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REVIEW ARTICLE

STEM CELLS FOR PERIODONTAL REGENERATION

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ABSTRACT

Periodontal regeneration is considered to be biologically possible but clinically unpredictable. In periodontitis, inflammation manifests clinically as loss of supporting periodontal tissues and regeneration of damaged tissue is the main goal of treatment. For decades, periodontists have sought to repair the damage through a variety of surgical procedures, and use of grafting materials and growth factors, and of barrier membranes. Reports have emerged that demonstrate which populations of adult stem cells reside in the periodontal ligaments of humans and other animals. This opens the way for new cell-based therapies for perio-dontal regeneration. This review provides an overview of adult human stem cells and their potential use in perio-dontal regeneration.

Keywords: Periodontitis; Stem cells; Therapy.

INTRODUCTION

Periodontitis is an inflammatory disease which manifests clinically as loss of supporting tissues including periodontal ligament and alveolar bone, which potentially leads to tooth loss. In the world population, around 35.0% of adults suffer from moderate form of periodontitis, while 15.0% are affected by a severe generalized form of perio-dontitis at some stage in their lives [1]. The significant burden of periodontal disease and its impact on general health and patient quality of life point to the need for more effective management of the condition [2]. Once damaged, the periodontium has a limited capacity for regeneration. During the early phases of the disease, some minor regeneration of the periodontium may be seen. However, once periodontitis becomes established, only therapeutic intervention has the potential to induce regeneration [3]. Procedures to achieve periodontal regeneration have included root surface conditioning, bone graft placement, guided tissue regeneration and growth factor application. However, current regenerative procedures have limitations in attaining complete and predicable regeneration, especially in advanced periodontal defects [4]. For successful perio-dontal regeneration, formation of a functional epithelial seal, insertion of new connective tissue fibers into the root, reformation of a new acellular cementum on the tooth sur-face and restoration of alveolar bone height are required. The complex events associated with periodontal regeneration involve recruitment of locally-derived progenitor cells that can differentiate into periodontal ligament cells, mineral-forming cementoblasts, or bone-forming osteoblasts [5,6].

Advances in stem cell biology and regenerative medicine have presented opportunities for tissue en-

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gineering and gene-based approaches in periodontal therapy [7,8]. These new approaches, offers interesting alternatives to existing therapies for the repair and regeneration of the periodontium.

We here review current understanding of stem cells, their potential application in regenerative periodontal therapy, and discuss the challenges of translating stem cell research into clinical practice.

The Types of Stem Cells. Stem cells are the foundation cells for every organ and tissue in the body, including the periodontium [9]. They have two defining characteristics: the ability for indefinite self-renewal to give rise to more stem cells, and the ability to differentiate into a variety of specialized daughter cells to perform specific functions [10]. When a stem cell divides asymmetrically, one daughter cell retains the stem cell characteristics, while the other is destined for specialization under specific conditions [11]. A pluripotent stem cell can differentiate into all cell types of the body, whereas a multipotent stem cell can differentiate into many different cell types.

The two types of stem cells – embryonic and adult – are classified according to their origin and differentiation potential. Human embryonic stem cells are pluripotential and differentiate into all types of specialized body cells [12]. Their use for clinical therapy is a relatively new endeavor. Adult, or tissue-specific, stem cells are found in the majority of fetal and adult tissues. They are derived from tissues that continually replenish themselves (peripheral blood, dermis and gastrointestinal epithelium) [13]. They are multipotential [14] and are thought to function by replacing cells that are injured or loss. Their most common source is the bone marrow (hematopoietic stem cells) or bone marrow stromal cells (mesenchymal stromal stem cells). These last can be potential candidates for perio-dontal regeneration [15]. They can differentiate into endothelial, perivascular, neural, bone or muscle cells [16].

Mesenchymal stem cells can effectively regenerate destroyed periodontal tissue. Those derived from bone marrow or adipose tissue have been used in experimental animal models. They have been shown to form cementum, periodontal ligament and alveolar bone in *vivo* after implantation into periodontal defects in beagle dogs [17]. Mesenchymal stem cells have also been identified in adipose tissue [18]. As adipose tissue requires less-invasive methods and is abundant, it is very appealing as a source of cells for regenerative periodontal therapy.

Stem Cells in Dental and Periodontal Tissues. The identification and manipulation of stem cells has greatly advanced regenerative medicine and has contributed to development of tissue engineering-based clinical therapies [19]. One of the critical requirements for a tissue engineering approach is the delivery of *ex vivo* expanded progenitor populations or the mobilization of endogenous progenitor cells capable of proliferating and differentiating into the required tissues.

The periodontal ligament, a highly fibrous and vascular tissue, has one of the highest turnover rates in the body. Its cells include cementoblasts, osteoblasts, fibroblasts, endothelial and epithelial cells, and a population of "progenitor cells" [20] that exhibit some of the features and characteristics of mesenchymal stem cells.

The first human dental stem cells, isolated from dental pulps tissue of extracted third-molar teeth, were characterized relative to bone marrow mesenchymal stem cells [21]. Periodontal ligament stem cells have been shown to give rise to adherent clonogenic clusters resembling fibroblasts that may develop into adipocytes, osteoblast-like cells and cementoblast-like cells in *vitro*, and into cementum-like and periodontal ligament-like tissues in *vivo* [22]. They are similar to stem cells of dental pulp, and to bone marrow mesenchymal stem cells.

Mesenchymal progenitor cells, isolated from the dental follicle of human third-molar teeth [23] can generate perio-dontal ligament-like tissue [24], implying that they may be a useful for regenerative periodontal therapy. However, it remains to be determined which source of dental mesen-chymal stem cells is most suitable for regenerative therapy. This prospect represents a step forward in development of more predictable biologically-based therapy for the perio-dontium.

Stem Cells in Periodontal Regeneration. In dentistry, the identification of mesenchymal stem cell-like populations has presented possibilities for the application of tissue engineering in the development of novel strategies for regenerative periodontal therapy. One approach to perio-dontal regeneration involves incorporation of progenitor cells in a periodontal defect [25]. Tissue-engineering strategies have been applied to reconstruct damaged perio-dontium [26]. Autologous bone marrow mesenchymal and adipose-derived stem cells do regenerate alveolar bone and periodontal ligament-like structures after transplantation [27]. An ideal source may be human adult dermal fibro-blasts reprogrammed to pluripotency and to production of enough cells for regenerative periodontal therapy [28].

These results from animal models are paving the way for human regenerative periodontal therapy [29,30]. They demonstrate the feasibility and potential of dental and non dental stem cells for functional periodontal and tooth regeneration. They also indicate that periodontal ligament can be an efficient autologous source of stem cells with a high expansion capacity and ability to differentiate into osteogenic cells that can colonize and produce a biocom-patible scaffold [31,32].

Differentiation Potential of Periodontal Ligament Stem Cells. Previous studies have demonstrated that periodontal ligament stem cells can build a typical cementum-periodontal ligament-like structure [33]. Expanded perio-dontal stem cells are heterogeneous in morphological characteristics, differentiation potential and proliferative capacities [34].

Periodontal Regeneration. A main goal of periodontal therapy is regeneration of the affected tissues to their original architecture and function. Polypeptide growth factors such as epidermal growth factor, fibroblast growth factor, platelet-derived growth factor and bone morpho-genetic proteins [6] have been used to facilitate periodontal regeneration. The clinical results have been encouraging and these factors seem capable of promoting regeneration of periodontal tissues, albeit not in a completely predictable or consistent manner [35].

The successful use hematopoietic bone marrow reconstitution in cancer patients has led to investigation of other stem cells as potential therapy for other diseases and congenital defects [36]. The presence of different mesenchy-mal stem cells in dental or craniofacial tissues invites clinical investigations into regeneration of orofacial and perio-dontal regions [37]. Cells with characteristics of putative mesenchymal stem cells were found in regenerating periodontal tissues [38].

Biological Challenges. Despite biological evidence that periodontal regeneration can occur in humans, complete and predictable regeneration remains an exclusive clinical goal and the molecular processes that underlie stem cell proliferation and differentiation are largely unknown. While the use of stem cells can minimize the processing time compared with somatic cells, posible karyotypic instability and gene mutations of the cells after prolonged culture can limit their usefulness. Immune rejection after administration, oncogenic properties of stem cells and functional integration on transplanted tissues into the host [39] are significant challenges. Use of autologous stem cells to overcome immune rejection [19] is a possible solution.

Restoration of tissues destroyed by periodontitis to their original form and function has been a long-standing goal of periodontal therapy. Current available regenerative therapies are poor clinical predictability and there is a need for novel regenerative technologies to be developed based on contemporary understanding. A number of studies have reported that stem cells, in conjunction with different physical matrices and growth factors, have the capacity to regenerate periodontal tissues in *vivo*. In spite of these significant advances there are still numerous biological, technical and clinical hurdles to be overcome. It is not clear if human stem-cell derivatives can integrate into the recipient tissue and fulfill the specific functions of lost or injured tissue [40]. Demonstration that stem cells develop into stable cells and display the characteristics and functions of normal host cells following their transplantation is essential. It is auspicious that Ding *et al.* [30] have elevated full-thickness periodontal flaps and applied a mesenchymal-stem-cell and platelet-rich plasma to the root surface and adjacent defect space resulting in a 4 mm reduction of periodontal pocket depths and disappearance of bleeding and tooth mobility. In addition, radiographic assessment showed that the bone defect had been reduced in depth. Thus, mesenchymal stem cells may prove useful for periodontal tissue regeneration, treatment of esthetically sensitive sites, and reduction of patient morbidity.

With the first reports of adult human stem cells populations residing in the periodontal ligament, the next phase will be to determine the clinical utility of these cells. Thus, future research efforts might be focused on the potential use of this cell population in tissue engineering and in their maintenance and differentiation in *vitro* and in *vivo*.

CONCLUSIONS

In conclusion, great progress has been made in the areas of stem cells, biomaterial design and manufacturing and other related areas. Based on these data, we speculate that enhanced stem cells techniques will be a way to achieve the desired periodontal regeneration.

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