription factors, B cells could become macrophages [107], and fibroblasts could become neurons [108], cardiac cells [109], and hepatocytes [110]. Additionally, miRNA, episomal vectors, proteins, and small molecules have also been used to generate desired cells by bypassing the pluripotent state [111,112]. Similar to iPSCs, in the early days, transdifferentiation was induced by a transgene method using transcription factors. The use of a viral vector such as a retrovirus or lentivirus to overexpress transgenes could cause cancer by transgene inactivation and insertional mutagenesis; therefore, a non-integrating viral approach with an adenovirus, and another method using an episomal vector and excisable vector could be alternatives to reduce the risk of carcinogenesis [92]. Epigenetic memory, which is a limitation of reprogramming, should be correctly erased in the original cells, and memory should be newly adapted to target cells. It seems that transdifferentiation would be a better alternative to iPSCs for reducing the effort needed for dedifferentiation and the risk of carcinogenesis; however, this possibility has yet to be clearly established due to the epigenetic changes that could occur in the process of transdifferentiation. In this context, several studies have reported changes in the epigenetic landscape during transdifferentiation procedures [113-115]. The shift in DNA methylation is also involved in transdifferentiation from B cells to macrophages [116], adipocytes to osteoblasts [117], and gingival fibroblasts to osteoblasts [118]. Treatment with a DNA methyltransferase inhibitor, 5-aza-2'-deoxycytidine (5-aza-dC), changed the level of DNA methylation on the promoter of peroxisome proliferator-activated receptor gamma and alkaline phosphatase, and sequential Wnt3a treatment induced transdifferentiation from adipocytes to osteoblasts [117]. In a similar way, pre-treatment of 5-aza-dC and sequential BMP2 induced direct conversion from gingival fibroblasts to osteoblasts [118]. Histone modification also induced transdifferentiation. Transient expression of reprogramming factors induced transdifferentiation from fibroblasts to cardiomyocytes with decreased H3K27me3 and increased H3K4me3 at the Oct3 promoter. The level of H3K4me2 was changed during transdifferentiation, and increased in the muscle-specific miR-1-2/miR-133a-1 cluster [119,120]. Additionally, several studies have also addressed the possibility of transdifferentiation into cardiomyocytes or neurons through modulation of miRNA or lncRNA [121-123]. As such, various *in vitro* and *in vivo* pre-clinical trials to induce transdifferentiation have been performed (**Table 5**) [117,118,124-131]; however, well-designed and controlled practical protocols should be established for the next step, clinical application.

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Table 5. Experimental methods for transdifferentiation

Types	Method	Transdifferentiation (from/to)	References
Transgene overexpression	Viral vectors including Brn2, Mty1l, and miRNA-124	Dermal fibroblasts/Neurons	[124]
	Viral vectors including Runx2 and MKP-1	Adipocytes/Osteoblasts	[125]
	Viral vectors including Hnf1a, Hnf4a, and Foxa3	Fibroblasts/Hepatocytes	[126]
	Electroporation of Ascl1, Brn2, Myt1l, and Ngn2	Blood T cells/Neurons	[127]
Endogenous gene activation	CRISPR/dCas9 application on Myod1	Fibroblasts/Myocytes	[128]
Endogenous gene silencing	CRISPR/Cas9 application on Myod1	Myoblasts/Adipocytes	[129]
Pharmacological agent	Treatment of 5-azacytidine	Fibroblasts/Myocytes	[130]
	Polyinosinic-polycytidylic acid	Skin fibroblasts/Endothelial cells	[131]
	Treatment of 5-aza-2 dC and Wnt3a	Adipocytes/Osteoblasts	[118]
	Treatment of 5-aza-2 dC and BMP2	Gingival fibroblasts/Osteoblasts	[117]

CONCLUSION

Regenerative medicine using dental-derived cells has been gradually developing. Identification and isolation of stem cells, cell reprogramming, and transdifferentiation with dental-derived cells are innovations in the field of tissue engineering to obtain the desired cells for regenerative medicine. Currently, stem cell therapies are applied as treatment modalities for potentially fatal diseases, including spinal cord injury, retinal regeneration, and heart failure. In addition, the generation of target cells from somatic cells via iPSCs or transdifferentiation using biomolecules such as chemical compounds, transcription factors, or growth factors have expanded the field of applications and opened new opportunities for cell therapy and disease modeling. The use and application of cell reprogramming with dental-derived cells have emerged recently and continue to be researched, and epigenetic studies related to epigenetic memory are being conducted. Dental tissue-derived cells should be an excellent cell source for all processes, as they are easy to procure and have a good proliferation or differentiation ability based on accumulated scientific evidence. However, considerable heterogeneity may exist between cells derived from the same source of dental stem cells, which can affect the clinical outcomes, and cell delivery methods are also likely to affect the success of clinical trials. Several clinical trials using autologous dental-derived stem cells for tissue regeneration have already been tried, but the long-term results of these studies have not been well reported. Therefore, it is necessary to understand the mechanism of how to control the fate and function of delivered cells, and more pre-clinical and clinical trials are required to ensure and optimize the efficacy of cell therapy and to apply cell therapy in clinical settings. Although more in-depth and careful research is needed to overcome obstacles, the valuable regenerative benefits of dental-derived cells for prolonging and improving human health can be ascertained.

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