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STEM CELLS, TISSUE ENGINEERING AND PERIODONTAL REGENERATION: A REVIEW

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ABSTRACT:

In this review we aim to discuss the clinical utility of stem cells in regeneration of periodontal tissue from recent studies. We contemplate the main stem cells used for periodontal regeneration, along with bone marrow-derived mesenchymal stem cells. Furthermore we elaborated about the stem cells derived from dental pulp, periodontal ligament, exfoliated human deciduous teeth, apical papilla along with dental follicle precursor cells. These stem cells in future can be utilized for the tissue regeneration in periodontal treatment.

Keywords: Periodontal tissue, Stem cells, Tissue regeneration.

INTRODUCTION

The irreversible destruction of the tooth attachment along with the adjacent bone is seen in the periodontal disease.[1] The outcomes of untreated periodontal diseases have expansive ramifications on a person's quality of life, which can impact ones wellbeing and incur financial burden. Present traditional techniques for the treatment of periodontal diseases show a restricted potential for total periodontal recovery. An improved comprehension of periodontal biology combined with current advances in the improvement of scaffolding matrices has presented novel treatment options that utilize cell and gene therapy to upgrade periodontal tissue reconstruction and its biomechanical integration.

Wound healing of the periodontium

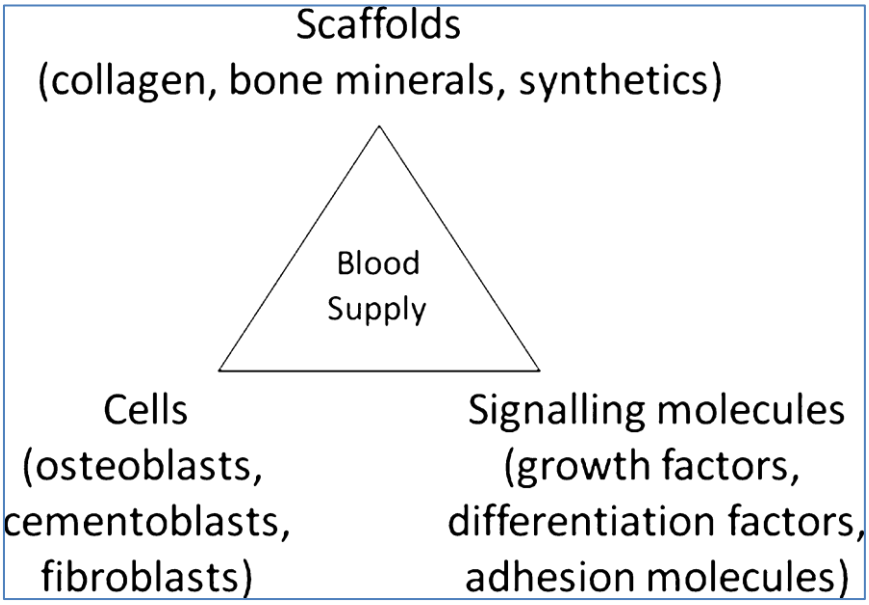
Periodontal healing is a complex process.[2] In traditional techniques the treatment is done by reducing inflammation by modifying the periodontal microbiology and the surrounding environment. Present non-surgical techniques, like the subgingival debridement, and surgical procedures, like open flap debridement, aim to remove diseased tissue and clean the root surface to encourage reattachment of tissues. These methods stereotypically end in a process of repair (Table 1), leading to the healing of the wound site by creation of a long junctional epithelial attachment.

Table 1. Periodontal wound healing responses by repair and regeneration

Repair	Regeneration
Control of inflammation	Formation of new functional attachment, including formation of cementum, periodontal ligament and alveolar bone
Formation of long junctional epithelium	
Re-attachment of connective tissue to adjacent root surface	
New bone separation from the root surface by long functional epithelium, accompanied by root resorption, and/or ankylosis	

(Adapted from Narayanan AS, Bartold PM. Biochemistry of periodontal connective tissues and their regeneration: a current perspective. Connect Tissue Res 1996;34:191–201)

Fig. 1 Schematic representation of periodontal tissue engineering.



The Contemporary treatment regenerative methods

Various methods have been depicted to advance valid and predictable recovery of the periodontium since the 1980s. To depict the most recent patterns, principles of these treatment approaches incorporate the utilization of graft materials to make up for the bone loss resulting from periodontal disease,[3] utilization of barrier membranes for guided tissue regeneration,[4,5] and utilization of bioactive molecules.[6,7]

Bone grafts

Different kinds of bone grafts incorporate alloplastic materials (mostly synthetic fillers), autografts (grafted tissue from same individual), allografts (tissue between people of similar species however with various genetic composition) and xenografts (grafted materials between

various species).

Guided tissue regeneration

This method, named guided tissue recovery, has, as of late become a generally acknowledged clinical strategy, and is presently viewed as the 'gold standard' whereupon to base and compare regenerative therapies.[8,9] Guided tissue regeneration includes usage of barrier membranes to forestall undesirable epithelium and gingival connective tissue from entering the recuperating site while recruiting cells from the periodontium to re-populate the defects.

Bioactive materials

Another way to induce periodontal regeneration has included the direct delivery of bioactive polypeptide growth factors to the root surface to encourage wound healing leading to new cementum and connective tissue development. Among those considered to date are the platelet- derived growth factor (PDGF) and insulin-like development factor-I (IGF-I) which have appeared to upgrade regeneration in beagle canines and monkeys with periodontal diseases.[10,11] Furthermore, bone morphogenetic proteins (BMPs) have additionally demonstrated potential to animate bone and cementum regeneration.[12] The most widely clinically tried of these is the enamel matrix derivative (EMD), known to control the epithelial mesenchymal collaborations associated with tooth development. Emdogain is a combination of enamel matrix proteins fundamentally containing amelogenins taken from creating porcine teeth. Moreover, Emdogain has TGF-b and BMP development factors and, accordingly, the expansion of these proteins to intrabony deformities may advance periodontal regeneration by reiterating the environment during initial tooth attachment.[6,7,13]

Periodontal regeneration summary

For regeneration to happen, healing events should advance in an arranged and customized succession both transiently and spatially, repeating the vital events in periodontal development.[14] Recent proof shows that subset populations taken from the periodontal ligament have qualities of stem cells. As a result, present research trends have been coordinated towards creating cell based methods for periodontal regeneration.

Cell-based tissue engineering

With regards to periodontal treatment, a potential tissue engineering way to deal with periodontal regeneration includes consolidation of progenitor cells in a pre-assembled three-dimensional, which is accordingly embedded into the deformity site (Fig. 2). [14] An effective result of periodontal tissue engineering requires the accompanying fundamental variables: (1) a satisfactory supply of progenitor cells with the ability to differentiate into the necessary mature tissue-shaping phenotypes, including osteoblasts, cementoblasts and fibroblasts; (2) the proper signs to modulate cellular differentiation and tissue neogenesis; and (3) a conductive three-dimensional extracellular matrix scaffold to help and encourage these processes.[15] One of the most basic components in tissue engineering is the decision of scaffold and optimal stem cell population to utilize.

Scaffold-based tissue engineering

For effective tissue engineering to be accomplished a scaffold should be joined with living cells, as well as biologically active molecules. This will make a 'tissue engineering construct' to be utilized to advance regeneration of tissues.[16,17] This can be accomplished providing optimal stiffness together with predetermined external and internal geometrical shapes. Tissue engineering constructs should likewise give adequate initial mechanical strength and

solidness to fill in for the deficiency of mechanical function of the diseased, harmed or missing tissue. To accomplish stable biomechanical conditions and vascularization at the host site, unremitting cell and tissue remodelling is significant. It is currently perceived that for effective tissue development, remodelling, and maturation at the defect site it is fundamental to comprehend and control the scaffold degradation process. Besides, tissue in-development doesn't equate to tissue maturation and remodeling, in other words a defect filled with immature tissue should not be considered 'regenerated'.

Stem cells

By definition, a stem cell alludes to a clonogenic, moderately undifferentiated cell that is equipped for self- renewal and multi-lineage differentiation.[18] Stem cells have now been isolated from a wide assortment of tissues and upon their characterization, these populations have been categorized according to their respective developmental potential (Fig. 3). Embryonic stem cells are pluripotent cells gotten from the early mammalian undeveloped embryo with the ability to multiply widely and differentiate into cells with features of every one of the three undeveloped germ layers. Notwithstanding their formative potential, the utilization of embryo to acquire human undeveloped stem cell lines raises genuine moral concerns, which as of late incited endeavors to genetically reprogrammed somatic cells back to their pluripotent state. These endeavors brought about the generation of induced prompted pluripotent stem (iPS) cells that are practically like embryonic stem cells. These cells are equivalent to embryonic stem cells in their morphology, gene expression profiles, proliferation and differentiation capacities.[19-21] However, genetic manipulations fundamental to generation of iPS cells may modify their growth and developmental characteristics, which hinders the consistency of their conduct and, all things considered, limits their utilization in tissue-regenerative purposes. Besides, embryonic stage stem cells and iPSCs both convey tumourigenic properties, raising a huge safety challenge in the utilization of these cells for regenerative therapies.[22,23] Initially, MSCs were separated from bone marrow and stroma of spleen and thymus.[24,25] To represent the biologic properties of multi-potential, clonogenic, plastic-adherent cells obtained from different stromal tissues, the International Society for Cellular Therapy (ISCT) has proposed the utilization of the term 'mesenchymal stem cell' and abbreviation 'MSC'.[26] MSCs are viewed as appropriate contender for cell-based tissue engineering procedures inferable from their extensive expansion rate and potential to differentiate into cells of multiple organs and systems. Moreover, MSCs appear to be not just hypoimmunogenic and in this manner appropriate for allogeneic transplantation, yet they further show immunosuppressive properties upon transplantation.[27] Considering their potential in regenerative applications, a variety of stem cells have been distinguished in many organs and tissues in the body. [28-30]

Cells for periodontal regeneration

Dental-tissue-derived MSC-like populations which can be simply obtained chairside rather than via an invasive bone marrow aspiration procedure in a secondary clinic. Both extraoral and intraoral tissues have stem cell populations that address a viable and accessible alternative source to harvest and expand multipotent colonies for likely use in periodontal tissue sources have been explored in preclinical animal studies for the treatment and regeneration of the periodontium. According to the studies from the preclinical trials to date, bone marrow- derived MSCs have the ability to promote periodontal regeneration through

enhanced generation of alveolar bone and neovascularization. The transplanted bone marrow-derived MSCs have additionally been accounted for the development of new cementum and periodontal ligament. However, despite their demonstrated ability to regenerate periodontal tissues, the trouble related with the ascertainment of these cells for use in the clinical setting has induced investigation of dental-tissue-determined MSC-like populations which can be simply obtained chairside instead of an invasive bone marrow aspiration procedure in a secondary clinic.

Adipose-derived stromal cells

Adipose-derived stromal cells (ADSCs) blended in with platelet rich plasma have been shown to advance regeneration of periodontal ligament like structures alongside alveolar bone in rats.[31] These perceptions propose that ADSCs might be helpful in future clinical cell-based treatment for periodontal tissue designing and present a positive cell candidate because of simplicity of availability of human lipoaspirates and low morbidity related with their acquisition.

Intraoral (dental-derived) mesenchymal stem cells for periodontal tissue engineering

Dental-tissue- derived mesenchymal stem cell-like populations are among numerous other isolated and characterized stem cells living in specialized tissues. Except for enamel, which needs ameloblasts or other cell components following tooth development, the periodontium and dentine continue to retain some regenerative or reparative capacities. At first, dental MSCs were isolated from human pulp tissue and, upon their characterization, were named postnatal dental pulp stem cells (DPSCs).[32]Subsequently, three additional kinds of dental-MSC-like populations were isolated and described: stem cells from shed deciduous teeth (SHED)[33]; periodontal ligament stem cells (PDLSCs)[36]; and stem cells from apical papilla (SCAP).[34,35] Recent investigations have likewise distinguished more dental-tissue-inferred progenitor cell populations, from the dental follicle and gingiva.[37,38] The developmental relationship between these different mesenchymal stem cell-like populations presently can't seem to be resolved. The different cell populations contrast in parts of their development rate in culture, quality and protein expression profiles and cell differentiation capacities, albeit the degree to which these distinctions can be ascribed to tissue of origin, function or culture conditions stays unclear. Nonetheless, the previously mentioned intraoral progenitor cells have as of late been utilized for tissue engineering studies in animal models to evaluate their potential in preclinical applications.Specifically compelling is the limit of progenitor cell populations obtained from periodontal ligament as the presence of various cell types inside periodontal ligament recommends that this tissue contains progenitor cells that keep up tissue homeostasis and regeneration of the periodontal tissues. Prior proof has demonstrated that periodontal ligament contains cell populations that can separate into either cementoblasts or osteoblasts.[39,40] These cells can clone colonies with qualities of postnatal stem cells, are self-renewable and have the capacity to offer range of dental and non-dental tissues, including cementoblast-like cells, adipocytes and collagen-structuring cells. When relocated into immunocompromised rodents, PDLSCs show the ability to produce a cementum/PDL-like construction and add to periodontal tissue repair.[36]

In vivo differentiation capacity of periodontal ligament stem cells

In an early report autologous re-implantation of removed dental roots fixed with PDL cells in minipigs brought about the development of connective tissue, resembling PDL and copying

the direction of the fiber packs, inside about a month of implantation.[41] Twelve weeks post implantation, root surfaces were covered by coordinated connective tissue looking like periodontal ligament and arranged fiber groups were joined to alveolar bone and root, entering the bone and root surfaces similarly as Sharpey's fibres. [41]In ensuing investigations reimplanted cultured cells from the periodontium embedded into experimental furcation and interdental defects in various animal models brought about arrangement of new cementum, bone, and new attachment.[42-45]More recently periodontal ligament cell sheets have arisen as a novel elective methodology for periodontal tissue engineering as the specialized treatment of implanted cells bypasses interruption of critical cell surface proteins, for example, ion channels, growth factor receptors and cell-to-cell intersection proteins.[42] Despite the overall agreement seen in preclinical animal studies evaluating the capability of PDLSCs in periodontal regenerative treatment, just two human clinical examinations have been led to date.[43,44] These investigations have additionally exhibited possible viability and safety of implanting autologous cells and showed clinical advantages from the treatment.

CONCLUSIONS

Complete and predictable regeneration or recovery of periodontal tissues lost because of injury or illness presents a significant challenge. The periodontal ligament is presently known to be a rich source of MSCs, and keeping in mind that this tissue seems to have high regenerative potential, it is hard to tackle and use this limit with regards to its clinical utility. Until this point, extraoral and dental-tissue-derived stem/ progenitor cells have been utilized for tissue designing investigations in animal models to evaluate their potential in preclinical applications. While there might be a staggering group of proof to help the idea that MSCs can be utilized for periodontal regeneration, there are a few principle objectives that should be tended to before the improvement of effective cell based treatments for regenerative dentistry. This requires better comprehension of: (a) the mechanisms of self-renewal to adequately manage adult stem cell development in vitro to create adequate cell numbers required for various applications; (b) the regulation of stem cells during differentiation and maturation into tissue-specific cell types, just as during wound healing; (c) the associations between stem cells and the immune system, specifically, with respect to utilization of allogeneic cell populations; and instruments expected to control and forestall ex vivo-extended mesenchymal stem cells from transformation.

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