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SPECIAL ISSUE

Adult Stem Cell Therapy for Periodontal Disease

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Periodontal disease is a major cause of tooth loss and characterized by inflammation of tooth-supporting structures. Recently, the association between periodontal disease and other health problems has been reported, the importance of treating periodontal disease for general health is more emphasized. The ultimate goal of periodontal therapy is regeneration of damaged periodontal tissues. The development of adult stem cell research enables to improve the cell-based tissue engineering for periodontal regeneration. In this review, we present the results of experimental pre-clinical studies and a brief overview of the current state of stem cells therapy for periodontal diseases.

Keywords: Adult stem cells, Stem cell transplantation, Periodontal diseases, Regeneration, Dental implants

Periodontal disease

Periodontal disease is characterized by inflammation of tooth-supporting structures which are composed of gingiva, cementum, periodontal ligament and alveolar bone. Periodontitis (a typical form of periodontal diseases) involves progressive loss of the alveolar bone around the teeth, and if left untreated, can lead to the loosening and subsequent loss of teeth.

Periodontal disease is caused by specific microorganism from the biofilm within the periodontal pocket. However, more detail on the pathogenesis point of view, periodontal disease initiated by bacteria but propagated by host factors. Susceptibility may increase owing to the interaction of environmental, acquired and genetic risk factors that modify the host response to the putative pathogenic microbes (1, 2).

Traditionally, the presence and severity of periodontal disease have been determined by pocket probing depth, clinical attachment loss and bleeding on probing measurements and by evidence of radiographic alveolar bone loss. These data are collectively interpreted contextually for each patient in order to establish a diagnosis of periodontal disease that includes both the extent and severity of disease (3).

Recently, the association between periodontal disease and other health problems, such as diabetes, cardiovascular disease and adverse pregnancy outcome, has been reported (4, 5), the importance of treating periodontal disease for general health is more emphasized.

Therefore, periodontal disease is a major public health issue and the development of effective therapies to treat periodontal disease and regenerate periodontal tissue is a major goal of the dental field (6).

Treatment of periodontal disease

Conventional periodontal therapy (most mechanical and surgical periodontal procedures) largely involves repair of the gingival connective tissues and the coronal portion of periodontal ligament with virtually no repair of cementum or alveolar bone. These events do not constitute regeneration but repair of the periodontium (7). However, the regeneration of damaged periodontal tissue is the ultimate goal of periodontal treatment.

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In the 1980s, guided tissue regeneration (GTR) was proposed in which a physical barrier was introduced by surgically placing a membrane between the connective tissue of the periodontal flap and the curetted root surface. This novel procedure can be considered to have been a useful approach; however, its shortcomings are manifest because of its limited predictability and subjected complications (8, 9).

Guided bone regeneration (GBR) is similar to GTR but it focused on development of hard tissues instead of soft tissues of periodontal attachment. As mentioned earlier, the progression of periodontal disease causes alveolar bone destruction and loss of tooth. The deficiency of alveolar bone causes the limitation of placing dental implants. Therefore, GBR is predominantly applied in to support new hard tissue growth on an alveolar ridge to allow stable placement of dental implants.

Stem cell-based tissue engineering for periodontal regeneration

Tissue engineering is the general term for a number of ways by which tissue lost as a result of trauma and disease might be restored. A potential tissue engineering approach to periodontal regeneration involves incorporation of progenitor cells and instructive messages in a prefabricated three-dimensional construct, which is subsequently into the defect site (7, 8).

Stem cells are undifferentiated cells characterized by their ability at the single cell level to both self-renew and differentiate to produce mature progeny cells (10, 11). There are two major categories of stem cells, the embryonic stem cells and the adult stem cells. Adult stem cells are undifferentiated cells found in specialized tissues and organs of adults. Compared to the embryonic stem cells, adult stem cells that exist in various organs of the body are easily accessible and less controversial in ethical terms (12, 13).

There is a plenty of adult stem cells available for possible cell-based tissue engineering. Since a long time, bone marrow-derived mesenchymal stem cells (BMSCs) have been studied for bone regeneration. BMSCs are capable of differentiating into multiple cell lineages when grown in defined conditions *in vitro*, including osteogenic, chondrogenic, adipogenic, myelosupportive stroma, myogenic and neurogenic lineages (14). The ability of BMSCs to give rise to multiple specialized cell types along with their extensive distribution in many adult tissues have made them an attractive target for use in periodontal regeneration (7).

In the dental field, many reports with superior outcomes using BMSCs in periodontal regeneration and sinus augmentation procedure have been reported (15-25).

Kawaguchi et al. (17) showed that auto-transplantation of bone marrow mesenchymal stem cells in a novel option for periodontal tissue regeneration. In the experimental groups, the denuded root surface was almost completely

Table 1. Animal and human studies using BMSCs for periodontal regeneration

Authors	Species	Cell source & carrier	Defect type	Effect
De Kok et al., 2003	Canine	BMSCs+HA/TCP	Alveolar saddle defect	Increased bone regeneration
Kawaguchi et al., 2004	Canine	BMSCs+collagen gel	Experimental ClassIII furcation defect	More periodontal regeneration
De Kok et al., 2005	Canine	BMSCs+HA/TCP	Extraction socket	BMSCs remained and contributed to bone regeneration.
Hasegawa et al., 2006	Canine	BMSCs+atelocollagen	Experimental ClassIII periodontal defect	Enhancement of periodontal tissue regeneration
Ito et al., 2006	Canine	BMSCs+fibrin & PRP	Peri-implant defect (circumferential type)	Increased bone regeneration & bone implant contact (BIC)
Pieri et al., 2008	Swine	BMSCs+PRP & luorohydroxyapatite FHA)	Sinus augmentation	Increased bone formation & BIC
Sun et al., 2008	Rabbit	BMSCs+inorganic material	Sinus augmentation	Increased new bone formation
Shayesteh et al., 2008	Human	BMSCs+HA/TCP	Sinus augmentation	41.34% New bone formation, no control
McAllister et al., 2009	Human	BMSCs+allograft	Sinus augmentation	High percentage of vital bone content, after a relatively short healing phase, no control
Pieri et al., 2009	Minipig	BMSCs+PRP & FHA	Alveolar defect (3.5 mm diameter and 8 mm depth)	Addition of MSCs to PRP-FHA enhances bone formation

covered with new cementum, and regenerated periodontal ligament separated the new bone from the cementum.

McAllister et al. (24) studied to evaluate the bone formation following sinus-augmentation procedures using an allograft cellular bone matrix containing native mesenchymal stem cells. They showed the high percentage of vital bone content, after a relatively short healing phase, may encourage a more rapid initiation of implant placement or restoration when a cellular grafting approach is considered.

Animal and human studies using BMSCs for periodontal regeneration are listed in Table 1.

Dental stem cell

Dental-tissue-derived mesencymal stem cell (MSC)-like populations are among many other stem cells residing in specialized tissues that have been isolated and characterized (14). Up until now, 5 different human dental stem/progenitor cells have been reported: dental pulp stem cells (DPSCs), stem cells from exfoliated deciduous teeth (SHED), periodontal ligament stem cells (PDLSCs), stem cells from apical papilla (SCAP) and dental follicle progenitor cells (DFPCs) (26-31). These cells are easily accessible and, in contrast to bone-marrow-derived mesenchymal stem cells, are more intimately associated with dental tissues (13).

The presence of progenitor cells within the postnatal periodontal ligament (PDL) has been speculated from old times (32, 33). These cells are believed to provide a renewable cell source for normal tissue homeostasis and periodontal wound healing (8, 34). A few studies have reported the transplantation of periodontal ligament cells to periodontal defects in animal models regardless of positive proof that adult stem cells exist in the periodontal tissue (35-41).

Recently, the evidence of being these progenitor cells from the periodontal ligament has been formally proven. Seo et al. (28) reported that PDLSCs expressed the mesenchymal stem-cell markers STRO-1 and CD146/MUC18. Under defined culture conditions, PDLSCs differentiated into cementoblast-like cells, adipocytes, and collagen-forming cells. When transplanted into immunocompromised rodents, PDLSCs showed the ability to make a cementum/PDL-like structure and contribute to periodontal tissue repair. These findings suggest that PDL contains stem cells that have the potential to make cementum/PDL-like tissue *in vivo*. Transplantation of these cells,

Table 2. Animal studies using PDL cells & PDLSCs for periodontal regeneration

Authors	Species	Cell source & carrier or membrane	Defect type	Effect
Boyko et al., 1981	Canine	PDL cells+demineralized root	Re-implantation of roots bearing cells in alveolar bone	Formation of new PDL
van Dijk et al., 1991	Canine	PDL cells	Artificial periodontal defects	New connective tissue attachment
Lang et al., 1998	Minipig	Alveolar bone cells or PDL cells+Teflon membrane	Experimentally induced furaction and interdental defects	New cementum and alveolar bone formation
Nakahara et al., 2004	Canine	PDL cells+collagen sponge scaffold	Periodontal fenestration defects	Induced cementum regeneration
Akizuki et al., 2005	Canine	PDL cell sheet+hyaluronic acid carrier	Dehiscence defects	Formation of new cementum
Flores et al., 2008	Immunocompromised rat	PDL cell sheet (human) (cultured with osteogenic differentiation medium)	Periodontal fenestration defects	Periodontal regeneration
Iwata et al., 2009	Canine	Multi-layered PDL-derived cell sheets	Three-wall periodontal defects	Regenerated new bone and cementum
Seo et al., 2005	Immunocompromised mouseand rat	PDLSCs (human)+HA/TCP	Subcutaneously & periodontal defects	Generate a cementum/PDL-like structure
Liu et al., 2008	Swine	PDLSCs+HA/TCP	Induced periodontitis defects	Regenerated periodontal tissues
Kim et al., 2009	Canine	PDLSCs or BMSCs+HA/TCP	Peri-implant saddle-like defects	Increased new bone formation

which can be obtained from an easily accessible tissue resource and expand *ex vivo*, might hold possibilities as a therapeutic approach for reconstruction of tissues destroyed by periodontal diseases.

Since then, dental stem cells, especially PDLSCs, come under the spotlight in dental tissue engineering. Up to now, these cells have been used for tissue engineering studies in large animals to assess their potential in preclinical applications (42, 43).

Liu et al. (42) explored the potential of using autologous PDLSCs to treat periodontal defects in a porcine model of periodontitis. When transplanted into the surgically created periodontal defect areas, PDLSCs were capable of regenerating periodontal tissue, leading a favorable treatment for periodontitis. This study demonstrates the feasibility of using stem cell-mediated tissue engineering to treat periodontal diseases.

Kim et al. (43) isolated autologous PDLSCs and BMSCs from canine, these cells were expanded *ex vivo* and applied to the canine peri-implant defects model. They suggested that transplantation of dental stem cell such as PDLSCs could be an effective method for alveolar bone regeneration in surgically created peri-implant saddle-like defects.

Consequently, PDL tissues are clinically accessible in routine clinical practice like tooth extraction, possibly providing a readily available source of stem cells and these PDLSCs may be an ideal source for clinical periodontal regenerative therapy (28, 42, 44, 45).

Animal studies using PDL cells & PDLSCs for periodontal regeneration are listed in Table 2.

Future directions

Introduction of adult stem cells in periodontology contribute to the advancement of cell-based regenerative periodontal therapy. Especially, the presence of PDLSCs which have existed conceptually was gives a great impact on regenerative periodontal therapy. However, little is known about the characteristics of PDLSCs because PDL is composed of heterogeneous cell populations and thus far no highly purified PDLSCs clone has yet been established from human PDL tissue (44, 46, 47). The challenge lies in the ability of identifying a PDLSC-specific marker that allows for the selection of a pure PDLSC population (6).

Additional studies should be carried out to further evaluate characterization of dental stem cells and the therapeutic efficacy of stem cell-based regenerative periodontal therapy should be evaluated through further pre-clinical and clinical trials. Prospectively, the dental stem cell biology might provide significant insights into the development of dental tissues and cellular differentiation processes. Dental stem cells could also be practicable tools for dental tissue engineering.

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Potential Conflict of Interest

The authors have no conflicting financial interest.

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