Regenerative Therapy 14 (2020) 72–78

Contents lists available at ScienceDirect

Regenerative Therapy

journal homepage: http://www.elsevier.com/locate/reth

Review

Mesenchymal stem cell-based tissue regeneration therapies for periodontitis

Takehito Ouchi*, Taneaki Nakagawa

Department of Dentistry and Oral Surgery, Keio University School of Medicine, Shinjuku-ku, Tokyo, 160-8582, Japan

ARTICLE INFO

Article history:
Received 16 May 2019
Received in revised form
5 November 2019
Accepted 24 December 2019

Keywords:
Periodontitis
Periodontal tissue
Tissue regeneration
Mesenchymal stem cells
Pluripotent stem cells

ABSTRACT

Periodontitis is commonly observed and is an important concern in dental health. It is characterized by a multifactorial etiology, including imbalance of oral microbiota, mechanical stress, and systemic diseases such as diabetes mellitus. The current standard treatments for periodontitis include elimination of the microbial pathogen and application of biomaterials for treating bone defects. However, the periodontal tissue regeneration via a process consistent with the natural tissue formation process has not yet been achieved. Developmental biology studies state that periodontal tissue is composed of neural crest-derived ectomesenchyme. To elucidate the process of periodontal regeneration, it is essential to understand the developmental background and intercellular cross-talk. Several recent studies have reported the efficacy of transplantation of mesenchymal stem cells for periodontal tissue regeneration. In this review, we discuss the basic knowledge of periodontal tissue regeneration using mesenchymal stem cells and highlight the potential of stem cell-based periodontal regenerative medicine.

Contents

1. Introduction

Periodontal tissues include soft tissues such as gingiva and periodontal ligaments (PDLs) and hard tissues such as the alveolar bones. Periodontitis is usually defined as bone resorption and periodontal tissue destruction due to acute (sometimes aggressive) or chronic inflammation. And periodontitis is very important concerns not only in dental health but also systemic health. The primary treatments for periodontal tissue inflammation include scaling and root planing and periodontal surgery for periodontal tissue reconstruction. Periodontal tissue regeneration using guided tissue regeneration and enamel matrix derivatives are being used

Abbreviations: BMMSCs, bone marrow MSCs; BMP, bone morphogenetic protein; C-MSCs, clumps of MSC/ECM complexes; DFSCs, dental follicle stem cells; ECM, extracellular matrix; FGF, fibroblast growth factor; GDF-5, growth/differentiation factor-5; HERS, Hertwig epithelial root sheath; IFN-γ, interferon-gamma; IGFBP-6, insulin-like growth factor binding protein-6; iPSC-MSCs, iPSC-derived MSCs; iPSCs, induced pluripotent stem cells; LepR, leptin receptor; MSCs, mesenchymal stem cells; NCCs, neural crest cells; PDGFRα, platelet derived growth factor receptor α; PDL, periodontal ligament; PDLSCs, periodontal ligament stem cells; scRNA-seq, single-cell RNA sequence; TNF-α, tumor necrosis factor-alpha; Wnt, wingless-INT.

* Corresponding author. Fax: +81 3 3357 1593.
E-mail address: mindscape0107@keio.jp (T. Ouchi).

Peer review under responsibility of the Japanese Society for Regenerative Medicine.

https://doi.org/10.1016/j.reth.2019.12.011

for 2–3-wall alveolar bone defects [1,2]. These methods depend on mesenchymal stem cells (MSCs) residing in the periodontal tissues, space provision for the differentiation of MSCs, and the availability of growth factors. In addition to resident MSCs, circulating MSCs also can contribute to periodontal tissue regeneration. The purpose of this review is to understand stem cell biology based on developmental background on periodontal tissues in order to realize stem cell therapy for periodontal tissue regeneration. This review article outlines developmental of periodontal tissues, application of tissue stem cells and tissue engineering for periodontal tissue regeneration. We will discuss on the utilities of pluripotent stem cells in the last section.

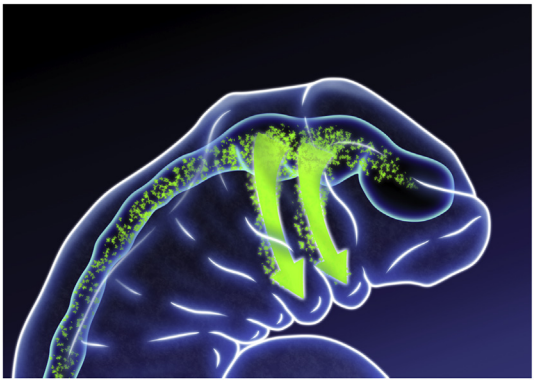

Fig. 1. Neural crest cells move from the dorsal region to the pharyngeal arch present in the ventral region.

2. Development of periodontal tissue

Periodontal tissue originates from cranial neural crest-derived mesenchyme. Neural crest cells (NCCs) are transient cells and are first identified during neural tube closure in the embryonic stage. After neural tube closure, the NCCs migrate to the craniofacial region and are involved in the development of craniofacial bones and neural tissues [3,4]. The periodontal tissue is organized by migration of NCC-derived mesenchymal cells via the two-component Cre-loxP strategy [5]. The absence of somite structures in the cranial region allows unobstructed NCC migration in this region, unlike that in the body trunk region (Fig. 1). This anatomical background enables the cranial NCCs to migrate like mesoderm

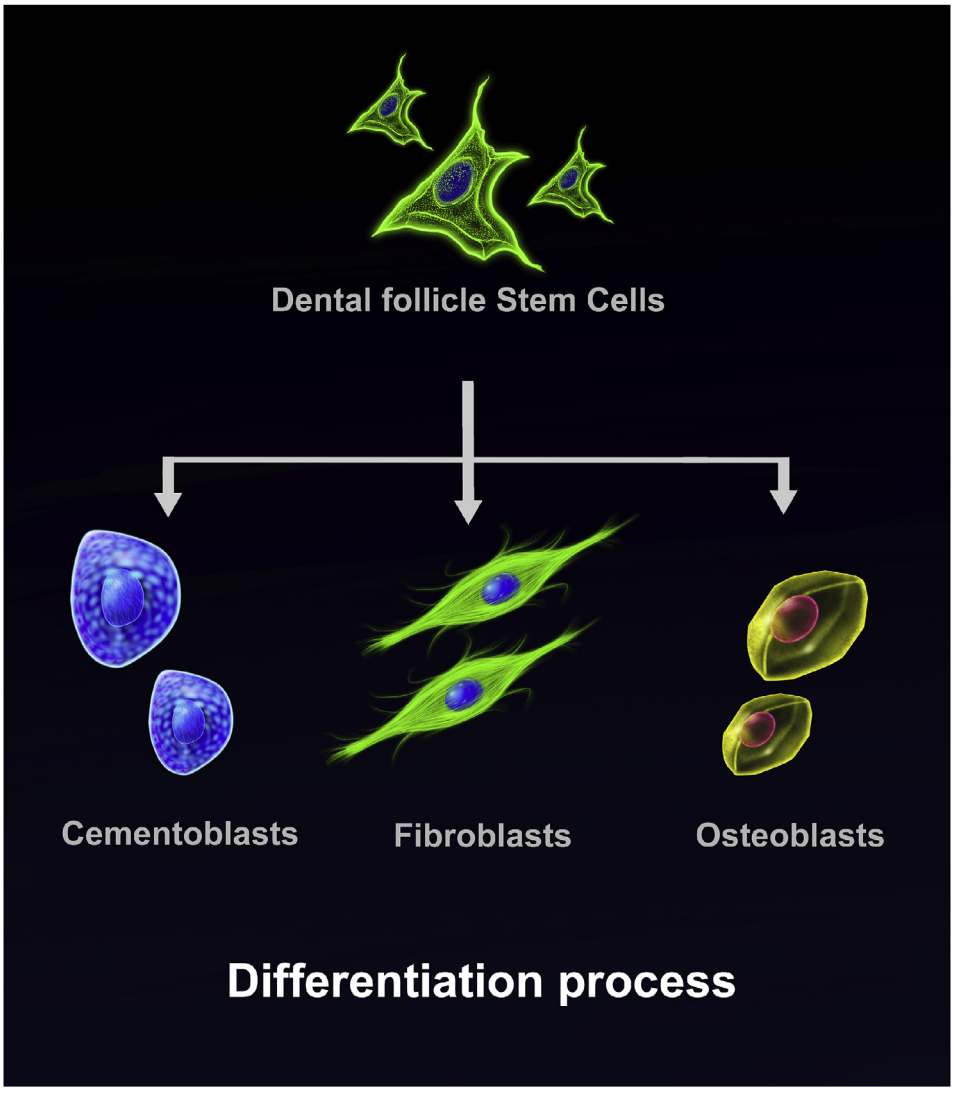

Fig. 2. Dental follicle stem cells are top-most in the cellular hierarchy and are capable of differentiating into cementoblasts, fibroblasts, and osteoblasts.

cells. NCCs arise from the dorsal region and migrate to the pharyngeal arch present on the ventral region; the pharyngeal arches interact with each other and form craniofacial tissues [6,7]. Once the NCCs reach the cranial region, they are termed as neural crest derived-mesenchymal cells or ectodermal mesenchymal cells, and they proliferate and differentiate to form the dental organs and periodontium. Ectodermal mesenchymal cells form dental papilla and dental follicle, which give rise to dental pulp, dentin, and periodontium. Dental follicle stem cells (DFSCs) have potentials to differentiate into periodontal lineage cells, which are cementoblasts, fibroblasts, and osteoblasts (Fig. 2). In the embryonic stage, the odontogenic epithelium invaginates the odontogenic mesenchymal tissue in response to cross-talk via the bone morphogenetic protein (BMP), fibroblast growth factor (FGF), and wingless-INT (Wnt) signaling pathways [8,9]. In the early stage, dental cells condense and form a bud shape (Fig. 3A and B); further proliferation and differentiation of cells in this bud leads to the cap phase and an agglutination mass (Fig. 3C). During the cap phase, periodontal tissue formation begins and enamel matrix proteins are secreted from the enamel epithelium; these proteins induce the bell phase of development (Fig. 3D and E). The Hertwig epithelial root sheath (HERS) deteriorates and the residual cells form clusters termed as the epithelial rests of Malassez (Fig. 4A).

DFSCs derived from ectodermal mesenchymal cells function as dental MSCs and proliferate to form PDL fibers (Fig. 4B). Owing to the disintegration of the HERS and the formation of epithelial rests of Malassez, the DFSCs migrate around the root of the tooth and differentiate into cementoblasts, which lead to cementum formation, thereby completing the root formation process [10]. Some groups reported the possibility that acellular cementum developmentally derived from epithelium. *In vitro* assay revealed that HERS cells developed to mesenchymal cells with expression of mesenchymal markers and snail via epithelial–mesenchymal transition [11]. HERS cells initially express dental epithelial cells marker, then cells produce extra cellular matrix, which is similar to acellular cementum [12]. However, the hypothesis on cementum formation derived from epithelium is still controversial because it's reported that HERS is just embedded in cementum, which means that epithelial cells do not develop to cementum itself [13].

DFSCs differentiate into osteoblasts, thereby forming the alveolar bones (Fig. 4C). As described earlier, the ectomesenchyme derived from cranial NCCs is capable of differentiation into periodontium. PDL in adults is identified as the niche of neural crest derived-stem cells capable of differentiation into hard tissue cells [14]. These reports and information support the concept that NCCs, and their descendant MSCs regulate and control the development and homeostasis of periodontal tissues.

3. Periodontal tissue regeneration with somatic NCCs and MSCs

Owing to their embryological involvement, the periodontal tissue lineage cells were analyzed as potential candidates for periodontal tissue regeneration. PDL-committed progenitor and stem cell populations were reported to exhibit cementogenic potential [15]. Cementum-derived cells or PDL-derived cells promoted periodontal regeneration in an experimental three-wall intrabony periodontal defect [16]. Moreover, PDL stem cells (PDLSCs) express CD271, a marker for NCCs and MSCs. $CD271^{+}$ cells show osteogenic potential with strong induction of osteogenic markers such as DLX5, RUNX2, and BGLAP [17]. Feng et al. reported that PDL-derived cells, mixed with bone-grafting material, were implanted into periodontal pockets area, and patients were monitored over the course of 6 years. This investigation showed that PDL-derived cells may be effective in periodontal tissue regenerative therapy [18]. Thus, PDL-derived cells hold the potential of stem cells to form bone, cementum and PDL-like structures and to enhance periodontal tissue regeneration. DFSCs are also considered potential candidates owing to their ability to differentiate into PDL or cementum. Oshima et al. used a dental implant and embryonic

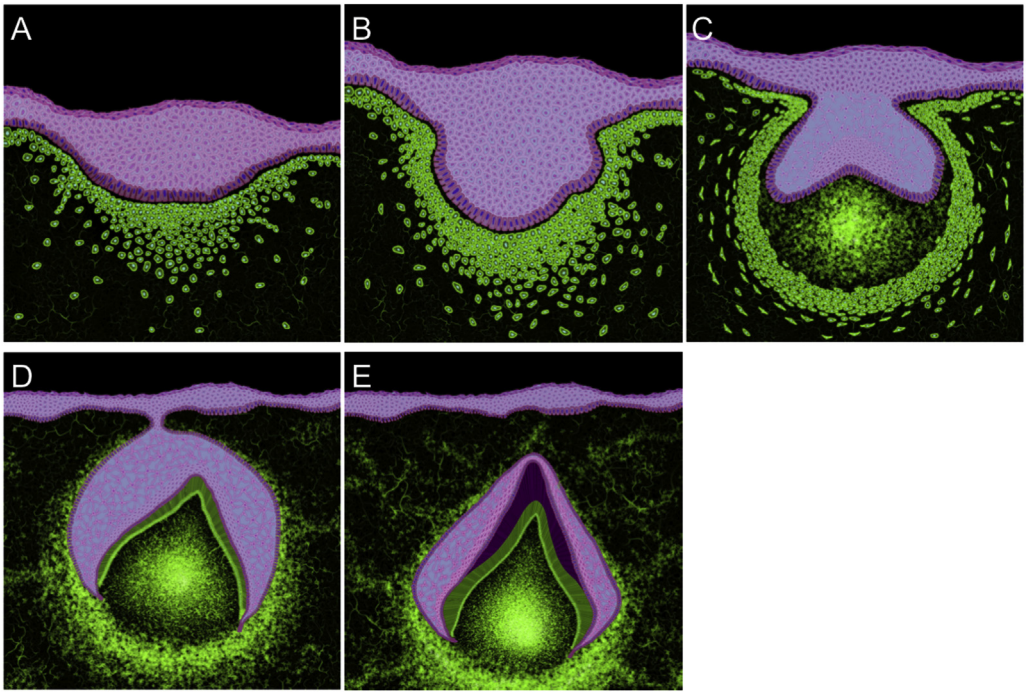

Fig. 3. Dental and periodontal tissue development is achieved via the interaction and invagination of epithelial (pink color) and mesenchymal cells (green color). Developmental stage is classified to placode phase (A), bud phase (B), cap phase (C), early bell phase (D), and late bell phase (E).

dental follicle tissue to develop a bio-hybrid dental implant with the ability to sense pain. In response to invasive pressure, dental follicle cells differentiate into PDL-like tissue [19]. However, it is difficult to obtain sufficient quantities of PDLSCs and DFSCs because of their tiny population and ethical issues. Therefore, other adult derived stem cells were investigated for their therapeutic potential. Khorsand et al. demonstrated the application of dental pulp-derived MSCs for canine periodontal tissue regeneration [20]. Dental pulp cells have the characteristics of NCCs and the potential to differentiate into bone mineralized tissue [21]. Yamada et al. conducted implantation of dental pulp cells into a surgically created periodontal defect area in dog model, and this study showed that promotion of regeneration by well-formed mature bone with neovascularization [22]. Dental pulp cells were applied for repairing human bone defects in clinical study. Cells obtained from the molars were combined with a collagen sponge scaffold and implanted into the extracted tooth space to prevent post-operative bone loss. Bone regeneration was achieved by optimal bone repairing process [23].

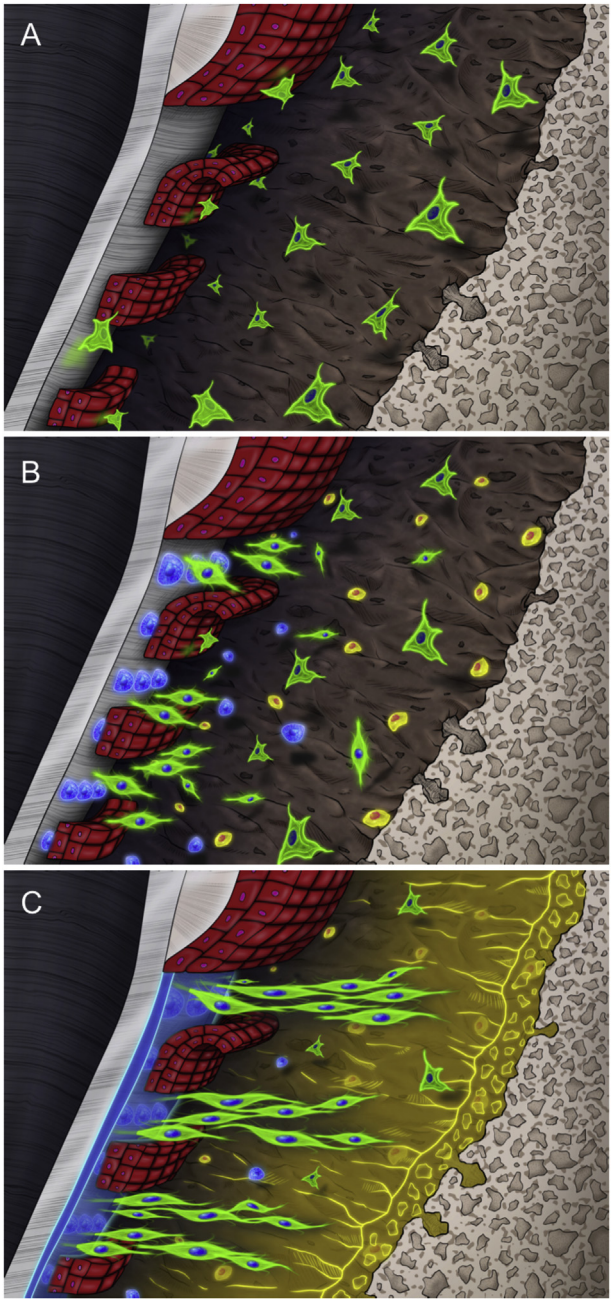

Fig. 4. The Hertwig epithelial root sheath deteriorates. The residual cells form the epithelial rests of Malassez (red color) (A). Dental follicle stem cells (DFSCs) (green color) proliferate and develop into periodontal ligament fibers (B). DFSCs migrate around the root of the tooth and enable cementum formation (blue color). DFSCs also differentiate to form the alveolar bone (yellow color) (C).

In addition, non-odontogenic MSCs such as bone marrow MSCs (BMMSCs) also contribute to periodontal tissue regeneration by local transplantation [24]. BMMSCs injected into periodontal defects exerted anti-inflammatory and immunomodulatory effects, and contributed to the regeneration [25]. Systematic transplantation of BMMSCs were recruited to periodontal tissue defects [26]. A recent study involving lineage tracing revealed that BMMSCs have the characteristics of NCCs. Neural crest-derived Nestin^{+} cells comprise platelet derived growth factor receptor α (PDGFRα)$^{+}$ MSCs [27]. These data indicate the possibilities of existence of the neural crest-derived stem cells in bone marrow, and their contribution to healing of periodontal tissues. For previous decades, cell surface maker-based gating strategy identified legacy MSCs markers and revealed that Nestin, PDGFRα, and Leptin receptor (LepR) are expressed within similar MSCs cluster [28]. However, David T. Scadden's group very recently reported that Nestin^{+} cells are molecularly defined as distinct to LepR^{+} MSCs by using rigorous single-cell RNA sequence (scRNA-seq) and cellular taxonomy [29]. Now, scRNA-seq is utilized for production of mapping for BMMSCs and elucidation of their differentiation path [30]. Gating strategy and scRNA-seq technology will reveal that what marker definitively contributes to periodontal tissue regeneration in future. MSCs derived from fat tissue also can be utilized for periodontal tissue regeneration [31]. Adipose tissue-derived stem cells acquire cementoblast features treated with DFSCs conditioned medium [32]. Sawada et al. demonstrated that adipocyte derived cells secreted growth factors, including insulin-like growth factor binding protein-6 (IGFBP-6), and IGFBP-6 is crucial regulatory roles in differentiation of adipose derived cells-induced periodontal regeneration [33]. Thus, the non-odontogenic MSCs have potential to be used for cytotherapy. However, MSCs from dental tissues and those from other tissues show different marker expression and differentiation potential [34]. Furthermore, dental MSCs are distinct from other MSCs such as BMMSCs with respect to the regulation of T-lymphocyte survival and proliferation [35]. Therefore, further studies should focus on investigating the utility of dental MSCs and non-odontogenic MSCs for periodontal tissue regeneration.

4. Tissue engineering for periodontal tissue regeneration

The tissue engineering approach involves the use of cells, a scaffold, and the appropriate growth factors [36]. Recent tissue engineering techniques provide several approaches for regenerative medicine. Akazawa et al. reported cell sheet transfer technology, which provides a novel and unique cell transplantation method for bone regeneration in the clinical setting [37]. The use of a combination of PDL-derived cell sheets and beta-tricalcium phosphate/collagen scaffold serves as a promising approach for periodontal regeneration [38]. PDL-derived cell sheets enable periodontal regeneration without adverse effects [39]. A clinical study revealed that autologous PDL-derived cell sheets showed high stability and efficacy during mid-long-term follow up in patients with periodontitis. This cytotherapeutic approach based on cell sheet engineering is an innovative strategy to treat periodontal defects [40]. Takewaki et al. reported that MSCs produce collagen-rich extracellular matrix (ECM), which leads to periodontal tissue

regeneration [41]. This study enabled the use of scaffold-free transplantation systems termed three-dimensional cultured clumps of MSC/ECM complexes (C-MSCs) [42]. Cryopreservation does not alter the characteristics of such C-MSCs because of the abundant production of type I collagen [43]. Interferon-gamma (IFN-γ)-pretreated C-MSCs express indoleamine 2,3-dioxygenease, which is known to suppress T cell response, and were useful for xenotransplantation and differentiation to hard tissues [44].

Furthermore, the growth factors include important factors that promote periodontal tissue regeneration. Recombinant human basic FGF-2 promotes migration and proliferation of PDL cells, and creates suitable microenvironment [45]. Periodontal tissue regeneration was induced by basic FGF-2 in class II furcation defects in beagle dogs and primate models [46,47]. These studies showed that basic FGF-2 can increase not only new bone, cementum volume but also Sharpey's fibers, fibrous attachments, the peripheral nerves, and Ruffini nerve endings [46,47]. Now basic FGF-2 is used as Regroth®, approved by Ministry of Health, Labour and Welfare in Japan. On other cytokines for new bone regeneration, PDGF with β-tricalcium phosphate as GEM21S®, and BMP-2 with absorbable collagen sponge as INFUSE® are also used under the US Food and Drug Administration approval [48,49]. Thus, application of recombinant growth factors is one of promising tools for acquiring of mineral formation.

Growth factors are released by stem cells themselves. PDLSC-conditioned medium enhanced periodontal tissue regeneration by suppressing the inflammatory response via tumor necrosis factor-alpha (TNF-α) production [50]. Moreover, cytokine enrichment was reported in conditioned medium derived from other dental tissues. The delivery of deciduous teeth-derived MSCs into periodontal tissues induced M2 macrophage polarization, reduced inflammation in the periodontal tissue, and enhanced periodontal regeneration [51]. Apical tooth germ cell-conditioned medium enhanced the differentiation of PDLSCs into periodontal ligament and cementum-like tissue [52]. Thus, controlled scaffold conditions combined with localized growth factor delivery may improve periodontal tissue regeneration (Fig. 5).

5. Periodontal tissue regeneration using pluripotent stem cells

MSCs with NCC-like characteristics are effective cell sources for periodontal tissue regeneration. However, isolation of tissue MSCs requires an additional surgical process to obtain a small quantity of MSCs. Therefore, induced pluripotent stem cells (iPSCs) were considered as attractive cell sources for tissue regeneration. iPSCs are generated treating somatic cells with transcriptional factors such as NANOG, OCT3/4, SOX2, and KLF4 [53]. The properties of iPSCs with respect to proliferation and differentiation into multilineage cells are similar to those of embryonic stem cells. iPSCs have the potential to develop into MSCs, and Eto et al. generated MSCs via the mesodermal or neural lineage [54]. The use of appropriate induction methods enabled the generation of MSCs via the development of neural crest-like cells, and such MSCs could contribute to bone formation [55]. Hynes et al. reported the induction methods for generating iPSC-derived MSCs (iPSC-MSCs), which have the potential for tissue regeneration to treat periodontal tissue defect [56]. They also reported less bone tissue destruction and inflammation in the jaws of an iPSC-MSC–treated mouse model of periodontitis generated via oral inoculation with Porphyromonas gingivalis, compared to the control group [57]. Yin et al. reported the differentiation of BMMSCs and iPSC-MSCs into periodontal tissue-specific lineages in the presence of the growth/differentiation factor-5 (GDF-5) in vitro and in vivo. Thus they highlighted the potential of using iPSC-MSCs, recombinant GDF-5, and hydrogel composites as an efficient approach for clinical settings [58]. Yang et al. reported that overexpression of TNF-α–stimulated gene-6 in iPSC-MSCs decreased inflammation in experimental periodontitis and inhibited alveolar bone resorption [59]. Injectable BMP-6 and iPSC-hydrogel complex regenerated periodontal tissue defect in rats [60]. Human iPSCs are considered as the preferred cell source because of the establishment of a cell bank suitable for HLA match [61]. Moreover, the unlimited differentiation potential of iPSCs is an attractive property for periodontal tissue regeneration. And if specific factors, which give cells develop to periodontal cells are identified by iPSC technology, these factors will be applied for

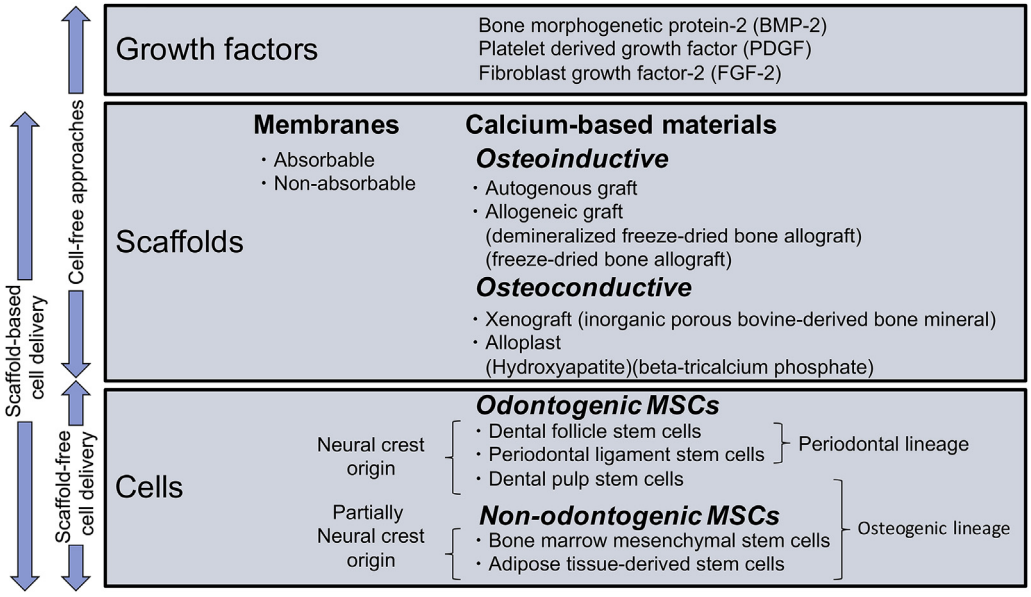

Fig. 5. Periodontal tissue engineering is established based on material-based therapy (growth factors, biomaterial scaffold) and cell-based therapy (odontogenic, non-odontogenic MSCs).

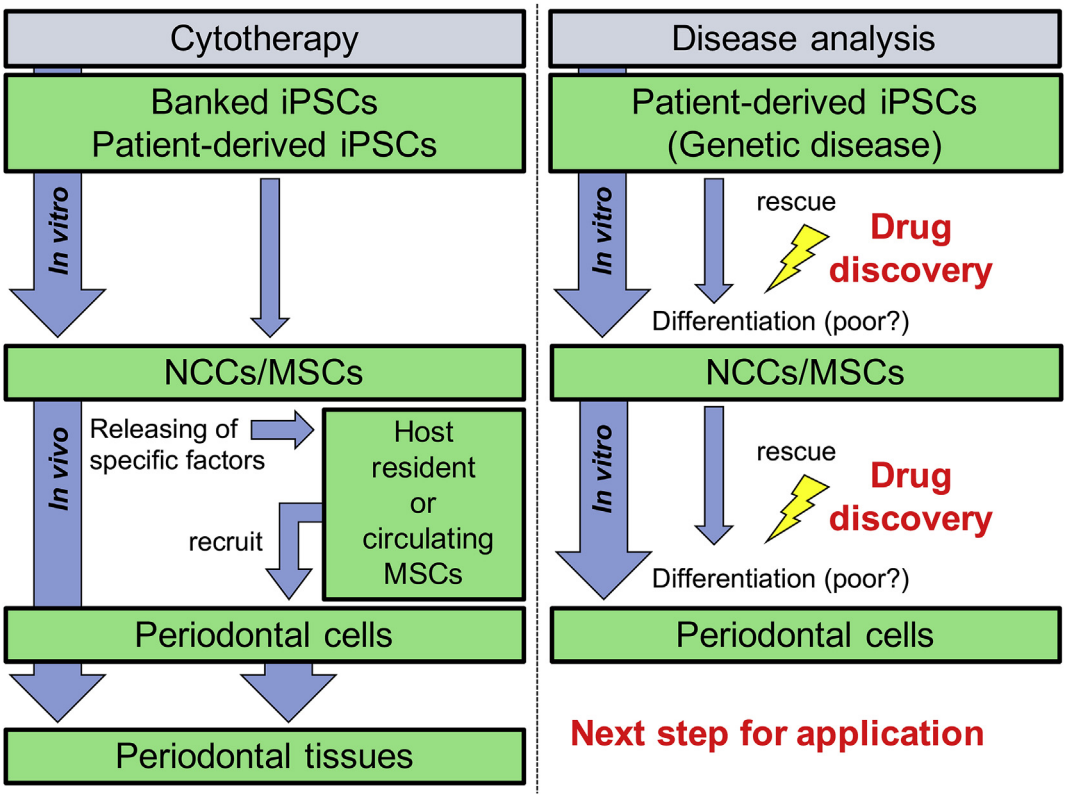

Fig. 6. Flowchart shows application of iPSCs to cytotherapy and drug discovery. Both will be available for periodontal tissue regeneration.

periodontal regenerative therapy. In addition, genetic disease such as hypophosphatasia with disturbed cementum formation can be one of the target disease to be analyzed by iPSCs technology. Disease analysis by iPSC-technology can lead drug discovery. Thus, the researches on NCCs/MSCs by iPSC-technology will provide us periodontal regeneration via dual aspects of cytotherapy and disease analysis (Fig. 6).

6. Discussion

Periodontal tissue regeneration therapy was developed via application of some biomaterials, growth factors, and cells. However, the clinical applicability of these regenerative therapy approaches is limited. For example, in large bone defects, MSCs from the other organ need to be isolated and transplanted in the defects; such adjunctive surgery for harvesting stem cells is a heavy burden for the patients. Although MSCs have been cultured and analyzed in vitro via adhesion culture, these methods involve the application of cell separation technology to ensure better purity of cells. And the use of MSCs with NCC origin is reliable for periodontal tissue regeneration. Therefore, application of these cell separation techniques to iPSCs enable the use of a selective marker to obtain large quantities of pure MSCs via NCC induction. Periodontal tissue regeneration therapy using iPSC-derived MSCs occurs via the regeneration of mineral tissues. The three-layer structure of membrane connective tissue consisting of the periodontal ligament, cementum, and alveolar bone is hoped as future periodontal tissue regeneration. To achieve the natural periodontal tissue regeneration, MSCs should be controlled them to differentiate into periodontal cells and also develop to the three-layer structure as same as natural periodontium developmental manner. However, for cytotherapy using somatic MSCs and iPSCs-derived MSCs, several issues including ethical problems and difficulties for managing of running cost are remained. To overcome them, application of growth factors with close interaction to MSCs capable of developing to periodontal tissues will be strong tool for periodontal tissues regenerative therapy as acellurar treatment.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgments

This work was supported by the Japan Society for the Promotion of Science KAKENHI, grant numbers 18K17034 (TO). We would like to thank Editage (www.editage.jp) for English language editing. The authors are grateful to KAAK studio (Keisuke Koyama: Dentist and Oral Surgeon) for preparing the illustrations.

References

[1] Nyman S, Lindhe J, Karring T, Rylander H. New attachment following surgical treatment of human periodontal disease. J Clin Periodontol 1982;9:290–6.
[2] Hammarström L. Enamel matrix, cementum development and regeneration. J Clin Periodontol 1997;24:658–68.
[3] Chai Y, Maxson Jr RE. Recent advances in craniofacial morphogenesis. Dev Dynam 2006;235:2353–75.
[4] Kaucka M, Ivashkin E, Gyllborg D, Zikmund T, Tesarova M, Kaiser J, et al. Analysis of neural crest-derived clones reveals novel aspects of facial development. Sci Adv 2016;2:e1600060.
[5] Chai Y, Jiang X, Ito Y, Bringas Jr P, Han J, Rowitch DH, et al. Fate of the mammalian cranial neural crest during tooth and mandibular morphogenesis. Development 2000;127:1671–9.
[6] Gendron-Maguire M, Mallo M, Zhang M, Gridley T. Hoxa-2 mutant mice exhibit homeotic transformation of skeletal elements derived from cranial neural crest. Cell 1993;75:1317–31.
[7] Zhao H, Bringas Jr P, Chai Y. An in vitro model for characterizing the post-migratory cranial neural crest cells of the first branchial arch. Dev Dynam 2006;235:1433–40.

[8] Thesleff I. Epithelial-mesenchymal signalling regulating tooth morphogenesis. J Cell Sci 2003;116:1647–8.
[9] Sharpe PT. Dental mesenchymal stem cells. Development 2016;143:2273–80.
[10] Huang X, Bringas Jr P, Slavkin HC, Chai Y. Fate of HERS during tooth root development. Dev Biol 2009;334:22–30.
[11] Akimoto T, Fujiwara N, Kagiya T, Otsu K, Ishizeki K, Harada H. Establishment of Hertwig's epithelial root sheath cell line from cells involved in epithelial-mesenchymal transition. Biochem Biophys Res Commun 2011;404:308–12.
[12] Zeichner-David M, Oishi K, Su Z, Zakartchenko V, Chen LS, Arzate H, et al. Role of Hertwig's epithelial root sheath cells in tooth root development. Dev Dynam 2003;228:651–63.
[13] Yamamoto T, Yamamoto T, Yamada T, Hasegawa T, Hongo H, Oda K, et al. Hertwig's epithelial root sheath cell behavior during initial acellular cementogenesis in rat molars. Histochem Cell Biol 2014;142:489–96.
[14] Coura GS, Garcez RC, de Aguiar CB, Alvarez-Silva M, Magini RS. Trentin AG Human periodontal ligament: a niche of neural crest stem cells. J Periodontal Res 2008;43:531–6.
[15] Shinagawa-Ohama R, Mochizuki M, Tamaki Y, Suda N, Nakahara T. Heterogeneous human periodontal ligament-committed progenitor and stem cell populations exhibit a unique cementogenic property under in vitro and in vivo conditions. Stem Cells Dev 2017;26:632–45.
[16] Nuñez J, Sanz-Blasco S, Vignoletti F, Muñoz F, Arzate H, Villalobos C, et al. Periodontal regeneration following implantation of cementum and periodontal ligament-derived cells. J Periodontal Res 2012;47:33–44.
[17] Alvarez R, Lee HL, Wang CY, Hong C. Characterization of the osteogenic potential of mesenchymal stem cells from human periodontal ligament based on cell surface markers. Int J Oral Sci 2015;7:213–9.
[18] Feng F, Akiyama K, Liu Y, Yamaza T, Wang TM, Chen JH, et al. Utility of PDL progenitors for in vivo tissue regeneration: a report of 3 cases. Oral Dis 2010;16:20–8.
[19] Oshima M, Inoue K, Nakajima K, Tachikawa T, Yamazaki H, Isobe T, et al. Functional tooth restoration by next-generation bio-hybrid implant as a bio-hybrid artificial organ replacement therapy. Sci Rep 2014;13(4):6044.
[20] Khorsand A, Eslaminejad MB, Arabsolghar M, Paknejad M, Ghaedi B, Rokn AR, et al. Autologous dental pulp stem cells in regeneration of defect created in canine periodontal tissue. J Oral Implantol 2013;39:433–43.
[21] 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;97:13625–30.
[22] Yamada Y, Ito K, Nakamura S, Ueda M, Nagasaka T. Promising cell-based therapy for bone regeneration using stem cells from deciduous teeth, dental pulp, and bone marrow. Cell Transplant 2011;20:1003–13.
[23] d'Aquino R, De Rosa A, Lanza V, Tirino V, Laino L, Graziano A, et al. Human mandible bone defect repair by the grafting of dental pulp stem/progenitor cells and collagen sponge biocomplexes. Eur Cells Mater 2009;18:75–83.
[24] Paknejad M, Eslaminejad MB, Ghaedi B, Rokn AR, Khorsand A, Etemad-Moghadam S, et al. Isolation and assessment of mesenchymal stem cells derived from bone marrow: histologic and histomorphometric study in a canine periodontal defect. J Oral Implantol 2015;41:284–91.
[25] Du J, Shan Z, Ma P, Wang S, Fan Z. Allogeneic bone marrow mesenchymal stem cell transplantation for periodontal regeneration. J Dent Res 2014;93:183–8.
[26] Kimura Y, Komaki M, Iwasaki K, Sata M, Izumi Y, Morita I. Recruitment of bone marrow-derived cells to periodontal tissue defects. Front Cell Dev Biol 2014;2:19.
[27] Isern J, García-García A, Martín AM, Arranz L, Martín-Pérez D, Torroja C, et al. The neural crest is a source of mesenchymal stem cells with specialized hematopoietic stem cell niche function. Elife 2014;3:e03696.
[28] Matsuzaki Y, Mabuchi Y, Okano H. Leptin receptor makes its mark on MSCs. Cell Stem Cell 2014;15:112–4.
[29] Baryawno N, Przybylski D, Kowalczyk MS, Kfoury Y, Severe N, Gustafsson K, et al. Cellular taxonomy of the bone marrow stroma in homeostasis and leukemia. Cell 2019;177:1915–32.
[30] Wolock SL, Krishnan I, Tenen DE, Matkins V, Camacho V, Patel S, et al. Mapping distinct bone marrow niche populations and their differentiation paths. Cell Rep 2019;28:302–11.
[31] Venkataiah VS, Handa K, Njuguna MM, Hasegawa T, Maruyama K, Nemoto E, et al. Periodontal regeneration by allogeneic transplantation of adipose tissue derived multi-lineage progenitor stem cells in vivo. Sci Rep 2019;9:921.
[32] Wen X, Nie X, Zhang L, Liu L, Deng M. Adipose tissue-deprived stem cells acquire cementoblast features treated with dental follicle cell conditioned medium containing dentin non-collagenous proteins in vitro. Biochem Biophys Res Commun 2011;409:583–9.
[33] Sawada K, Takedachi M, Yamamoto S, Morimoto C, Ozasa M, Iwayama T, et al. Trophic factors from adipose tissue-derived multi-lineage progenitor cells promote cytodifferentiation of periodontal ligament cells. Biochem Biophys Res Commun 2015;464:299–305.
[34] Huang GT, Gronthos S, Shi S. Mesenchymal stem cells derived from dental tissues vs. those from other sources: their biology and role in regenerative medicine. J Dent Res 2009;88:792–806.
[35] Yamaza T, Ren G, Akiyama K, Chen C, Shi Y, Shi S. Mouse mandible contains distinctive mesenchymal stem cells. J Dent Res 2011;90:317–24.
[36] Langer R, Vacanti JP. Tissue engineering. Science 1993;260:920–6.
[37] Akazawa K, Iwasaki K, Nagata M, Yokoyama N, Ayame H, Yamaki K, et al. Double-layered cell transfer technology for bone regeneration. Sci Rep 2016;14(6):33286.
[38] Tsumanuma Y, Iwata T, Washio K, Yoshida T, Yamada A, Takagi R, et al. Comparison of different tissue-derived stem cell sheets for periodontal regeneration in a canine 1-wall defect model. Biomaterials 2011;32:5819–25.
[39] Tsumanuma Y, Iwata T, Kinoshita A, Washio K, Yoshida T, Yamada A, et al. Allogeneic transplantation of periodontal ligament-derived multipotent mesenchymal stromal cell sheets in canine critical-size supra-alveolar periodontal defect model. Biores Open Access 2016;5:22–36.
[40] Iwata T, Yamato M, Washio K, Yoshida T, Tsumanuma Y, Yamada A, et al. Periodontal regeneration with autologous periodontal ligament-derived cell sheets e A safety and efficacy study in ten patients. Regen Ther 2018;24:38–44.
[41] Takewaki M, Kajiya M, Takeda K, Sasaki S, Motoike S, Komatsu N, et al. MSC/ECM cellular complexes induce periodontal tissue regeneration. J Dent Res 2017;96:984–91.
[42] Kittaka M, Kajiya M, Shiba H, Takewaki M, Takeshita K, Khung R, et al. Clumps of a mesenchymal stromal cell/extracellular matrix complex can be a novel tissue engineering therapy for bone regeneration. Cytotherapy 2015;17:860–73.
[43] Motoike S, Kajiya M, Komatsu N, Takewaki M, Horikoshi S, Matsuda S, et al. Cryopreserved clumps of mesenchymal stem cell/extracellular matrix complexes retain osteogenic capacity and induce bone regeneration. Stem Cell Res Ther 2018;9:73.
[44] Takeshita K, Motoike S, Kajiya M, Komatsu N, Takewaki M, Ouhara K, et al. Xenotransplantation of interferon-gamma-pretreated clumps of a human mesenchymal stem cell/extracellular matrix complex induces mouse calvarial bone regeneration. Stem Cell Res Ther 2017;8:101.
[45] Murakami S. Periodontal tissue regeneration by signaling molecule(s): what role does basic fibroblast growth factor (FGF-2) have in periodontal therapy? Periodontol 2000;2011(56):188–208.
[46] Murakami S, Takayama S, Kitamura M, Shimabukuro Y, Yanagi K, Ikezawa K, et al. Recombinant human basic fibroblast growth factor (bFGF) stimulates periodontal regeneration in class II furcation defects created in beagle dogs. J Periodontal Res 2003;38:97–103.
[47] Takayama S, Murakami S, Shimabukuro Y, Kitamura M, Okada H. Periodontal regeneration by FGF-2 (bFGF) in primate models. J Dent Res 2001;80:2075–9.
[48] McKay WF, Peckham SM, Badura JM. A comprehensive clinical review of recombinant human bone morphogenetic protein-2 (INFUSE Bone Graft). Int Orthop 2007;31:729–34.
[49] Bashutski JD, Wang HL. Periodontal and endodontic regeneration. J Endod 2009;35:321–8.
[50] Nagata M, Iwasaki K, Akazawa K, Komaki M, Yokoyama N, Izumi Y, et al. Conditioned medium from periodontal ligament stem cells enhances periodontal regeneration. Tissue Eng A 2017;23:367–77.
[51] Gao X, Shen Z, Guan M, Huang Q, Chen L, Qin W, et al. Immunomodulatory role of stem cells from human exfoliated deciduous teeth on periodontal regeneration. Tissue Eng A 2018;24:1341–53.
[52] Yang ZH, Zhang XJ, Dang NN, Ma ZF, Xu L, Wu JJ, et al. Apical tooth germ cell-conditioned medium enhances the differentiation of periodontal ligament stem cells into cementum/periodontal ligament-like tissues. J Periodontal Res 2009;44:199–210.
[53] Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 2006;126:663–76.
[54] Eto S, Goto M, Soga M, Kaneko Y, Uehara Y, Mizuta H, et al. Mesenchymal stem cells derived from human iPS cells via mesoderm and neuroepithelium have different features and therapeutic potentials. PLoS One 2018;13:e0200790.
[55] Ouchi T, Morikawa S, Shibata S, Fukuda K, Okuno H, Fujimura T, et al. LNGFR(+)THY-1(+) human pluripotent stem cell-derived neural crest-like cells have the potential to develop into mesenchymal stem cells. Differentiation 2016;92:270–80.
[56] Hynes K, Menicanin D, Han J, Marino V, Mrozik K, Gronthos S, et al. Mesenchymal stem cells from iPS cells facilitate periodontal regeneration. J Dent Res 2013;92:833–9.
[57] Hynes K, Bright R, Marino V, Ng J, Verma PJ, Gronthos S, et al. Potential of iPSC-derived mesenchymal stromal cells for treating periodontal disease. Stem Cell Int 2018. 20182601945.
[58] Yin X, Li P, Li Y, Cai Y, Wen J, Luan Q. Growth/differentiation factor-5 promotes in vitro/vivo periodontal specific differentiation of induced pluripotent stem cell-derived mesenchymal stem cells. Exp Ther Med 2017;14:4111–7.
[59] Yang H, Aprecio RM, Zhou X, Wang Q, Zhang W, Ding Y, et al. Therapeutic effect of TSG-6 engineered iPSC-derived MSCs on experimental periodontitis in rats: a pilot study. PLoS One 2014;9:e100285.
[60] Chien KH, Chang YL, Wang ML, Chuang JH, Yang YC, Tai MC, et al. Promoting induced pluripotent stem cell-driven biomineralization and periodontal regeneration in rats with maxillary-molar defects using injectable BMP-6 hydrogel. Sci Rep 2018;8:114.
[61] Okita K, Matsumura Y, Sato Y, Okada A, Morizane A, Okamoto S, et al. A more efficient method to generate integration-free human iPS cells. Nat Methods 2011;8:409–12.