TYPES OF BARRIER-MEMBRANE IN PERIODONTAL THERAPY OF GUIDED TISSUE REGENERATION

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Abstract
The present resorbable and non-absorbable membranes act as a physical barrier to prevent the fall of the connective and epithelial tissue in defect, favouring the regeneration of periodontal tissues. These conventional membranes have many structural, mechanical and biofunctional limitations. It is clear that the “ideal” membrane for use in periodontal regenerative therapy has not yet been developed. Based on a biomaterial-based approach, it was assumed that a biologically designed and functionally sized nanofibre material closely mimicking native ECM could succeed as the next generation of GTR / GBR membranes for periodontal tissue engineering.

Keywords: guided tissue regeneration, barrier-membrane, periodontal surgery

The strategy of isolating a periodontal defect with a material (resorbable or non-resorbable) which will function as a physical barrier to prevent gingival cell invasion led to the creation of GTR / GBR membranes [1]. These membranes must have: (1) biocompatibility to allow integration with host tissues without giving inflammatory responses, (2) adequate resorption profile to match the new tissue formation, (3) appropriate mechanical and physical properties to allow for in vivo placement and sufficient resistance to be able to help prevent membrane collapse and to fulfil the barrier function [2].

The RTG / ROG membranes are divided into two groups, non-resorbable and resorbable, depending on their degradation characteristics.

Stability / degradation characteristics of GTR / GBR membranes
The so-called non-resorbable membranes (Table 1) for the RTG / ROG procedures currently on the market are (1) high-density polytetrafluoroethylene, PTFE (for example, Cytoplast® TXT-200, Osteogenics Biomedical, Lubbock, TX, US) and (2) high density polytetrafluoroethylene reinforced with titanium (for example, Cytoplast® Ti-250, Osteogenics Biomedical, Lubbock, TX, USA).

PTFE membranes are inert and biocompatible, act as a cellular barrier, provide space for tissue regeneration and allow tissue integration. It has been suggested that there is a favourable correlation between the level of bone regeneration and the protection of space [3]. Studies have shown that titanium reinforcement of high density PTFE membranes results in a higher regenerative capacity compared to traditional extended PTFE membranes, mainly due to the additional mechanical support provided by the titanium frame to the compression forces exerted by the superimposed soft tissue. One of the disadvantages of non-resorbable membranes is the need for additional surgery to remove them, which
involves not only additional pain and discomfort, but also an economic burden.

To eliminate the second surgical procedure, resorbable barrier membranes have been developed [4]. Processing techniques based on either melting (ie, polymer heated above melting temperature or melting temperature of glass) or solvent casting were used to manufacture polymer based membranes for GTR / GBR applications. Solvent formation / particle leaching and phase inversion [5] are common methods of fabricating porous, three-dimensional, and / or membranous schemes for tissue engineering. In the solvent / particulate-lyophilization molding method, a porogen which can be leached, usually an inorganic salt (for example, sodium chloride or organic sugars) of the desired particle size, is combined with a polymer solution in a matrix. After evaporation of the solvent, the salt or sugar crystals are dissolved in water, which leaves a porous polymeric structure [6]. In this technique, the pore size and the porosity level of the membrane / scaffold can be adjusted by adjusting the particle size and salt or sugar / polymer ratio respectively. Unfortunately, the organic solvents commonly used in this technique can adversely affect the response of cells and tissue after implantation.

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<th>Table 1. List of available membranes</th>
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<td>Resorption degree</td>
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Most synthetic polymer resorbable membranes for periodontal regeneration on the market are based on either polyesters (for example, poly (glycolic) acid (PGA), poly (lactic acid) (PLA), poly (caprolactone) and their copolymers or collagen derived from tissue [7]. Polyester-based membranes (Table 1) are biocompatible, biodegradable, and clinically manageable compared to PTFE membranes and allow tissue integration. Their resorption rate is important because these membranes must function for at least 4-6 weeks to allow successful regeneration of the periodontal system. In general, biodegradation of these polyesters involves the non-enzymatic cleavage of PGA and PLA into the bypassed acids and, respectively, lactic acids, which are common end products of digestion. carbohydrates.
Milella et al. [8] evaluated the morphological and mechanical characteristics of polyester based membranes available on the market (for example, Resolut® LT and Biofix®). Although the membranes initially showed high resistance (~ 12-14 MPa), they completely lost their structural and mechanical properties within 4 weeks of incubation in culture medium. The maximum resistance after 14 days of exposure decreased significantly (below 1 MPa). In a study by Li et al. [9], performed on nano-hydroxyapatite / polyamide-66 -processed membranes with a porosity gradient, it was suggested that the addition of n-HAp guarantees a membrane with good tensile strength (2-3 MPa). In addition, the reported cellular response limits their use in GTR / GBR applications.

Collagen is a major component of the natural extracellular matrix (ECM). Collagen-based membranes derived from tissues of human skin (AlloDerm®, LifeCell, Branchburg, NJ, USA), bovine tendon (Cytoplast® RTM Collagen, City, State, USA) or porcine skin (Bio-, Osteohealth, Shirley, NY, USA) are important alternatives for synthetic polymers in GTR / GBR procedures due to their excellent cell affinity and biocompatibility [10]. However, type I collagen may have limitations in its use, due to the high cost and poor definition of its commercial sources, which makes it difficult to control the degradation and mechanical properties.

AlloDerm® is a lyophilized acellular dermal matrix graft (Figure 1) composed mainly of type I collagen derived from human cadaveric skin. According to its manufacturer, this process itself does not cause the destruction of the biochemical structural cues necessary to maintain tissue regenerative properties and leaves behind an extracellular collagen matrix that provides the basis for tissue structure and guides cellular functions [11].

The biomechanical properties and stability of the collagen matrix can be improved by physical / chemical cross-linking, ultraviolet (UV), genipine (Gp), glutaraldehyde, 1-ethyl-3-(3dimethylaminopropyl) carbodimide (EDC) hydrochloride. Exogenous cross-linking agents, such as Gp, have been reported to not only significantly enhance the stability of collagen-based tissues, but also reduce its antigenicity. The formation of additional inter- or intramolecular crosslinks in collagen fibres enhances the
mechanical properties of biological tissues [12]. Bottino et al. [7] investigated the addition of a natural cross-linking agent, genipin (Gp), to the AlloDerm® rehydration protocol, demonstrating that it affects the mechanical properties and stability of the collagen matrix. A significant increase in tensile strength compared to control was observed when the Gp exposure time increased from 30 min to 6 hours. Calorimetric analyses of differential scanning revealed a considerable change in the temperature of denaturation of the cross-linked samples, which coincides with the increase of the enthalpy of denaturation. This finding is in agreement with previous investigations into the use of a crosslinking agent to enhance the stabilization of collagen matrices derived from different biological tissues [12].

The critical disadvantages of both PTFE-based resorbable membranes and of resorbable membranes, mainly those based on collagen (for example, insufficient mechanical properties, unpredictable degradation profiles), have led to the study of alternative membrane materials. Several research groups have investigated the possibility of using membranes with a functionally classified structure to maintain sufficient mechanical properties during operation, predictable degradation rate and bioactive properties [13]. Bone formation would be stimulated by calcium phosphate nanoparticles or growth factors (eg, BMP-2, TGF-β, among others), and bacterial colonization would be inhibited by antibacterial drugs delivered to the interface soft tissue / membrane [13].

Membranes designed for area-dependent bioactivity
Numerous research groups have tried to design and develop periodontal GTR / GBR membranes with the characteristics and properties required by combining natural and synthetic polymers. These studies prepared the membranes using film casting, dynamic filtration and synthetic e-spinning (eg PCL) and collagen, chitosan [9]. The membranes were prepared with or without therapeutic drugs, growth factors and / or calcium phosphate particles [14]. A material with adequate mechanical, degradation and biological properties is still required to guarantee its in vivo performance for GTR / GBR.

Most of these methods result in membranes with very low clinical potential due to their high density (ie, handling difficulties) and heterogeneity (ie non-uniform degradation rate). The e-spinning technique has shown great membrane processing potential for periodontal regeneration [13]. E-spinning is a very promising technique for the synthesis of biomimetic nano-matrices, including membranes for GTR / GBR applications.

Perspectives in the field of membrane biomaterials
While several of the above strategies can be used to successfully develop polymeric biomaterials for periodontal tissue regeneration, especially those based on a stepwise approach, hydrogels also offer high versatility in design and synthesis [15]. Since many hydrogel systems have already been examined for tissue engineering purposes, the necessary technology is available and can be used and adapted to periodontal tissue engineering needs. The synergistic combination of hydrogel properties for specific periodontal problems is particularly advantageous in these applications. Such hydrogel systems could be designed taking into account the specific target values for the selected physical, chemical and biological properties. For example, the physical-chemical and mechanical properties can be adapted either by interconnection or by combination with other scaffolding materials to control degradation behaviour,
sustained drug release and protein/cell adhesion. In addition, since the hydrogels are conductive enough to migrate cells throughout most of the scaffold, biological properties such as bioactivity can be regulated and biomolecules (e.g., growth factors) can be added to guide, enhance or prevent cell adhesion and growth [16].

Many researchers have explored ways to control and improve the mechanical properties of hydrogels but the control of mechanical strength during initial degradation is unclear. The rate of degradation will influence the mechanical properties, as well as the mechanisms of surface or body degradation. The possibilities of improving the mechanical strength of the hydrogels lie in the generation of interpenetrated (IPN) or nanocomposite hydrogel networks [17]. Such elastomeric hydrogels have superior mechanical properties compared to their polymeric controls. Often, a combination of different crosslinking mechanisms allows the generation of mechanical strength, resistance and self-healing characteristics, all of which are suitable parameters for use as a periodontal regeneration membrane.

Making these degradable hydrogels should allow target values in terms of mechanical strength (for example 5-8 MPa) and the rate of degradation (for example, 4-6 weeks) [18]. Control of swelling or shrinkage of hydrogel networks in changing physiological conditions is essential for maintaining mechanical properties over time. This problem can usually be minimized by adapting the synthetic procedures or by formulating hydrogels with biomolecules, salt or nanoparticles [17].

Maintaining biocompatibility during degradation is most important for designing functional hydrogel networks. The hydrogels, as well as their degradation products, must be biocompatible and, as mentioned earlier, the degradation profile must be adjusted to engage in tissue engineering of the periodontium.

However, because in vitro and in vivo degradation cannot always be compared, flexibility is required in regulating degradation times, if deemed necessary. Hydrogel systems that provide such flexibility in regulating degradation properties usually consist of polymer networks that incorporate hydrolyzed or enzymatically degradable crosslinkers or degradable units within the polymer column.

The biological properties of hydrogels can be most efficiently regulated if the bioactive modification is performed on hollow gel or bio-inert matrices such as polyethylene glycol or in a biopolymeric hydrogel when the biomolecules are incorporated in the hydrogel or covalently attached to the polymer column [15]. Within a hydrogel, biomolecules, such as growth factors, can be soluble or immobilized by physical interactions that provide the ability to control cell migration.

Taken together, the current technology and results from the literature suggest that both e-spun nanomaterial and biologically active hydrogel combinations, functionally classified, have significant potential for use in periodontal tissue engineering.

Future directions include, of course, the rational design of hydrogels that require not only the control of degradation and mechanical properties, but also the consideration of biological variables. Although in vitro results with e-spun scaffolds show promise for creating a biologically active synthetic membrane, there is a significant limitation associated with these scaffolds. Due to the dense packing of e-spun nanofibres during the spinning process, the resulting matrix has pore sizes that are usually small to allow cell infiltration into the body [19] and limits tissue growth and vascularization in vivo. Although techniques such as the salt
leaching method and the selective removal of soluble fibres [20] could improve cell infiltration into the fibrous matrix, endanger structural and mechanical integrity, or result in macroscopic delamination of the layer. To maximize periodontal regeneration, the implant must support bone cell infiltration from the bone defect. In addition, vascularization of biomaterial / cellular construction is an essential step in tissue healing, as this process ensures the survival of the nutrients and oxygen needed by bone cells, while facilitating the removal of cellular waste products.

Therefore, in order to accelerate the application of periodontal regeneration therapies, the next step should be to perform in vivo pre-clinical implantation tests to evaluate the behaviour of barrier membranes in animal models, to determine their biomechanical integrity and biodegradation, healing, properties vascular as well as regeneration and remodelling.

References