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Review

Stem cell-delivery therapeutics for periodontal tissue regeneration

Fa-Ming Chen [a,b,*,1], Hai-Hua Sun [c,1], Hong Lu [a,1], Qing Yu [b,c]

[a] Department of Periodontology and Oral Medicine, School of Stomatology, Fourth Military Medical University, Xi'an 710032, Shaanxi, PR China
[b] Translational Research Team, School of Stomatology, Fourth Military Medical University, Xi'an 710032, Shaanxi, PR China
[c] Department of Operative Dentistry and Endodontics, School of Stomatology, Fourth Military Medical University, Xi'an 710032, Shaanxi, PR China

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ABSTRACT

Periodontitis, an inflammatory disease, is the most common cause of tooth loss in adults. Attempts to regenerate the complex system of tooth-supporting apparatus (i.e., the periodontal ligament, alveolar bone and root cementum) after loss/damage due to periodontitis have made some progress recently and provide a useful experimental model for the evaluation of future regenerative therapies. Concentrated efforts have now moved from the use of guided tissue/bone regeneration technology, a variety of growth factors and various bone grafts/substitutes toward the design and practice of endogenous regenerative technology by recruitment of host cells (cell homing) or stem cell-based therapeutics by transplantation of outside cells to enhance periodontal tissue regeneration and its biomechanical integration. This shift is driven by the general inability of conventional therapies to deliver satisfactory outcomes, particularly in cases where the disease has caused large tissue defects in the periodontium. Cell homing and cell transplantation are both scientifically meritorious approaches that show promise to completely and reliably reconstitute all tissue and connections damaged through periodontal disease, and hence research into both directions should continue. In view of periodontal regeneration by paradigms that unlock the body's innate regenerative potential has been reviewed elsewhere, this paper specifically explores and analyses the stem cell types and cell delivery strategies that have been or have the potential to be used as therapeutics in periodontal regenerative medicine, with particular emphasis placed on the efficacy and safety concerns of current stem cell-based periodontal therapies that may eventually enter into the clinic.

1. Introduction

Periodontitis is a common and widespread disease in the oral and maxillofacial region that causes the destruction of the tooth-supporting tissues including alveolar bone, the periodontal ligament (PDL) and root cementum. If left untreated, periodontitis will result in progressive periodontal attachment and bone loss that may eventually lead to early tooth loss [1]. As a consequence, periodontal disease is one of the most important concerns for dentists, patients and the public dental healthcare system. Of note, conventional treatment strategies, either non-surgical or surgical therapy, fail to restore true periodontal supporting structures damaged through periodontal disease [2]. The significant burden of periodontal disease and its negative impact on patient quality of life indicate the need for more effective management of this condition [3,4].

Following disease control interventions such as tooth cleaning/scaling, root planning and periodontal debridement, several procedures have thus far been attempted to achieve periodontal regeneration, including bone graft placement, guided tissue/bone regeneration (GTR/GBR) and the use of various growth factors and/or host modulating agents (e.g., Emdogain® and parathyroid hormone) [5,6]. These techniques have proven at least somewhat effective in promoting the reconstruction of the appendicular musculoskeletal system. However, periodontal regeneration is especially challenging, as it requires predictable regeneration of three quite diverse and unique tissues (e.g., cementum, PDL, and bone) and a triphasic interface between these different tissues to guarantee the restoration of their complex structure [7,8]. Unfortunately, current regenerative procedures that are used either alone or in combination have limited success in achieving this ambitious purpose, especially in advanced periodontal defects [3].

Recent insights into the reparative capability of the periodontium in conjunction with advances in stem cell biology and

* Corresponding author. Department of Periodontology and Oral Medicine, School of Stomatology, Fourth Military Medical University, Xi'an 710032, Shaanxi, PR China. Tel./fax: +86 29 84776096.
E-mail address: cfmsunhh@fmmu.edu.cn (F.-M. Chen).
[1] These authors contributed equally to this manuscript.

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regenerative medicine enable the development of novel therapies using either endogenous regenerative technology [8] or cell-based therapeutics that are likely to achieve robust regeneration with greater efficacy and predictability [3]. The acceleration of a patient's endogenous regenerative mechanisms that recruit host stem/progenitor cells, a biological process known as cell homing, for periodontal regeneration has been considered as a highly useful and practical approach for clinical utility [8–10]. In comparison, it has been recently demonstrated in pre-clinical studies that stem cell delivery is likely to produce more reliable and effective results in management of periodontal defect, and several clinical trials involving the use of *ex vivo* expanded stem cells into human patients have already begun or are in preparation [11]. The major difficulties facing widespread clinical implementation of existing cell delivery strategies for periodontal therapy are the qualification, cost and time required for *ex vivo* culture of a patient's autologous cells prior to re-implantation, and the potential risks and availability constraints associated with transplanting allogeneic (foreign) cells. Although the regenerative potential of a patient's own cells may be harnessed to promote tissue regrowth without *ex vivo* cell culture, spontaneous healing may be restricted by an age-related decline in host stem/progenitor populations or by the intrinsically low regenerative potential of certain tissues such as the periodontium [8,12].

Cell homing and cell delivery, each having its own advantages and disadvantages, are both meritorious approaches in periodontal bioengineering that equally warrant further scientific investigation. Multifaceted technologies are increasingly required to produce and interrogate cells *ex vivo*, or to signal and recruit cells *in vivo*, and, ultimately, to enhance cell integration for therapeutic benefit. In light of the development of medical devices that establish key interactions with host cells in ways that unlock the body's innate powers of organization and self-repair and its implications in periodontal regenerative medicine has been reviewed elsewhere [8–10,12], this article will specifically scrutinise the types of stem cells that have potential applications in regenerative periodontal therapy and explore the strategies that are used to deliver them, highlighting the opportunities and challenges of their clinical use as an effective approach to periodontal tissue regeneration.

2. Stem cells as powerful therapeutics

Pluripotent adult stem cells can be found in a number of tissues; most of these cells are lineage-restricted (multipotent) and are generally referred to by their tissue of origin, such as mesenchymal stem cells (MSCs), dental stem cells and adipose-derived stem cells (ASCs) [2,3,11,13]. Likewise, the healthy PDL harbours stem cell niches throughout adulthood that play key roles in the maintenance of the regenerative capacity of the periodontium. However, in a diseased periodontal environment, tissue repair does not occur naturally because of the lack of robust stem cells. Therefore, exogenous regenerative 'tools' such as *ex vivo* expanded/manipulated stem cells will be needed to replenish the host cell niche and facilitate tissue regeneration [4]. In such therapeutic approaches, stem cells and/or progenitor cells are manipulated *in vitro* and administered to patients as living and dynamic biological agents [14]. The transplanted cells may participate in the repair of damaged or diseased tissue, serving as or producing building blocks, or regulate regeneration via secretion of trophic factors, instead or in addition to directly participating in regeneration of the tissue [15].

Of note, a variety of cell populations with stem cell properties have now been isolated from different parts of the tooth that are generally termed dental stem cells. These populations include dental pulp stem cells (DPSCs) [16,17], stem cells from exfoliated deciduous teeth (SHED) [18], PDL stem cells (PDLSCs) [19], stem

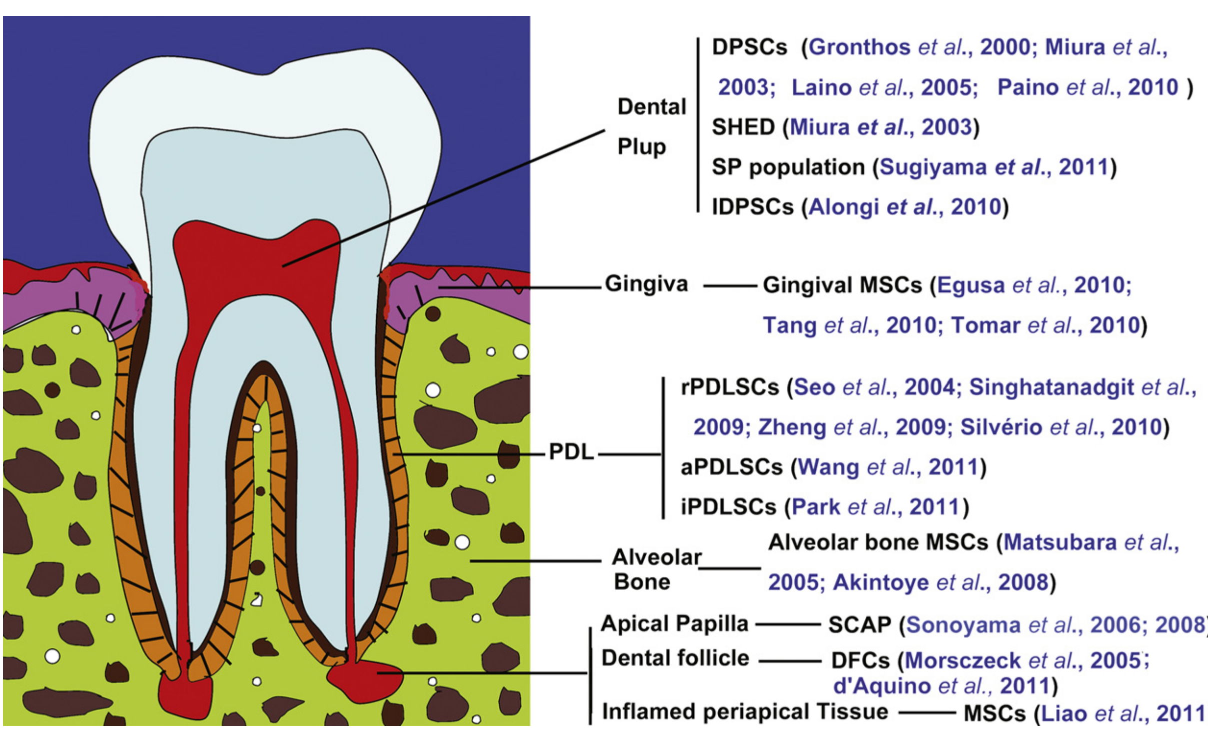

Fig. 1. Selected stem/progenitor cell populations identified from different tissues/regions in or around a tooth that may have the potential to regenerate lost/damaged periodontal tissues. DPSCs, dental pulp stem cells; SHED, stem cells from human exfoliated deciduous teeth; SP cells, side population cells isolated from dental pulp tissue; iDPSCs, dental pulp stem cells from inflamed dental pulp tissue; Gingival MSCs, mesenchymal stem cells from gingiva; rPDLSCs, periodontal ligament stem cells (PDLSCs) isolated from the PDL from the root surface following tooth extraction; aPDLSCs, PDLSCs isolated from the remaining PDL on the alveolar bone surface of the extraction sockets; iPDLSCs, PDLSCs isolated from the inflamed PDL tissue; SCAP, stem cells from root apical papilla; DFCs, dental follicle cells.