Review Article

Periodontal Tissue Engineering

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Abstract:
Periodontal disease is a major public health issue and the development of effective therapies to treat the disease and regenerate periodontal tissue is an important goal of today's medicine. Regeneration of periodontal tissue is perhaps one of the most complex process to occur in the body. Langer and colleagues proposed tissue engineering as a possible technique for regenerating the lost periodontal tissues. Concerted efforts have been and still are being made to accelerate and augment periodontal tissue and bone regeneration. More recently, tissue-engineering strategies, including new cell- and=or matrix-based dimensions, are also being developed, analyzed, and employed for periodontal regenerative therapies. The focus of this review paper is to furnish and update the current knowledge of periodontal tissue engineering.
Key words: Cells; periodontal regeneration; scaffolds; tissue engineering.

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This article may be cited as: Kaur RK. Periodontal Tissue Engineering. J Adv Med Dent Scie Res 2014;2(4):152-155.

Introduction

Periodontal Tissue engineering: A promising Periodontitis is one of the most common inflammatory diseases of humans and a leading cause of tooth loss in adults. It is characterized by progressive destruction of the tooth-supporting apparatus, including gingiva, alveolar bone, periodontal ligament (PDL), and root cementum; if left untreated, it can lead to the loosening and subsequent loss of teeth.[1] Conventional periodontal treatment is generally unable to promote regeneration of the damaged periodontal structures.[2] The major challenges in contemporary periodontal therapy are to establish soft tissue attachment to newly formed cementum on the root surface and to restore lost bone. This requires regeneration of gingival connective tissue destroyed by inflammation, formation of new cementum and restoration of bone loss and most importantly, new attachment of connective tissue fibers to previously diseased root surfaces.[3] Recently, several studies have investigated the use of tissue engineering to facilitate predictable periodontal regeneration.[2]

Principles of tissue engineering

It is the effective and efficient use of “Triad of Tissue Engineering”: Cells; Matrices (scaffolds); and Regulators (signaling molecules); along with consideration for physical and biological factors like physiological environment, cellular response, phenotype, culture conditions etc.[4]

Types of Therapeutics Used For Tissue Regeneration

Currently, there are five main categories of therapeutics used or in development for tissue regeneration: Conductive therapeutic: It is a biocompatible scaffold that guides the regeneration of the tissue by passively allowing the attachment and growth of vascular elements and progenitor stem cells that reside in the tissue defect; Inductive therapeutic: It is a biocompatible scaffold that guides the regeneration of the tissue by carrying one or more biologically active factors that recruit vascular events and progenitor stem cells from the immediate vicinity to the tissue defect: Cell-based therapeutic: It is a biocompatible scaffold that contains progenitor stem cells or differentiated cells; Gene-based therapeutic: It is a biocompatible scaffold carrying single or multiple genes that transform the nonprogenitor cells already present within the tissue defect into both progenitor and mature tissue-specific cells; and RNA-based therapeutic: It is based on the principle of RNA interference (RNAi), a novel mechanism of action by which RNAs silence gene expression.[3]

Cells

Promising results in animal models using dental stem cells have paved the way for human regenerative periodontal therapy suggesting the feasibility and potential of using dental and non dental stem cells for functional periodontal and tooth regeneration.[3] Stem cells are immature progenitor cells capable of self renewal and multi-lineage differentiation through a process of asymmetric mitosis that leads to two daughter cells, one identical to the stem cell (daughter stem cell) and one capable of differentiation into more mature cells (progenitor cells). Stem cells may be: totipotent, pluripotent, or multipotent. Depending on the development stage of the tissues from which the stem cells are isolated, stem cells can be broadly divided into two categories: Adult stem cells and embryonic stem cells.[5]

The routes by which cell reprogramming can be achieved include: nuclear transfer; induced pluripotent stem cells; lineage switching back to a branch point and out again in a different direction induced by tissue-specific genes; and direct conversion induced by cell-specific genes.[3]

Growth Factors

Growth factors are biologically active polypeptide hormones that affect immune function as well as differentiation of cells from the epithelium, bone, and connective tissue. These proteins are endogenously secreted in the cell bodies themselves (autocrine) or as a result of communication with surrounding cells (paracrine). In periodontal tissue engineering, of particular importance are PDGF, IGFs, FGF, TGF-beta, and BMPs, and those that regulate the epithelial–mesenchymal interactions involved in initial tooth formation (e.g., Embdogain, Biodenix Technologies, Richmond, Canada) have been used in preclinical and clinical trials for the treatment of large periodontal or intrabony defects and around dental implants. Proper periodontal healing is guided by stringent regulation of these agents as well as a local microenvironment that favors their activity. Two of these growth factors, PDGF and IGF-1, enhance regeneration in beagle dogs and monkeys with periodontal disease, especially when combined.[1]

Scaffolds

Scaffolds for tissue engineering must have: Microstructure to accommodate cells & functions; chemical composition to influence cell adhesion and phenotypic expression; must be absorbable; and provide temporary support to the growing tissues.[4]

Biomaterials used as scaffolds in tissue engineering are classified into two broad categories: Naturally derived and synthetic. Liao *et al*. in a study compared porous beta-tricalcium phosphate/chitosan composite scaffolds with pure chitosan scaffolds. Composite scaffolds showed higher proliferation rate of human periodontal ligament cells (HPLCs) and up-regulated the gene expression of bone sialoprotein and cementum attachment protein. *In vivo*, HPLCs in the composite scaffold not only proliferated, but also recruited vascular tissue ingrowth; thus, suggesting the benefit of using these composite scaffolds.[5],[6]

Potential applications of tissue engineering in periodontal regeneration

Bone grafts

Bone-graft materials are widely used in periodontal surgery. In comparison with open-flap debridement procedures carried out to treat intrabony defects, bone-replacement grafts generally increase the bone level and clinical attachment levels, and reduce probing depths. Bioceramics are suitable for grafting because of their good handling characteristics, biologic activity and availability in various sizes. The most commonly used ceramic alloplastic materials are hydroxyapatite and tricalcium phosphate. Hydroxyapatite and bone allografts provide similar improvements in clinical measures for the treatment of intrabony defects.[2]

In general, there are two types of bone grafts, autogenic and allogenic grafts. Allogenic and xenogenic grafts are widely available and do not require a second surgical site for the patient to harvest autogenous bone. However, allogenic bone must undergo processing techniques such as lyophilization, irradiation, or freeze-drying to remove all immunogenic proteins, to avoid any risk of immunological reactions. In turn, these processing techniques have a negative effect on the osteoinductive and osteoconductive potential of the allografts, which consequently decreases their biological performance as compared with autografts.[1]

Guided tissue regeneration

Guided tissue regeneration is a surgical procedure that specifically aims to predictably restore the tooths supporting periodontal tissues. A meta-analysis comparing guided tissue regeneration with open-flap debridement reported greater clinical attachment gain (of 1.22 mm) and greater probing depth reduction (of 1.21 mm) in guided tissue regeneration-treated sites.[2],[7] Traditionally, periodontal defects, if left empty after open flap debridement, fill with the first cells, that is, epithelial cells and fibroblasts, to reach the area after cell proliferation, which generates a core of fibro-epithelial tissues that ultimately prevent the subsequent orderly and sequential regeneration of true periodontal tissues. The GTR technique therefore employs a barrier membrane of variable porosity, to prevent epithelial down-growth and fibroblast trans-growth into the wound space, thereby also facilitating the maintenance of the space site for target periodontal tissue regeneration. Thus, it can be seen that the goal of the membranes is to retard the migration of oral epithelium into the space between the decontaminated root surface and adjacent alveolar bone, thereby avoiding the formation of a long junctional epithelial attachment. This is believed to afford time for selective repopulation of the root surface by undifferentiated stem cells from within the PDL space.[1]

Emdogain

The use of Emdogain has some advantages over other methods for regenerating periodontal tissues. Emdogain is used not only for periodontal flap surgery but also for tooth-transplantation. The effects of Emdogain are thought to be the induction of proliferation, migration, adhesion, mineralization and differentiation of cells in periodontal tissue. Emdogain also appears to control inflammation induced by immune cells.[2]

Platelet rich plasma

Since physiologic concentrations of growth factors may not be sufficient to stimulate local bone formation, the use of exogenous growth factors to supplement endogenous biological mediators has been explored. Platelet rich plasma (PRP) is a volume of autologous plasma that contains a platelet concentration above baseline values. The development of PRP from autologous blood by simple, sterile (office based and Food and Drug Administration (FDA) cleared devices) by gradient density centrifugation produces a concentration of platelets with enhanced growth factors including PDGF, TGF-β, and insulin growth factor-1. It has been reported that PRP preparations may increase the concentrations of platelets up to 338%.[5],[8] PRP works through transmembrane receptors and intra cytoplasmic signaling pathways, as do all other growth factor preparations.[5]

Conclusion

Though, a number of unknowns still remain to be answered, with the continued development of improved methods for gene delivery to cells, as well as advances in our knowledge of the molecular basis of periodontal homeostasis, it is reasonable to anticipate that a simple chairside protocol could be developed in the future.[9] Tissue engineering has enlarged our vision and thus made the fascination of being able to achieve regeneration of periodontal complex in its entirety a reality.[5]

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Source of Support: Nil

Conflict of Interest: None declared