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Review Article

An application of decellularized membrane as guided tissue regeneration

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ABSTRACT

Decellularized Extracellular Matrix (DECM) has been established as a biomaterial that retains the natural properties of a tissue, promotes cell proliferation and cell differentiation. Periodontal regeneration requires the neovascularization niches and the proliferation and differentiation of the involved cells. DECM have various advantages and qualities in terms of stimulating periodontal tissue regeneration. Several methods for improving mechanical strength of the scaffolds have been identified like, crosslinking which is to enhance regenerative potential. This review focuses on the ability of DECM to repair damaged tissue in periodontal tissue engineering and addresses the future direction of periodontal regeneration in particular area.

1. Introduction

Periodontitis is defined as an inflammatory condition of the teeth's supporting structures brought by particular microorganisms leading to the continuous destruction of the periodontal tissues with the development of periodontal pockets, gingival recession and bone destruction.[1] The great majority of nations experience a serious public health issue with periodontal disease which affects around 20-50% of the global population.[2] The formation of microorganisms from dental plaque and inflammatory mediators of periodontal tissues correlates to other systemic conditions. High prevalence rate means, this disease affects human populations all around the world which makes it a serious public health issue. Periodontal disease has a variety of clinical presentations and the symptoms can be either acute or chronic.

Regenerative surgical techniques consist of different membranes with excellent treatment for periodontal health such as Guided Tissue Regeneration (GTR) membrane, Bone graft and root bio modifiers. GTR acts as a barrier membrane to temporarily separating gingival epithelium and connective tissue from root surface using GTR membrane, allows repopulation of area by cells from the periodontal ligament and bone during post surgical healing phase. Bone grafting results in actual regeneration involving new attachment onto the root surface or repair via a long junctional epithelium. A recent systematic review of the effectiveness of root surface conditioning concluded that "the use of citric acid, tetracycline or ethylenediaminetetraacetic acid (EDTA) to modify the root surface provides "NO" benefit to clinical significance of tissue regeneration in patients with chronic periodontitis. Two different strategies used to deal with surgical treatment are- a) The removal of the periodontal pocket through resection; this approach is based on the idea that the lesions

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are completely healed and the pocket serves as a reservoir for periodontal bacteria. b) The prospect of covering the periodontal pocket by periodontal tissue remodeling is achieved using grafting materials which provides an additional benefit.

Conventional periodontal therapy ends by healing with a long junctional epithelium, emergence of new connective tissue fibers, cementum, and the remodeling of alveolar bone. Although radicular resorption was seen when granulation tissue (originating in the connective gingiva or alveolar bone) when first reached the root surface along with re-epithelialization which had a beneficial effect in eliminating this phenomenon. Primary objectives of periodontal therapy is to eradicate the disease through infection control and to rectify anatomical flaws through regeneration from the tissues that support the teeth. This premise has led to the use of various bone grafts and other materials, categorized as autografts (obtained from the same patient), allografts (the same species but a different individual), xenografts (different species), and alloplastic grafts (synthetic material or foreign body graft) with the need for a bone replacement that is osteoconductive, osteoinductive, and osteogenic. Autologous bone grafts are still regarded the benchmark for bone defect restoration; however, a donor site morbidity and size limitations are key concerns. Furthermore, in some of the defects where bone growth was visible histologically, an epithelial layer was always present between the newly produced bone and surface of the root. These findings were later verified in other independent investigations, revealing that the bulk of periodontal regeneration procedure remains same in character and lacks biological science reinforcement.[3]

However, there is currently no agreement in the academic literature on whether root surface biomodification with ethylene diamine tetra acetic acid (EDTA) improves clinical outcomes of soft tissue root coverage.[4–6] Enamel matrix derivative (EMD) on the other hand accelerates migration, attachment, proliferation and differentiation of endothelial cells, periodontal ligament cells, cementoblasts and osteoblasts. It is commercially available in a gel formulation containing porcine-derived enamel matrix proteins, propylene glycol alginate (PGA) and water (Emdogain®). The goal of using root biomodifiers is to enhance the adhesion of periodontal regenerative structures of root. It was anticipated that by removing the smear layer and exposing the collagen fibers using EDTA would be able to stabilize the connection between the fibrin of the blood clot and the root surface.[7,8] In an *in vitro* investigation , EDTA alone or in combination with EMD increased fibroblast proliferation and density. EMD also increased ECM protein production and the quantity of transforming growth factor, which aided in tissue repair and regeneration.[9]

According to published studies, when compared to debridement treatment, bone graft results in bone deposition with 60% to 65% of flaw repairment. This is justified by their osteoconduction potential and chemical combination which allows them to stimulate the development of new bone which is already present in the defect walls which serves as a framework for the progress. This category includes xenografts, which are made from animal bone, usually bovine bone and are chemically treated to remove the organic component with retaining all of the alloplastic characteristics.

2. Guided Tissue Regeneration (GTR)

Periodontal regeneration can be achieved through combination of bone grafting which plays a significant role in reconstruction and recovery of intraosseous defects in patients. Simultaneously, it improves the aesthetics of patient's oral condition which mainly concentrates on restoring damaged periodontal structures by altering tissue responses that is frequently aided in regaining periodontal attachment. On the assumptions that they impede regeneration of connective tissue and gingiva which uses a barrier technique that uses both non-resorbable and bioresorbable membranes such as methylcellulose membranes (Millipore filters), expanded polytetrafluoroethylene (PTFEe), and Teflon-PTFE as first group. Many substances including collagen of both animal and human origin, lyophilized grafts, polyglactin 910, polyglycolic acid, polylactic acid, poly orthoester, polyurethane and polyhydroxybutirate have been initiated as bioresorbable membrane or second group.

2.1. Non-resorbable membrane

Expanded polytetrafluoroethylene (PTFEe) membranes undergone the greatest research and is the current standard for evaluating other periodontal regenerative methods. Periodontal regeneration in furcation defects is possible in specific clinical settings, as demonstrated by the selected literature, particularly in maxillary and mandibular Class II defects. This has also been demonstrated histologically in various reports. Class II invasions of maxillary molars and class III furcation however shows no variations from conventional debridement in the results, which strongly favors GTR when it comes to class I and class II furcation invasions. The non-resorbable Gore-Tex Periodontal Material (W.L. Gore & Assoc., Flagstaff, Arizona) made of ePTFE was the first commercially available GTR barrier (ePTFE). Non-resorbable barriers have the disadvantage of deducting subsequent surgical procedure. GUIDOR Bioresorbable Matrix Barrier@ was introduced in 1993 as the first US FDA approved resorbable GTR barrier. Furthermore, non-resorbable membranes require a second surgery to be removed, interfering with

patient,[10] also increasing the risk of exposing newly regenerated bone to bacteria and infection after exposure.

2.2. Bio resorbable membrane

Biodegradable membranes, which are almost entirely polymer-based (natural and synthetic polymers) have the advantages with few difficulties and low cost, as well as the elimination of the need for secondary procedures. Availability of collagen membrane was introduced to overcome the limits of non-resorbable membranes. Collagen is a naturally occurring and abundant protein found in the ECM that serves as an important component of physical and physiological structure in the body.[11] Collagen's chemotactic nature promotes fibroblast migration, proliferation and differentiation of specialized cells. Furthermore, collagen is vital in wound healing, including platelet activation and angiogenesis.[12] Clinical outcomes are enhanced in furcation defect repair but not in intrabony defect repair when employing bone replacement grafts and absorbable collagen membranes.

PLGA, a synthetic copolymer of poly lactic acid (PLA) and poly glycolic acid (PGA) has been used to make a variety of therapeutic materials such as tissue grafts, surgical sutures, bone tissue engineering scaffolds and drug carrier systems due to their high biocompatibility, controlled biodegradability, variable degradation rates, mechanical qualities, and thermal processability. Cross-linked type I collagen extracted from bovine Achilles tendons is used to make the BioMend TM absorbable collagen membrane (Colla Tec Co, Integer Life Sciences, Plainsboro, NJ). This barrier is able to break epithelial downgrowth despite lacking a specific integration design, most likely by the combination of host and barrier collagen fibers. Collagen resorbs by enzymatic (collagenase) breakdown, which is an inflammatory process, unlike polyesters. According to reports, the substance is minimally immunogenic and fully resorbed within five weeks.

Now, further artificial resorbable barriers have been developed: The occlusive film used in RESOLUTTM Regeneration Material by Gore & Ass is composed of polylactide-co-glycolide with an 85/15 weight ratio. Pure polyglycolide fibers are irregularly connected to the occlusive covering as to obtain integration with the flap tissue. It is attached to the tooth via resorbable sling suture and meant to dissolve entirely in six months, it may begin to disintegrate as soon as three to four weeks later. The Vicryl Periodontal MeshTM, Polyglactin 910; is a woven mesh that was initially created for non-periodontal and submerged barrier uses (Ethicon Inc., Sommerville, NJ). It doesn't have a specific design for integrating tissue with 90/10 copolymer of polyglycolide and polylactide, Vicryl sutures that will secure the barrier to the tooth.

3. Rationale for Decellularization of Extra Cellular Matrix (ECM)

Among the different forms of scaffolds, decellularized extracellular matrix (dECM) scaffolds, which are biomaterials created by human or animal organs/tissues after the removal of immunogenic cellular components by decellularized technologies, are receiving considerations.[13] Extracellular matrix (ECM) is a three-dimensional (3D) framework that contains extracellular macromolecules such as collagen, elastin, fibronectin, laminin, and matricellular proteins. Meanwhile, after decellularization, the physicochemical signals and biological molecules of dECM can be retained and provide a substrate and a biological 3D carrier for further cell proliferation.[14] Each and every factor influences the composition and frameworkof the ECM, as well as the host tissue response to the ECM scaffold after implantation. dECM scaffolds are categorized into three types according on their origins: autogenous dECM, allogeneic dECM, and xenogeneic dECM. The tissues from which the ECM is extracted, the species from which it is derived for the methods of decellularization as well as ultimate methods like sterilization for these scaffolds all these will influence biological morphology. Allogeneic/xenogeneic dECM may have donor site morbidity, architecture and mass composition variations and immunogenicity due to insufficient decellularization. Protocol's for decellularization is to eliminate all cellular and nuclear components material as efficiently as possible while minimizing any defective composition, biological activity, and mechanical integrity of the residual ECM are all affected.

On assumption, physical and chemical treatments can have significant effects on the composition, mechanical behavior, and host response to biologic scaffolds derived from decellularization of tissue and organs with significant implications for subsequent use in vitro and in vivo. The removal of adhesive proteins and Glycosaminoglycans (GAGs)may slow cell migration onto the scaffold as scaffold's bioactivity. Disruption of the collagen network can alter the mechanical behavior and collagen fiber of the scaffold, affecting its load bearing capacity and changing the mechanical environment to which the cells are exposed. Another important factor relating to the mechanical and degradation characteristics of the scaffold that may be affected by decellularization. Chemical treatments could weaken the ECM scaffold and increase its susceptibility to enzymatic breakdown in vivo, resulting in a fast decline in scaffold strength.

Any combination of methods is unlikely to remove 100% of all cell components derived from a tissue or organ. However, it appears clear that methods that

Table 1: Biomaterials in periodontal regenerative procedures

Biomaterials	Target tissue	Charac teristics	Refrences
Inorganic biomaterials Hydroxyapatite (HA)	Alveolar bone; cementum	The inorganic phase of bone has a similar chemical composition and structure. Osteoconductive the effect of direct bonding to natural bone slow deterioration	15–18
Tricalcium phosphate (TCP)	Alveolar bone; cementum	Bioabsorbable Osteoconductive TCP and TCP have a similar chemical composition to the inorganic phase of bone.	19–23
Biphasic calcium phosphate (BCP)	Alveolar bone	HA and TCP mixture in varied ratios to modify the rate of breakdown and biological activity the inorganic phase of bone has a similar chemical composition and structure.	24–26
Bioactive glass (BG)	Alveolar bone; cementum	The compositions of bioactive glasses differ. BG ion dissolution promotes angiogenesis, osteogenesis, and antibacterial activity. The rate of degradation varies across a wide range.	27–33
Natural polymers Collagen	PDL	The most plentiful protein in the alveolar bone, PDL, and cementum ECMs. Biocompatible Mechanical strength is low. Problems with safety include pathogen transmission and immune response.	34–36
Gelatin	PDL; alveolar bone; cementum	Collagen hydrolysis product has no bacterial infection and no immune response. Simple to modify for crosslinking by light and chemical.	37–40
Chitosan	Alveolar bone; PDL; cementum	Biocompatible and antibacterial property derived from chitin	41–44
Synthetic polymers Poly (lactic-co-glycolicacid) (PLGA)	Alveolar bone; PDL	Biocompatible Variable rate of degradation there is no cell recognition motif.	45–48
Polycaprolactone (PCL)	Alveolar bone; PDL	Biocompatible Slow rate of deterioration there is no cell recognition motif.	49–52
Composite biomaterials PLGA + CaP	Alveolar bone	It is made up of two layers (smooth outer layer and rough microporous inner layer). In dogs, it is intended to support the GTR membrane and promote alveolar bone regeneration.	53
Collagen + HA	Alveolar bone	BMSCs seeded into the scaffold to promote alveolar bone formation in a dog' periodontal defect were created by freeze-drying both collagen and HA.	54
Chitosan+β-TCP	Alveolar bone	HPDLC planted into the scaffold was freeze-fried to allow host cells and stimulate osteoblast development.	55
PLGA + Magnesium	Alveolar bone	Mg in PLGA increased composite material mechanical strength, buffered the acidic byproduct of PLGA degradation, and improved in vivo bone production and osteogenic ability.	56
Gelatin methacrylate + HA	Alveolar bone	Methacrylate was introduced as a photo-crosslinkable material. In naked mice, the composite induced hPDLSCs to develop into osteoblasts and promoted new bone formation.	37
Gelatin+β-TCP	Alveolar bone	In a homogenizer, gelatin and -TCP were combined and freeze dried. In animal periodontal defect, bone tissue regeneration and fibres parallel to the bone surfaces.	57
PCL+ β-TCP + CaP coating	PDL; Alveolar bone	As the PDL layer, a PCL electrospun scaffold was created. To boost osteogenic ability of the PCL—TCP scaffold, on the surfacena fine layer of CaP was applied. CaP coating increased bone formation.	58
PGA PCL	PDL; Alveolar bone	The PDL layer includes microchannels were created to aid in the formation of fibres. A porous structure was created to enable cell proliferation. There is no organised fibre insertion in the PDL and bone interface.	59
PCL + HA	Alveolar bone; PDL; cementum	3D layer scaffolding were used to function the periodontium. There was no organised fibre insertion in the PDL or bone interface.	60
Chitin + PLGA + BCG	Alveolar bone; cementum; PDL	PLGA was added to improve mechanical stability and increase degradation time. BCG increased bone and cementum layer osteogenic capacity.	61

remove the majority or all of the visible cellular material result in biologic scaffold materials that are suitable for implantation. Human dermis (Alloderms, LifeCell, Corp.), porcine SIS (SurgiSISs, Cook Biotech, Inc.; Restores, DePuyOrthopaedics, Inc.) porcine urinary bladder (ACell, Inc.) and porcine heart valves are among the naturally forming ECM scaffolds and part of decellularization protocols have been granted regulatory authorization to use in human patients (Syner grafts, CryoLife, Inc.). Because of the growing number of biologic scaffolds used in tissue engineering/regenerative medicine and the continuous development of decellularization protocols is a clinically significant and crucial.

4. Factors Influence Guided Tissue Regeneration Therapy

GTR approach is widely progressive in implantology when performing directed bone regeneration and also improve patient success.[62] GTR is based on three fundamental principles: stem cell production, scaffolding, and growth factors. The goal of periapical wound healing following surgery is to repair missing alveolar bone, cementum, and periodontal ligament. GTR strategies are exploited to ensure this happens and they have proven to be effective and beneficial with GTR being a highly effective treatment option for intrabony defects. There is no use of grafting materials additionally to the membrane barrier when it comes to the treatment of intrabony defects. As a result, additional bone graft use in GTR for the treatment of intrabony defects is frequently unnecessary. GTR was found to be anticipated for narrow intrabony defects and class II mandibular furcation defects in a quantitative analysis. GTR barrier membranes are classified into two types: non-absorbable and absorbable membrane. Tissue engineering is a strategy that employs stem/progenitor cells, scaffolds, and bioactive molecules to construct biomimetic systems that stimulate the development of new tissue. In general, they have a lower mechanical strength than non-absorbable membranes. Recent advancements in GTR barrier membrane development have focused on optimizing mechanical and degradation properties in addition to incorporating new functions into GTR membranes. GTR membranes for example, were created using composites that combined the benefits of various biomaterials. Combination of natural and synthetic polymers consolidate bioactive recognition and improves synthetic materials' mechanical properties. GTR membranes have also been delivered as drug delivery carriers to improve tissue regeneration.[63] Electrospinning has recently produced a novel functionally graded membrane for periodontal regeneration. This membrane consist of one core layer and two functional surface layers that are in contact with bone (nano-hydroxyapatite) and epithelial tissue (metronizadole). Furthermore, when using allografts or xenografts, there is always the risk of disease transmission even though its small, the membrane has not yet been tested in a clinical setting. Its properties encourages cell adhesion and proliferation by improving osteoconduction, neutralizing acidic degradation products, and combating periodontal pathogens, as described in other reports.

5. Conclusion

Periodontal diseases commonly affect soft and hard tissues of oral cavity, which is treatable and preventable. Reduced incidence and prevalence of periodontal disease can lead to a reduction in systemic disorders and consequences are related with it. Main intention of periodontal disease treatment can reduce disease progression and its impact on health-care systems. Because of the high frequency of periodontal disease, essential to establish a community-wide oral disease surveillance system. Periodontal disease prevention programmers should use popular risk-reduction strategies severity of other chronic diseases. Cost-effective strategies would also be beneficial to improve interprofessional collaboration among health-care providers. Since the GTR principle little has changed to improve periodontal regeneration. Although new barriers have been created to make the procedures easier, they appear to be biological limitations for regeneration, at least from a clinical standpoint.

6. Source of Funding

None.

7. Conflict of Interest

None.

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