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Tissue Engineering in Periodontal Regeneration: A Novel Approach

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Abstract

Periodontal disease is a leading community health matter and the evolution of successful remedy to nurse the disease and restore periodontal tissue is prime aim of present medical science. Regeneration of periodontal tissue is possibly one of the most complicated action to happen in the body. Langer and colleagues put forward tissue engineering as a potential method for regenerating the missing periodontal tissues. Tissue engineering is an integrative field, which associate the implementation of the concept and techniques of engineering and life sciences to assist in the evolution of biological substitute to reconstruct, support or boost the role of injured tissues and organs. The aim of practicing tissue engineering as restorative function has been to tackle its capacity to make use of selected and primed cells at the same time with suitable blend of regulatory factors, to permit production and specialization of cells and matrix. A Google/Medline search was done and relevant literature checking out the budding part of tissue engineering in periodontal regeneration, which comprise histological studies and controlled clinical trials were assessed. A broad search was prepared. The available literature was examined and assembled. The analysis specifies tissue engineering to be a favourable, as well as productive novel approach to restore and engineer the periodontal apparatus.

Keywords: Tissue engineering, periodontal regeneration, biological substitute

Introduction

Since ancient times, the term "regeneration" has annoyed many doctors and dentists because we still don't have any highly predictable methods of attaining it with reliable outcomes. The need for replacement materials to treat sick or damaged organs is growing as the average lifespan of humans continually increases. Clinical periodontics has traditionally had difficulty treating periodontal defects, which can include the deterioration of the periodontal ligament, cementum, and the development of intrabony defects.

The term "tissue engineering" was initially defined as the "application of the principles and methods of engineering and life sciences towards fundamental understanding of structure-function relationship in normal and pathological mammalian tissues and the development of biological substitutes for the repair or regeneration of tissue or organ function" at the first National Science Foundation (NSF)-sponsored meeting in 1988. As produced tissues are absorbed within the patient, it provides a potentially long-lasting and focused treatment of the medical state in contrast to conventional medications.

The creation of alveolar bone, a new connective attachment made up of collagen fibres positioned in a functional manner on the newly formed cementum, and complete recovery of the periodontal tissues in height and function are all examples of periodontal regeneration [1].

By manipulating cells through their extracellular milieu, tissue engineering uses the concepts of biology, chemistry, physics, and engineering to build replacements that replace, heal, or increase the biological function of sick and injured human body parts. Depending on the structural and functional requirements, this three-dimensional extracellular architecture ("scaffold") can be created in the shape of the tissue we want to restore using either polymer hydrogel, self-assembly, non-woven matrix, nano-fibrous electrospun matrices, 3D weaving, or any other textile technology-based techniques. Guided tissue regeneration, a mechanical technique that regenerates periodontal abnormalities using non-resorbable membranes, is where this idea in periodontics first emerged. Guiding bone regeneration membranes are used for bone augmentation in dental implantology, either with or without mechanical support [2]. Langer and colleagues suggested tissue engineering as a potential method for replacing missing periodontal tissues in 1993[3].

The multidisciplinary area of tissue engineering uses engineering and life science ideas and techniques to create

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biological replacements that repair, preserve, and enhance the function of injured tissues and organs [4].

Tissue engineering seeks to accelerate healing and, ultimately, real regeneration of a tissue's form and function, more reliably, more swiftly, with less invasiveness, and with higher-quality results than passive procedures previously available [2, 5].

Because the purpose of tissue engineering is to restore tissue function by the administration of stem cells, bioactive chemicals, or artificial tissue structures created in the lab, it is sometimes referred to as "regenerative dentistry"[6].

Periodontal Tissue Engineering

With the help of two commercially available systems that use bone morphogenic protein-type 1 collagen sponge and platelet-derived growth factor-BB tricalcium phosphate (GEM 21), tissue engineering once thought to be a distant dream and purely experimental in nature is now practicable in clinical settings (INFUSE). Trials are being conducted to establish a third potential method using basic fibroblast growth factor-2 [7].

Three essential components are included in the tissue engineering approach to bone and periodontal regeneration to speed up regeneration.

1. Progenitor cells
2. A scaffold or a matrix of support
3. Molecules that signal

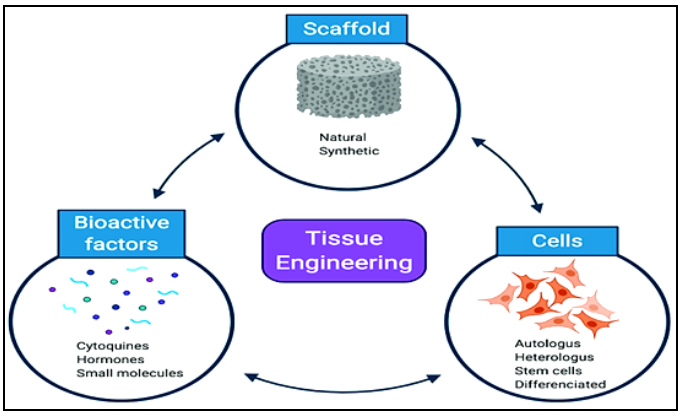

Fig 1: Tissue Engineering Triad

Cell Source for Progenitor Cells

Postnatal progenitor cells are an appealing possibility for use in tissue engineering applications due to their increased potential for regeneration over the past ten years. In instance, cell-based periodontal regeneration has been carried out employing diverse methods and tenets, and a number of superb reviews have lately been published [8].

Periodontal Ligament-Derived Cells

The multipotential properties of periodontal ligament-derived cells make them valuable sources for the regeneration of periodontal tissues, which include bone, cement, and periodontal ligament. In a periodontal fenestration defect model in dogs, Nakahara *et al*. implanted autologous dog periodontal ligament cells that were seeded onto a collagen sponge scaffold. This procedure resulted in the regeneration of alveolar bone and cementum in uniform layers on the root surface [8].

Periodontal ligament-derived mesenchyme stromal cells

Seo *et al*. isolated a population of multipotent stem cells from human periodontal ligament and found that these cells shared some traits with mesenchymal stromal cells, including multipotency, clonogenic capacity, high proliferation, and expression of the putative stem cell marker STRO-1 as well as the perivascular cell marker CD146 [9].

Periosteal Cells

The cultured periosteum expresses genes relevant to periodontal tissue and is capable of differentiating into an osteoblastic lineage. According to Yamamiya *et al*., platelet-rich plasma, hydroxyapatite, and cultured periosteum improved human infrabony defects clinically.[10]

Gingival Epithelium and Fibroblast

The development and therapeutic use of gingival epithelial sheets made from human gingival tissues as a therapy for persistent desquamative gingivitis. [11] A healthier epithelial connection and connective tissue resulted with the transplantation of gingival epithelial sheets, which also reduced inflammation. For patients with insufficiently connected gingiva, Mohammadi *et al*. administered autologous gingival fibroblasts and demonstrated an increase in the breadth of keratinized tissue.[12]

Bone Marrow-Derived Mesenchymal Stem Cells

Pittenger and colleagues (1999) demonstrated lineage-specific differentiation of MSCs into fat, cartilage, and bone under suitable *in vitro* culture conditions using bone marrow aspirates from more than 350 human donors. The human bone marrow-derived MSCs not only showed a high level of proliferative capacity, but also the ability to undergo directed differentiation into a variety of cell types, creating an intriguing cell source for possible tissue engineering [13]. Kawaguchi *et al*. showed that autotransplantation of mesenchymal stem cells from bone marrow caused periodontal regeneration in experimental canines with class III furcation abnormalities [14].

Scaffold or Supporting Matrices

Here is a list of the principal functions of supporting matrices [15]

1. It acts as a framework, preserving the defect's outline. In order to prevent the surrounding tissue from collapsing into the wound site, it offers physical support for the healing region.
2. It functions as a three-dimensional substratum for cellular adhesion, migration, proliferation, and extracellular matrix formation.
3. It acts as a barrier to selectively prevent cellular migration.
4. It could work as a means of delivering growth elements.

Biomaterials Used as Scaffolds

Ceramics

One of the earliest biomaterials to be utilised as a scaffold was HA (hydroxyapatite). It may be built entirely of synthetic materials, or it might be created from coralline or bone from cows. TCP, a naturally occurring calcium-and phosphorus-containing substance that is utilised as a ceramic bone replacement [16].

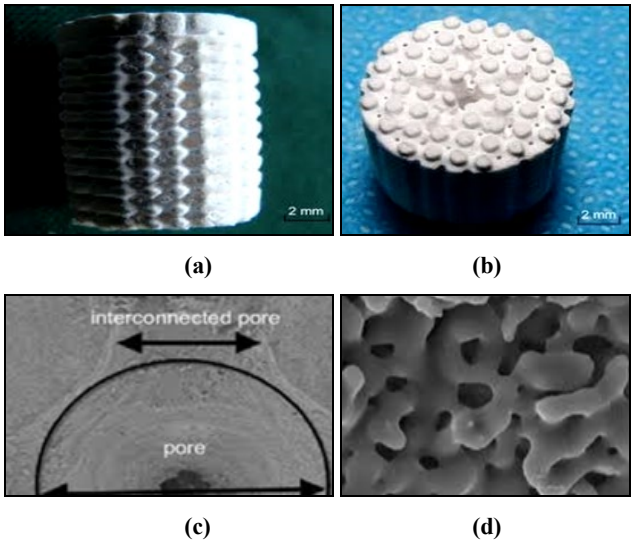

Fig 2: Ceramic Scaffold

Polymers
These include synthetic polyesters, such as polyglycolic acid, polylactic acid and polycaprolactone and natural polymers like collagen fibrin, albumin, hyaluronic acid.

Synthetic Polymer
PGA stands for glycolic acid polymer (polyglycolic acid). The first was the polymeric scaffold used in tissue engineering. In water, it won't dissolve. It is also used as a suture material and as an implant to treat bone fractures.
PLA is the name of the lactic acid polymer (polylactic acid). PLA is more hydrophobic and resistant to hydrolysis than PGA. PGA copolymers have been used to create biomaterials like as sutures and other products (vicryl).

Natural Polymer
Collagen Fiber
Commercial production of fibres with dimensions of 300 nm and higher has already taken place. They can be readily seeded with cells and twisted into wools using a scanning electron microscope image of the wool. The fibres are significantly more resistant to collagenase than foam or gel scaffolds when cross-linked using procedures that do not change the native 67 nm cross-banding.

Collagen Membrane Scaffolds
By letting collagen in solution dry on a surface that it won't adhere to, such as Teflon or polyethylene, collagen membranes can be created. The solution is neutralised and warmed to 37 °C to encourage the creation of fibrils, allowing the collagen to polymerize and create the fibrils. The solution is spread out on a suitable surface and allowed to dry before it starts to gel. Several techniques can be used to cross-link membranes in order to increase their wet strength. Aldehydic cross-linking, for instance, will hinder cell adhesion, while UV cross-linking will lessen collagenase resistance [3].

Signaling Molecules
The two primary strategies for using preparations containing biological mediators to boost the cells that fill the periodontal wound have been the subject of research. The first method made use of semi-purified preparations such autologous platelet-rich plasma and enamel matrix derivative. The second method made use of recombinant growth factors such bone morphogenic protein, recombinant platelet-derived growth factor-BB, and recombinant human basic fibroblast growth factor.

Platelet Rich Plasma preparation
Several growth factors, including platelet-derived growth factor, transforming growth factor beta-1, fibroblastic growth factor-2, epidermal growth factor, and vascular endothelial growth factor, are present in the enhanced platelets, which are 338% more abundant [17]. This combination of growth factors is thought to promote neovascularization, extracellular matrix production, and fibroblast and periodontal ligament cell proliferation. PRP is utilised to stabilise graft materials for implant site augmentation, even if it is inefficient for periodontal regeneration, and it seems to improve early soft tissue healing.[18]

Enamel Matrix Derivative
According to a new clinical case study, enamel matrix derivative (EMD) taken from growing porcine teeth can stimulate periodontal regeneration. It includes a variety of low molecular weight proteins that promote osteoblast development and mesenchymal cell proliferation [19]. Commercially accessible as Emdogain, enamel matrix proteins (EMPs) have been shown to have a positive impact on periodontal regeneration. Emdogain, Biora) purified stable, freeze-dried EMD for use in periodontal tissue regeneration.

Fig 3: Emdogain

Bone Morphogenetic Proteins (BMP)
Bone that has been demineralized with hydrochloric acid, lyophilized, and transplanted in ectopic places has the ability to stimulate bone production, according to research by Urist

and colleagues. The Bone Induction concept has been used to describe this occurrence [15].

The Bone Morphogenetic Family: Based on their presence in pure bone inductive extracts made from bone, the BMPs were identified. For appropriate protein purity, a lengthy purification (more than 300,000-fold) was necessary. This shows that osteoinductive proteins are less abundant than many other growth factors and are small components of bone matrix. Bone morphogenic protein-2 (OP-2), bone morphogenic protein-3 (osteogenin), and bone morphogenic protein-7 (OP-1) are three of the at least seven BMPs that have been identified from bovine and human sources and are of interest for periodontal regeneration [20].

Platelet Derived Growth Factor

PDGF, or platelet-derived growth factor, is the "hormone" of spontaneous wound healing. The body naturally produces it when soft tissue or a bone is injured. Lynch and his collaborators made the discovery in the late 1980's. [21]

Although platelet-secreted PDGF is crucial for the first stages of wound healing, macrophages also contribute to the continuation of wound healing by upregulating other growth factors and cells that eventually support fibroblastic and osteoblastic processes [22].

PDGF-BB was used by Moon *et al*. to encourage the migration and growth of fibroblasts in the periodontal ligament. They showed that PDGF can stimulate bone growth and periodontal regeneration *in vivo*, showing that it has potential to be a crucial adjuvant to periodontal surgery.[23]

Fig 4: Platelet derived growth factors

Insulin like Growth Factor

A powerful chemotactic agent for vascular endothelial cells, insulin like growth factor (IGF) promotes enhanced neovascularization. Many *in vitro* cells, including chondrocytes, osteocytes, and fibroblasts, are also stimulated to undergo mitosis by it [24]. By upregulating anti-apoptotic molecules and downregulating pro-apoptotic molecules, Han and Amar showed that *in vitro* IGF-I significantly improved cell survival in periodontal ligament fibroblasts compared to gingival fibroblasts [25].

Transforming Growth Factor Family

Transforming growth factor family (TGF) and TGF are the two polypeptides from this class of growth factors that have the best defined structures. TGF appears to be a key player in the regulation of cell division and replication. TGF1, TGF2, and TGF3 are the three different types of TGF that have been discovered. TGF isoforms play a variety of regulatory functions in the extracellular matrix's formation, upkeep, and turnover. For fibroblasts and cementoblasts, TGF is chemotactic, and it encourages fibroblast accumulation and fibrosis throughout the healing process. Other growth factors including PDGF, TGF, EGF, and fibroblast growth factor (FGF) can also be modulated by it, perhaps by modifying their cellular responses or by stimulating their production [26].

The mitogenic activity of TGF, interleukin-1, and PDGF in fibroblast cells generated from periodontal ligament was compared by Oates *et al* [27].

Fibroblast Growth Factor Family

Heparin-binding growth factor family members include fibroblast growth factors. The two types that have been most completely studied are basic FGF (bFGF) and acidic FGF (aFGF). Both aFGF and bFGF are single chain proteins that are produced by proteolysis from several precursor molecules to create 15,000 molecular weight physiologically active proteins. In the course of healing wounds, they encourage endothelial cell growth and PDL cell adhesion. Epithelial cells are reported to be more easily drawn to FGF-2 than FGF-1[28].

Hepatocyte Growth Factor

A protein called heparin sulphate glycosaminoglycan-binding hepatocyte growth factor (HGF) is secreted. Yamada *et al*. observed good cell proliferation and the release of vascular endothelial growth factor (VEGF) when fibroblasts were grown in a medium containing HGF. The findings imply that it could offer a fresh technique for treating gingival recession [29].

Tissue Engineering Applications in Periodontal Regeneration

1. **Enamel Matrix Derivative:** It has been demonstrated to be safe for usage in clinical settings and has proven successful in treating infrabony deformities. The question of whether commercial batches will always be reliable and deliver equivalent therapeutic outcomes is still a worry [19].
2. **Human Platelet-Derived Growth Factor Recombinant:** It can be purchased commercially together with a tricalcium phosphate carrier. According to preliminary investigations, it is simple to use, doesn't need barrier membranes, and produces outcomes that are on par with or better than those of other regenerating graft materials. [30]
3. **Human Fibroblast Growth Factor-2 Recombinant:** Significant periodontal tissue regeneration is brought about by the topical injection of fibroblast growth factor-2 into intraosseous lesions in alveolar bone [31].
4. **Application at Implant Site Preparation:** Regenerating enough hard and potentially soft tissue is the difficult part. For the preparation of implant sites, recombinant human bone morphogenic protein-2 and recombinant human platelet derived growth factor may be employed. According to animal research, the contact between regenerated bone and implants would be identical to that of natural bone [32].
5. **Gene Delivery-Based Approaches:** Many research on tissue regeneration have looked into different methods of gene transfer. With these methods, the cells are given a gene producing a therapeutic protein so they may express the target protein. By maintaining stable protein levels at

the location of the defect, this strategy avoids the issues with the protein delivery method [3].

Possible Challenges Ahead

1. Periodontium's structural and functional complexity Finding the ideal mix and dosages of growth factors is significantly more challenging since several tissues, including alveolar bone, periodontal ligament, root cementum, and gingiva, must be rebuilt [33].
2. Since cell culture medium frequently calls for xenogenic items (such as foetal bovine serum or mouse feeder layers), there is a danger of infectious disease because cell cultures may not be entirely pathogen-free [34].
3. The development of culture conditions prevents them from accurately simulating the *in vivo* cell microenvironment. The optimal matrix scaffold should resemble natural extracellular matrix, aid in cell adhesion, provide regulated release of bioactive substances, promote tissue development, and simplify laboratory handling [36].
4. Immune rejection that occurs following the introduction of stem cells into the host is a clinical problem in cell-based periodontal treatment. The use of autologous stem cells to combat immunological rejection offers a potential remedy for this issue [36].

Conclusion

We must seek beyond this place in order to realise the dream. Tissue engineering has expanded our range of view, enabling us to achieve the exciting objective of total regeneration of the periodontal complex. Although the task was challenging, the promise remained the same. Our ultimate goal must be achieved; therefore, we must leverage new scientific resources and insights, strengthen and expand our partnerships, make sure that research advancements are translated into useful technology, and, most importantly, make sure that our scientific endeavours are beneficial to people. Despite the grandiosity of recent findings, there are still more questions in the field of tissue engineering than there are answers. Not with standing these limitations, we are continually expanding our ability to provide regenerative therapies. It will be difficult to select the appropriate concentration of matrix, cells, and soluble regulators to design tissues *in vivo*. As a result, we must continue to understand more about the biochemical and physical factors required for specific tissue regeneration.

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