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Periodontal Tissue Regeneration: Fact or Fiction?

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Introduction

Periodontal diseases are one of the most primeval and frequent diseases that have plagued mankind. In its varied forms, periodontal disease has been enmeshed with the damage or loss of investing tissues of the teeth. Over time, the treatment strategies to tackle such long standing diseases have evolved as our understanding of the disease process has enhanced. Blossoming from the earlier concept of arresting tissue loss, the current norm of treatment is aimed at reclaiming the lost periodontal tissues. Regeneration of the lost periodontium to its former robust state is now the ultimate goal of periodontal therapy [1].

The History of the Past

Although, regeneration is the basis of any major treatment being carried out these days, it is not a new concept and was conceived in the 1980s [2]. After the emergence of this concept, various materials came into the picture that claimed to achieve the ultimate goal of periodontal regeneration. These materials were marketed in the form of both synthetic and semi- synthetic bone substitutes and barrier membranes which were used in the treatment of intra-bony defects [3,4]. Despite their imposing claims, these materials failed to accomplish what was being recognized as 'true regeneration'. The literature became replete with evidence that although these materials were showing attachment gain and 'apparent bone fill' mostly in 2D radiography, they failed to deliver authentic bone gain which was being analyzed by performing surgical re-entry [5,6]. Reynolds et al in a systematic review on the efficacy of bone replacement grafts in the treatment of periodontal osseous defects reported that most of the bone replacement grafts supported periodontal repair rather than regeneration [7]. Regeneration of periodontal tissues is highly technique sensitive and therefore a clinically demanding procedure. Not with standing evidence that some regeneration occurs after regenerative therapy, complete regeneration may be an unlikely event in many situations. The outcome of therapy has been varied and at present unpredictable, depending on numerous parameters some of which were outlined in the consensus report of the AAP Regeneration Workshop [8]. Defect morphology and location have a major contribution in any regeneration that occurs post therapy- deep one or two walled intra-bony defects and Grade III or IV furcation involvements show poorer results in terms of bone gain and also attachment gain [9]. Cortellini, et al. [10] evaluated the osseous healing response of 1-, 2-, and 3-wall combination infrabony defects treated with guided tissue regeneration. They observed that the 3- and 2-wall components were filled 95±6.2% and 82±18.7% of their original depth, respectively; however, the 1-wall component was filled only 39±62.4% [10]. Degree of membrane exposure and its subsequent microbial contamination also affect the outcome of therapy [11]. Ling, et al. [12] evaluated the influence of membrane exposure on guided tissue regeneration in patients with 2-wall or 3-wall intraosseous defects. Their results showed that membrane exposure sites tended to achieve a smaller clinical attachment gain and had significantly greater marginal tissue recession [12]. Recent literature has pointed that the surgical technique being employed during treatment plays a significant role in the extent of regeneration being attained post therapy [13,14]. Cortellini & Tonetti [15] compared the clinical and radiographic efficacy of the modified minimally invasive surgical technique in the treatment of intra-bony defects and concluded that with or without regenerative materials this technique resulted in significant clinical and radiographic improvements [15]. The importance of space provision and maintenance for regeneration, has been relentlessly asserted by countless authors ever since

the genesis of the concept [16,17]. Haney, et al. [18] reported a significant correlation between the space provided by the membrane and the newly formed bone [18]. Collapse of the barrier membrane over the defect and delayed degradation of bone substitutes in time for new bone formation, both pose an earnest problem in space maintenance and thus negatively influence the outcome of therapy.

The Gift of the Present

The culmination of these facts drew attention to the need of a better treatment option that was designed to deliver what it promised- the elusive goal of true periodontal regeneration. With this concept in mind, a conscious decision was made to adapt the knowledge of molecular biology as the foundation of potential regenerative periodontal treatment. Efforts were made to recapitulate the critical events that take place during wound healing and then to mimic these events to achieve the desired results. This approach was labelled as "Endogenous Regenerative Therapy" and thus, the era of biologically active molecules was ushered into the timeline of regenerative Periodontology [19]. The discovery of enamel matrix proteins was an important milestone in the field of periodontal regeneration. These proteins played important roles in the regeneration of periodontal ligament and cementum when they were being used as local adjuncts in periodontal surgery. Numerous clinical and histologic studies have proved that when enamel matrix derivative was used in the treatment of periodontal defects, regeneration did take place [20,21]. Sculean A, et al. [22] clinically and histologically evaluated healing of human intrabony defects following treatment with a combination of enamel matrix derivative and bioactive glass (BG) or BG alone. They reported that Healing in defects treated with EMD + BG was mainly characterized by new cementum with inserting collagen fibers and new periodontal ligament while treatment with BG alone resulted in epithelial down-growth and connective tissue encapsulation of the graft [22]. Some authors are now reporting that amelogenins also interact with osteoblasts and fibroblasts, thus suggesting their explicit role in the re-growth of periodontal tissues [23].

The study of molecular mechanisms of the events of periodontal growth advocated imperative roles played by growth factors. Therefore, by logical deduction it was hypothesized that these growth factors may also promote periodontal regeneration. Numerous growth factors including platelet derived growth factor, BMPs, TGF- β, insulin like growth factor, vascular endothelial growth factor and fibroblast like growth factor have been used in animal and periodontal defect models and screened for favorable regenerative results [24-27]. Despite a large body of evidence the application of these materials into everyday periodontal practice is still an abstract goal due many critical factors that impede their transformation into customary commonplace materials. These factors not only include our restricted understanding of the application of these materials to their exact target cells, but also encompass the lack of ideal carriers for these materials and high costs that are associated with their production [28]. Platelet rich plasma and platelet rich fibrin are autologous blood preparations that are enriched with these growth factors and have been extensively used in the treatment of periodontal defects. Both negative and positive outcomes of therapy have been reported with the use of platelet rich preparations. Döri F, et al. [29] clinically compare the healing of intrabony defects treated with either a combination of an organic bovine bone mineral (ABBM) and PRP to those obtained with ABBM alone. They did not use a barrier membrane to cover the defects to prevent masking of the clinical outcomes due to the barrier. They reported that at the end of one year, the use of PRP failed to improve the results obtained with ABBM alone [29]. These findings were challenged by those reported by Lekovic, et al. [30] who examines the suitability of autologous PRF as regenerative treatment for periodontal intrabony defects in humans. The results of their study indicated that PRF can improve clinical parameters by reducing pocket depth, improving clinical attachment levels and promoting defect fill [30].

The Mystery of Future

With transcending times, regenerative therapies are transforming from their earlier rustic avatars to newer and better techniques that hinge on the capitalization of the heightened de-novo tissue formation produced by stem cell therapy. These therapies are aimed at nurturing three dimensional tissue configurations that can be considered as clinically acceptable regenerated tissues. To this end, researchers are utilizing numerous strategies that range from the direct delivery of encapsulated stem cells at the site to trying to recruit the body's own cells to produce regeneration [31]. A systematic review has shown that when applied in actual bone defects, DPSCs were capable of regenerating bone in experimental animals [32]. However, these methods are facing their own set of complications which are to date, preventing their application in conventional clinical frameworks. Complications include the presence of endogenous retroviruses in xenogenic cells and paucity of harvested autogenous stem cells [33]. Extracellular matrix extracts or derivatives have been developed as commercial products for cell delivery. But, these materials

incorporate animal-derived products and/or allogenic tissues and thus constitute a potential source of pathogens [34]. A culmination of preceding endeavors led to the emergence of the cell seeded scaffold paradigm. This strategy involves the isolation of pertinent cell lineages derived from the patient, their in-vitro expansion, followed by their seeding into a specifically designed three dimensional scaffold which is then saturated with appropriate signaling molecules, and subsequently implanted at the defect site [31]. Various natural and synthetic materials are being utilized for the designing of these scaffolds-collagen, fibrinogen, fibronectin, beta-tricalcium phosphate and synthetic hydrogels amongst others. Periodontal defects in non-human primates were implanted with recombinant human transforming growth factor-beta 3 in Matrigel delivery system. Morphometric analyses after 60 days showed pronounced periodontal regeneration in experimental defects [35]. Very limited information is available on the morphological and structural characteristics of adult mesenchymal cells, and even less information is available on their differentiated cell lineages, such as osteogenic cells. Therefore, although tissue engineering comprises a highly attractive treatment prospect, cell-based therapy is still limited to clinical trials and is not performed in a routine clinical setting.

Conclusion

In this eon of evidence based dentistry, our literature stands in front of us like a mirror, reflecting a scenario of regenerative periodontology that is yet to achieve the stability that has been associated with conventional treatment modalities. Although, the concept of tissue engineering bestows an appealing approach to periodontal regeneration by utilizing cells and bioactive agents for therapeutics, it is still in its infancy. Considerable work is being carried out to overcome the practical shortcomings of these procedures and to assist the theoretic fundamentals of periodontal regeneration in reaching its full potential in clinical situations. The vision for our future will unquestionably be centered on a deeper understanding of the molecular biology of regenerative processes. However, the conversion of desired predictable clinical outcomes from fiction to fact still remains the elusive goal of regenerative therapy.

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