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Stem cells: the contemporaries of periodontal regeneration

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Abstract

The aim of periodontal therapy is to halt the disease advancement and regenerate the structure and function of the damaged tissues. The holy grail of periodontology is the regeneration of the tissue apparatus composed of different tissues, including bone, cementum, and periodontal ligament. The headway made in the stem cell biology and regenerative medicine have presented opportunities for tissue engineering and gene-based approaches in periodontal therapy. The aim of this review is to analyse the information on stem cell-based therapy for the regeneration of periodontal tissues and suggest new avenues for the development of more effective therapeutic protocols.

Keywords: Genetics; Periodontal therapy; Regeneration; Stem cells; Tissue engineering.

Introduction

In a utopian world, periodontal therapy would completely restore the periodontal attachment including cementum, periodontal ligament, and alveolar bone lost due to periodontal disease or trauma. In the past, many attempts have been made to unravel a promising material that would result in new clinical and histological attachment, but so far these attempts have only culminated in healing by repair.

To date, restoration of damaged or diseased periodontal tissues has relied almost entirely on the use of implantation of structural substitutes, often with little or no reparative potential [1].

Several treatment modalities have been developed to achieve periodontal regeneration, including guided tissue regeneration, use of bone grafts, application of growth factors and host modulating factors, and their combinations. Although there is some evidence showing that periodontal regeneration may be achieved by employing these techniques, all regenerative treatment modalities have shown limited success, especially in exacting clinical situations.

For successful periodontal regeneration, the formation of a functional epithelial seal, insertion of new connective

tissue fibers into the root, reformation of new acellular cementum on the tooth surface, and restoration of alveolar bone height are required. We are still on the lookout for other nonconformist treatment approaches to achieve anticipated periodontal regeneration.

Quantum leaps in stem cell technology and regenerative medicine have presented opportunities for tissue engineering and gene-based therapeutic approaches in periodontal therapy. Regeneration of the periodontal tissues is a nexus of various processes in a timely manner. Tissue engineering was proposed as a possible technique for regenerating lost periodontal tissues by Langer and Vacanti [2] in 1993.

Stem cells are endowed with indefinite cell division potential, can program into other types of cells, and have come to the fore as a front running regenerative medicine source in recent time, for reparation of tissues and organs anomalies occurring due to congenital defects, disease, and age associated effects. This review aims at gauging the potential of stem cells for periodontal regeneration and their potential for clinical application.

Stem/Progenitor Cells

The evidence that undifferentiated mesenchymal cells are present within the periodontal tissues was first provided by McCulloch et al. [3] by in vivo and histological studies (Figure 1).

A stem cell has two defining characteristics:

- The ability for indefinite self-renewal to give rise to more stem cells
- The ability to differentiate into a number of specialized daughter cells to perform specific function.

Classification Of Stem Cells: [4]

Stem cells can be classified according to their

Differentiation Potential

Totipotent: They are derived from the first few divisions of fertilized egg. These cells can divide into embryonic and extra embryonic cell types.

Pluripotent: They can give rise to every cell of an organism except its extraembryonic tissues such as placenta. Example: embryonic stem cells, induced pluripotent stem cells.

Multipotent: Can form multiple lineages that constitute an entire tissue or tissues. Example: haematopoietic stem cells.

Oligopotent: Able to form two or more lineages within a tissue. Example: a neural stem cell that can create a subset of neurons in the brain.

Unipotent: Forms a single lineage. Example: spermatogonial stem cells.

Based on their ORIGIN, stem cells are categorized as:

- Embryonic stem cells (ESC's) and
- Somatic/ adult stem cells (ASC's).

Adult stem cells are further divided into:

Mesenchymal stem cells (MSC)

Hematopoietic stem cells

Neural stem cells, etc

Another classification is based on the differentiation potential of dental stem cells either into formation of dentin or periodontium-associated tissues.

I group associated with dental pulp consisting of:

- Stem cells of human exfoliated deciduous teeth (SHED)
- Dental pulp stem cells (DPSC)
- Stem cells from apical papilla (SCAP)

II group is associated with periodontium consisting of:

- Periodontal ligament stem cells (PDLSC)
- Dental follicle Stem cells (DFSC)

Types of stem cells of non-dental origin:

a) Bone mesenchymal stem cells (BMSCs) and

b) Epithelial stem cells.

Embryonic stem cells are totipotent cells, capable of differentiating into virtually any cell type, as well as being propagated indefinitely in an undifferentiated state. Due to regulatory issues associated with the use of embryonic stem cells, and the difficulty in controlling their growth and differentiation, recent attention has been focused on stem cells derived from adult tissues [5].

From a practical standpoint, adult stem cells are more appropriate for periodontal tissue engineering purposes. Although, it is accepted that adult stem cells have a more restricted differentiation potential compared with the totipotent properties of embryonic stem cells, these cells still fulfill the basic characteristics of stem cells [6]. As the critical tissues that require regeneration in the periodontium (cementum, ligament, bone) are of mesenchymal origin, it is MSCs that are required for periodontal regeneration [7].

Mesenchymal Stem Cells Of Dental Origin

Stem cells from Human Exfoliated Deciduous teeth

Stem cells from human exfoliated deciduous teeth were first identified by Miura et al. [8] in 2003. These cells are able to differentiate into, not only, dental pulp-related cells, but also, other cell lineages, for example osteoblasts, adipocytes, neuronal-like cells and endothelial cells. SHED represent a population of multipotent stem cells that are perhaps more immature than previously examined postnatal stromal stem-cell populations.

Dental stem cells can be recovered immediately following exfoliation of a deciduous tooth, but are best recovered after the extraction of deciduous teeth as the teeth become mobile, but still maintain their circumferential gingival attachment.

Differentiation potential of SHEDs

Odontogenic/osteoblastic differentiation potential

The ability of SHEDs to differentiate into odontoblastic lineage is widely known. SHED showed similar osteogenic potency when comparing with BMMSCs (bone marrow mesenchymal stem cells), exhibiting significantly elevate levels of ALP (alkaline phosphate) activity after 1 week of induction [9]. In addition, several osteogenic markers such as RUNX2 (runt-related transcription factor 2), DSP (dentin sialoprotein) and OCN (osteocalcin) are also upregulated [10]. When cultured in an osteogenic medium, SHEDs formed mineralized nodules after 4 weeks of induction which indicate calcium deposition in vitro SHEDs can be induced to become functional odontoblasts in vitro [8].

Neurogenic differentiation potential

Neurogenic potential of SHEDs is expected due to their neural crest embryonic origin. These cells are prone to undergo neurogenic differentiation both in vitro and in vivo [11].

Angiogenic differentiation potential

Angiogenic potential of SHEDs is another aspect of interest for the benefit of connective tissue regeneration. The rapid and effective induction of vasculation is required for sufficiently supply of oxygen and nutrients as well as removing the toxic waste from the newly synthesized tissues. Unstimulated SHEDs expressed vascular endothelial growth factor 1 (VEGFR1) and neuropilin-1 (NP1), the known important receptors in angiogenesis [12].

Immunomodulatory property

SHEDs also modulate dendritic cell maturation. When co-cultured with SHEDs, mature dendritic cells decreased CD40 (cluster of differentiation 40), CD80, CD83 and CD86 expression. SHEDs treated monocyte-derived dendritic cells reduced CD4+ and CD8+ cell proliferation when co-cultured with peripheral blood lymphocyte as compared to the control [13].

Dental pulp stem cells

The dental pulp is the vital organ of the tooth, presenting very good repair and regenerative capacity. MSC was first isolated from the adult dental pulp by Gronthos et al. [14] and then, from primary dentition extracted during periodontal and oral surgery by Miura et al. [8]

DPSC with high proliferative capacity and multipotency are used in orthopedics and maxillofacial reconstruction for regeneration of bone and dental tissues, respectively. DPSC from primary dentition present higher proliferative capacity and differentiation potential, compared to DPSC from permanent teeth.

Odontogenic/osteoblastic differentiation potential

DPSCs can also differentiate into odontoblasts to further regenerate pulp-dentin complex tissues. The transcription factor Runx2 also control odontoblast differentiation by activating the dentin specific gene, dentin sialophosphoprotein (DSPP), responsible for encoding dentin sialoprotein and dentin phosphoprotein [14].

Periodontal Regeneration

The potential of DPSCs for periodontal regeneration may be questionable because of their limited capacity to form cementum. Xu et al. [15] have shown that these cells are not able to form distinct cementum-like structure after ectopic transplantation in a rat model. Another study by Park et al. [16] using a canine model, compared the regenerative potential of autologous DPSCs with that of autologous PDLSCs for the treatment of surgically created periodontal defects. In a 3-mm-wide circumferential periodontal defect, they reported only 0.35 mm attachment gain for sites treated with DPSCs group compared to 3.02 mm gain for sites treated with PDLSCs. Histological evaluations revealed that periodontal regeneration was not achieved in DPSCs group, while the defects in PDLSCs groups were regenerated by means of new cementum, bone, and Sharpey's fibers connecting the tooth to the alveolar bone.

Several studies have reported the ability of DPSCs to differentiate into chondroblasts. Induced DPSCs express other chondrogenic lineage specific proteins such as aggrecan, SRY (sex determining regionY)-box 9, type II collagen and type X collagen.

Neurogenic differentiation potential

Given their neural crest origin, DPSCs have significant neuroregenerative potential. They have been shown to differentiate into multiple neural crest lineage cell types, such as neuron-like cells, dopaminergic neurons, oligodendrocytes and Schwann cells [17].

More and more studies have begun to focus on DPSCs in recent years. DPSCs cultured together with odontogenic cells via epithelial-mesenchymal interactions may help stem cells adapt to dental cell lineages and make the scaffold matrix become a part of the tooth.

STEM cells from apical papilla

SCAPs were first discovered and isolated from the apical papilla tissue of incompletely developed tooth by Sonoyama et al. [18]. The apical papilla refers to the soft tissue that is loosely attached to the apices of immature permanent teeth. It is different from the pulp in terms of containing less cellular and vascular components than the pulp.

SCAPs express MSCs markers and can differentiate into different cell types such as neural cells, adipocytes, odontogenic cells, and formatting vascularized pulp-like tissue in vivo.

Periodontal Tissue Regeneration

On treatment of periodontitis, SCAPs showed their superiority compared with other MSCs such as non-dental-derived MSCs like BMMSCs and dental-derived MSCs including PDLSCs and DPSCs. As to BMMSCs, SCAPs had similar potential in osteo/dentinogenic

differentiation but higher proliferation rate, and they are easier to isolate [19]. SCAPs have been confirmed to have the ability to suppress the immune reaction through suppressing T cell proliferation which may help broaden the use of allogenic SCAPs transplantation by decreasing the immunoreaction [20].

Bone Regeneration

With the development of biocompatible materials and the discovery of stem cell sources, bone tissue engineering has become an alternative approach for repairing large bone defects instead of bone grafting. Ex vivo expanded SCAPs have the capacity to differentiate into osteoblasts after culture in osteogenic medium.

Bioroot Engineering

Currently, dental implants are regarded as the best clinical method for replacing missing tooth instead of fixed bridge and removable denture. However, with the development of tissue engineering and regenerative medicine, tooth regeneration has become a promising method [18].

More progress on stem cells made in non-dental tissues will help in adopting research strategies used in SCAPs.

Dental Follicle Stem Cells

Dental follicle cells (DFCs) are a group of mesenchymal progenitor cells surrounding the tooth germ, responsible for cementum, periodontal ligament, and alveolar bone formation in tooth development. Cascades of signaling pathways and transcriptional factors in DFCs are involved in directing tooth eruption and tooth root morphogenesis. Substantial researches have been made to decipher multiple aspects of DFCs, including multilineage differentiation, senescence, and immunomodulatory ability [21].

Osteogenic Differentiation

DFCs are responsible for formation of alveolar bone in tooth development to support and attach the tooth root, and are also capable of differentiating into osteoblasts and form mineralized matrix nodules with appropriate exogenous osteogenic stimulus, such as dexamethasone or BMPs [22].

Neural Differentiation

The neural lineage differentiation of DFCs is partially attributable to its origin from neural crest.

Periodontal Differentiation

One of the most important functions of DFCs is to form good root-bone interface, including PDL, cementum, and alveolar bone. Odontogenic matrix protein like dentin non-collagenous proteins (dNCPs) and enamel matrix derivatives (EMD) can stimulate DFCs to differentiate cementum-like tissues in vivo [23]. DFCs transplants isolated from human molars at a root-developing stage were able to produce a cementum/PDL-like structure, characterized by a thin layer of cementum-like mineralized tissues and PDL-like collagen fibers connecting with the newly formed cementum, which demonstrated a higher activity of DFC differentiation potential in developing stages [24]. In spite of the potential to differentiate PDL-like tissues, it is hard to recover the shape and function of natural PDL utilizing DFCs.

Tooth Root Regeneration

DFCs are responsible for forming a tooth root and its supporting tissues in odontogenesis. Previous studies isolated DFCs from developing root and loaded them on an absorptive root-shaped scaffold in regular sequence. By this way, they mimicked a biophysiological root in vivo and regenerated a functional root/periodontal tissue complex able to support a porcelain crown [25]. Clinical trials evaluating DFC application in bone or tooth tissue engineering should be carried out to identify the actual feasibility of clinical application.

Periodontal Ligament Stem Cells

PDLSCs were isolated and described for the first time by Seo et al. [26] and Trubiani et al. [27].

Self-renewal capacity of PDLSCs

Many researchers reported the self-renewal capacity of PDLSCs as well as other types of stem cells. Human PDLSCs revealed higher growth potential than human bone marrow-derived MSCs and human dental pulp stem cells (DPSCs).

Multipotency of PDLSCs

PDL tissues mainly consist of dental follicle-derived mesenchymal cells, therefore PDLSCs have been reported to possess the ability to differentiate into various types of mesenchymal-lineage cells. Seo et al. [26] could differentiate human PDLSCs into osteoblast-like cells that formed Alizarin Red-positive mineralized nodules and expressed bone-related marker genes. They also revealed the differentiation potential of human PDLSCs into adipocyte-like cells that contained lipid droplets in their cytoplasm and expressed adipose-related marker genes.

Xu et al. [28] succeeded to generate chondrocyte-like cells from human PDLSCs as well as osteoblast- and adipocyte-like cells. Seo et al. [26] found that the PDLSCs are similar to other mesenchymal stem cells with respect to their expression of STRO-1/CD146, implying that PDLSCs might be derived from a population of perivascular cells.

The osteogenic potential of PDL cells has been assessed previously with several cell-culture methods, and the ability of such cultures to form a mineralized matrix has been noted [27].

Several clinical trials that used autologous human PDLSCs have been performed; Feng et al. [29] reported autologous human PDLSCs transplants into the intrabony defects of deep periodontal pockets of three male patients; human PDLSCs isolated from third molars of each patient were mixed with a bone grafting material and inserted into periodontal defect areas. After 72 months of post-surgery, the surgical re-entry to the implanted area and X-ray analysis of two patients exhibited definitive regeneration of periodontium. Furthermore, at 3, 6, and 42 months, all three patients showed the significant decrease of tooth movement, probing depth (PD), and clinical attachment level (CAL).

A study compared the autologous and allogeneic PDLSCs for the treatment of induced periodontitis in a swine model of periodontal disease. Successful periodontal regeneration with both autologous and allogeneic PDLSCs was demonstrated. Importantly, it was reported that there were no significant differences in percentage of T cell-related immunological markers such as CD3, CD4, and CD8 between the autologous or the allogeneic PDLSCs, suggesting that transplanted allogeneic PDLSCs cause no immunological rejection [30].

PDLSCs show self-renewal, multipotency, and immunomodulatory properties, therefore they should hold great promise for the treatment of destructed periodontium.

Induced Pluripotent Stem cells (iPS)

Based on the hypothesis that the genes that have important significance in maintaining ESC identity also exert key effects in inducting pluripotency of somatic cells, Takahashi and Yamanaka [31] introduced different combinations of selected 24 genes, which were important transcripts of ESCs and oncogenes, as candidate reprogramming factors into mouse embryonic. They found that after introduction of the retroviral mediated factorsOct3/4, Sox2, Klf4, and c-Myc, mouse embryonic fibroblasts were reprogrammed into ES cell-like cells called iPSCs. Human iPSCs share similar biological characteristics with human ESCs including morphology, proliferation, surface antigens, gene expression, epigenetic

status of pluripotent cell-specific genes, and telomerase activity. Moreover, these cells could differentiate to cell types of the three germ layers in vitro and in teratomas.

Cell Sources for Deriving iPSCs and Approaches for Reprogramming

iPSCs have been procured from many varried species, such as humans, mice, pigs, rabbits, rats, and rhesus monkeys. The cell types that have been successfully reprogrammed are fibroblasts, marrow mesenchymal cells, gastric/intestinal epithelial cells, keratinocytes, hepatocytes, adipose stem cells, B and T lymphocytes, etc. Of these, fibroblasts are the most commonly used parental somatic cell type for the generation of iPSCs.

iPSCs Used in Periodontal Regeneration

iPSCs now provide a novel approach to the field of tissue engineering. In general, the rationale of applying iPSCs in periodontal regeneration includes the following aspects:

(1) iPSCs can be induced from dental derived cells, such as gingival fibroblasts and periodontal ligament fibroblasts;

(2) iPSCs can differentiate to osteogenic cells after stimulated by certain factors;

(3) combining with or without the scaffolds, iPSCs can facilitate the healing of man-made periodontal bone defect and form new periodontal tissues like alveolar bone, cementum, and periodontal ligament [32].

The Challenges and Future Perspectives Regarding iPSCs

At present, many limitations still affect the possible applications of iPSCs in clinical medicine. The foremost impediments are related to the reprogramming efficiency, biological safety, and large-scale expansion and directed differentiations.

Biological safety is another consternation in relation to the application of iPSCs in tissue regeneration. First, the integration of reprogramming factors into the genome by retroviral or lentiviral transduction is the method used now for reprogramming iPSCs. However, the use of cells containing viruses brings up the possibility that viruses integrate into host chromosomes and lead to replication-induced DNA mutation and potentially malignant transformation. Additionally, the existence of viruses may stimulate immunological reaction.

Second, the principles of iPSCs in regenerative medicine rely on their ability to self-renew and to differentiate to cells of the three germ layers. These properties predispose iPSCs to be tumorigenic and therefore hinder the clinical applications of these cells.

Another handicap for using iPSCs is the deficiency of large-scale expansion and directed differentiation approaches i.e. obtaining sufficient iPSCs and directing them to differentiate into osteoblasts, cementoblasts, and periodontal fibroblasts etc. Finally, challenge also remains to identify the best combination of iPSCs, biomaterials, and growth factors for various clinical situations [33].

Conclusion

The future for stem cell-based periodontal regeneration is very promising. However, as with all new technologies, questions often arise at a faster rate than answers. The plethora of animal studies carried out to date provide an overwhelming body of evidence to support the supremacy of stem cell regeneration. There are critical steps in moving the field towards human clinical utility. Issues such as appropriate delivery devices, immunogenicity, autologous cells vs. allogeneic cells, which tissues provide the most appropriate donor source, control of the whole process and cost-effectiveness are all important considerations that should not be overlooked. A multilevel approach involving cell biologists, matrix biologists, pharmacologists, biomaterials scientists / engineers and nanotechnologists will be required for periodontal regeneration via the stem cells to move to the next level.

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Legend Figure

Figure 1: Relevant studies on dental stem cells.