SHORT COMMUNICATION

Short communication: Stem Cells for Periodontal Tissue Regeneration

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Introduction

Periodontal disease is an inflammatory condition that causes pathological alterations in the periodontium, potentially leading to tooth loss [1]. In the world, 35% of adults in the population suffer from moderate periodontal disease, while up to 15 % were affected by a more severe form at some stage of their life [2, 3].The periodontium has always proved to be one of the structures with inherent regenerative capacities. It gives rise to osteoblasts, periodontal ligament (PDL) fibroblasts, and cementoblasts[4]. However, the periodontium – which includes the periodontal ligament, root cementum, alveolar bone and gingiva - has a limited ability to regenerate once damaged [4]. For decades, periodontists have sought to repair the damage from periodontitis and to achieve regeneration through a variety of non-surgical procedures and surgical procedures that include root surface conditioning, bone graft placement, guided tissue regeneration and the application of growth factors [5-7]. However, current procedures allow the periodontal tissue to be repaired rather than regenerated with some approaches showing some limited unpredictable regenerative outcome [8-12]. Recent advances in tissue engineering and stem cell biology have paved the way to develop novel approaches in the regenerative periodontal therapy or to supplement existing treatment modalities for periodontal disease.

Cell-based Tissue Engineering

In order to achieve a successful periodontal regeneration, healing events must occur in an ordered and programmed order, starting with the migration of appropriate progenitor cells into the wound site and attach to the denuded root surface [13]. These progenitor cells have the ability to proliferate and mature into the different component of the functional periodontium. The success of these progenitor cells is also dependant on the availability of the appropriate growth factors and contact with the extracellular matrix [14, 15]. This allows the formation of a functional epithelial seal with an insertion of a new connective tissue fibers into the root in conjunction with a new acellular cementum covering the root surface and the reestablishment of a proper alveolar bone height that can ensure a healthy regenerated periodontium [16, 17]. Current tissue engineering trends have utilized the principles of periodontal healing and cell biology in developing cellular-based techniques for periodontal regeneration.

In the context of periodontal therapy, cell-based tissue engineering involved incorporation of progenitor cells in a prefabricated three-dimensional biomaterial that is implanted into the defect site. This approach overcomes some of the limitations of conventional procedures and allows direct application of progenitor cells and growth factors in the defect area [18]. The success of the cell-based approach requires the following essential factors [19]: (1) appropriate progenitors cells that proliferate and mature to tissue-forming phenotypes, including fibroblasts, osteoblasts, and cement oblasts; (2) appropriate signals to control cellular differentiation and tissue formation; (3) a three dimensional scaffold to support the cells and facilitate the previous processes; and (4) good blood supply and promotion of new vascular networks. Consequently, the most critical factors in tissue engineering is the choice of optimal stem cell population that give rise to the progenitor cells and the selection of an appropriate biomaterial that can serve as a scaffold that both support these cells and possess adequate mechanical properties.

Stem cells

By definition, a stem cell is a clonogenic, relatively undifferentiated cell that is capable of self-renewal and multi-lineage differentiation depending on intrinsic signals modulated by extrinsic factors in the stem cell niche[20, 21]. Stem cells (SCs) are classified according to their origin and their differentiation potential[16, 22]. They can be broadly classified into three categories: (1) embryonic stem cells (ESCs); (2) induced pluripotent stem cells (iPSCs); (3) adult or postnatal SCs. ESCs are totipotent or pluripotent cell, which means that they possess the capacity to proliferate extensively and differentiate into almost all possible cell types. However, using embryos to obtain human embryonic stem cells has raised many ethical concerns and limited their usage. These concerns pushed researchers to investigate the possibility of genetically reprogramming somatic cells back to the pluripotent phase, which lead to the generation of iPSCs[23, 24]. They are comparable to the ESCs in their function, morphology, gene expression and wide differentiation capacity[23, 24]. Efforts were also made to obtain iPSCs from gingival and periodontal fibroblasts[25-27]. In general, the behaviour of iPSCs can be unpredictable because the genetic manipulations may alter their development and growth characteristics, thus, limiting their in tissue engineering[16]. Moreover, both the ESCs and the iPSCs convey tumorigenic properties that raise serious safety concerns that further limit their use in regenerative therapies.

Somatic adult or postnatal stem cells can be derived from the majority of fetal and adult tissues that continually replenish themselves (e.g. dermis, peripheral blood) [20, 28, 29]. They are multipotent and can differentiate into limited number of cell lineages such as endothelial, perivascular, neural, bone or muscle cells [30]. It is thought that they function in long-term tissue maintenance and replacing cells that are either lost or injured [31]. Despite their limited life span, SCs have extensive self-renewal capacity [32]. Even though adult SCs exhibit more restricted capabilities compares to ESCs, they are immunocompatible and are not associated with any ethical concerns (Han). Their most common sources are the bone marrow (hematopoietic stem cells) and bone marrow stromal cells (mesenchymal stromal stem cells) [33-35]. Hematopoietic stem cells were the first cells to be used in regenerative therapies, mainly in the treatment of blood malignancies and immunodeficiency syndromes, but they lack the ability to give rise to supporting connective tissues [36]. On the contrary, mesenchymal stem cells (MSCs) have been used to treat a range of musculoskeletal abnormalities and are capable of differentiate to connective tissue cells [36]. Consequently, MSCs serve as potential candidates for periodontal regeneration.

Human mesenchymal stem cells in periodontal regeneration

Human mesenchymal stems cells (hMSCs) are the most commonly used stem used in periodontal regeneration due to their extensive expansion rate, immunocompatibility (some may exhibit immunosuppressive properties), and extensive availability without any ethical restraints[37]. hMSCs used for periodontal regeneration can be obtained from both extraoral and intraoral tissues. Extraoral sources include bone marrow and adipose tissues. Past in vivo studies showed that implanted bone marrow-derived MSCs can induce the regeneration of cementum and alveolar bone up to 20% in experimental Class III defects [38], and can differentiate into cementoblasts, alveolar bone osteoblasts and PDL fibroblasts [38-41]. Small human clinical trials demonstrated that mixing bone marrow-derived MSCs with platelet-rich plasma (PRP) result in reduction in intrabony defect depth and resolution of bleeding, while mixing these cells with atelocollagen reduced the probing depth by 4mm [41]. Another potential extraoral source is adipose tissue. In vivo studies in rats demonstrated that adipose-derived stromal cells mixed with PRP promoted periodontal regeneration [42]. Future clinical studies are required to assess the candidacy of adipose-derived MSCs for periodontal regeneration, since they are more abundant, more easily accessible to lipoaspirates with lower morbidity compared to the more invasive procedures to obtain the bone marrow-derived MSCs.

Dental-tissue derived MSCs can be obtained intraorally from dental tissues (e.g. dentin or PDL or pulp) either from permanent or deciduous teeth [43-45]. They can be simply obtained using a chair side procedure or immediately after tooth extraction [43]. However, these cells have a more restricted cellular potency in comparison to bone marrow-derived MSCs, as bone tissues are known to undergo more remodelling than dental tissues [16]. There has a been a particular interest in assessing the regenerative capacity of mesenchymal stems derived from PDL (PDLSCs), since being first isolated in 2004[46].They showed an increased proliferative potential of cell populations that can differentiate into either cementoblasts, osteoblasts, fibroblasts and even adipocytes[47]. PDLSCs can exert different benefits on multiple levels including tissue regeneration, neovascularization and immunomodulation, by which PDLSCs can inhibit the immune response without an induction of an inflammatory response, thus enabling the use of allogenic PDL sources for periodontal regeneration[48, 49]. Animal studies showed that implanted PDLSCs in periodontal defects resulted in the new formation of cementum and alveolar bone, and new attachment apparatus[50-55]. Furthermore, a study conducted on mini-pegs demonstrated the formation of PDL- like tissue mimicking the orientation of the fibre bundles similar to Sharpey's fibers within four weeks[51]. The results from human clinical studies using PDLSCs are encouraging yet still very limited and variable [56-58].Recent studies even showed that MSCs can be derived from normal and inflamed gingival tissues which might be a more abundant potential source compared to PDL[59, 60]. More future studies are required to assess the benefits and safety of using MSCs from dental origin and important challenges need to be addressed before applying such treatment protocols to standard clinical practice[56].

Final remarks

The future applications of stem cells and tissue engineering in periodontal therapy are one of the most promising techniques capable of meeting a variety of patients' needs. However, many challenges need to be tackled before reaching a clear consensus regarding stem cells utilization. Biologically, it is essential to fully understand the key cellular events that occur during periodontal development, knowledge of the specific cell types, the inductive factors, the cellular and molecular processes involved in formation of the periodontium, and the mechanism in which stem cells promote differentiation. Technical challenges such as the appropriate delivery system and the most suitable scaffold matrix should be addressed by advancing the techniques used in handling stem cells. Concerning the clinical challenges, it is very important to understand the immune response after the delivery of the stem cells and the safety considerations related to the use stem cells. In addition, the cost effectiveness and the patient benefits should be considered. More high quality clinical research is essential to ensure that such novel approaches supported by robust data and are effective in meeting the patients' needs.

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