Research Advances and Clinical Practice in Periodontics: Bridging the Gap
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Chapter 9

Clinical Applications of Current Research in Periodontal Wound Healing & Regeneration

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Introduction

Clinical concepts in periodontal regeneration are constantly undergoing evaluation and evolution, however, the quest to repair periodontal tissues destroyed by inflammation to their original anatomic and functional form is not new. The literature documents the use of several cellular and non-cellular graft materials from natural and synthetic sources in an attempt to regenerate periodontal tissue (AAP Consensus report). Much of the earlier clinical work focused on the regeneration of bone, but eventually evidence of the participation of several tissue types in the healing periodontal wound provided an enhanced understanding of the underlying mechanisms (Aukhil 2000). This led to the guided cell repopulation theory that formed the basis for clinical techniques such as guided tissue regeneration (Melcher 1976, Murphy and Gunsolley 2003). With the advent of oral implantology, attempts were made to clinically extrapolate some of these techniques to the regeneration of bone around implants with an osseous deficit. Recent research has however dramatically affected our previous understanding of wound healing and this has led to the development of tissue engineering techniques that seek to harness biological principles of wound healing to enhance the results of periodontal regeneration (AAP Position Paper 1996). The use of various growth factor isolates, or autologous plasma concentrates, are examples of such efforts. Nevertheless, questions remain about current techniques and the continual quest to make periodontal regeneration economical and predictable. Distinctions must also be made between the kind of regeneration that is sought around teeth and implants as the composition of the tissues in either case is different. While certain principles may be biologically applicable in both situations, there is nevertheless a clinical difference.

Mechanisms of wound healing

Our current understanding of the mechanisms that underlie ideal periodontal or peri-implant wound healing can be best described by the Venn diagram in Figure 1. At least four principle factors typically play a key role, with the availability of a cellular source probably being the most important factor. The periodontal wound is characterized by various tissue types, that are in turn represented by their cellular precursors or by undifferentiated cells that could potentially differentiate into precursor cell lines (Wang and MacNeil 1998). The availability of the right cells in the healing wound is therefore primary to regenerative

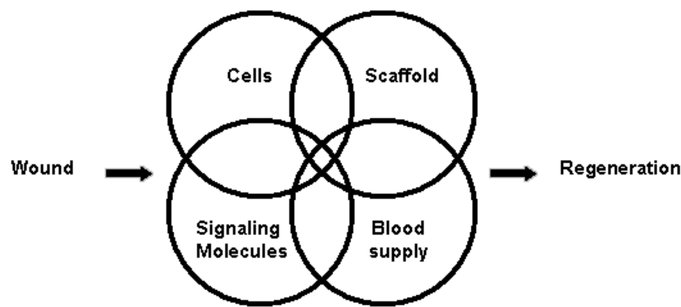

Figure 1. Venn diagram of the scheme of regeneration

success. The differentiation sequence is in turn wrought by a second and equally important factor; signaling molecules (AAP Position Paper 1996). These may represent a wide variety of biochemical constituents of the healing wound that work concomitantly to regulate the complex physiology of the regenerative process (Ripamonti and Reddi 1997). The ability of this system to bring about complete regeneration of the periodontal wound is sometimes limited by the extent of tissue deficit, and the need for a third factor in the form of a scaffold or matrix in such situations seems inevitable. A scaffold provides a mechanical matrix that offers physical support to regenerating tissue (Spector 1994). Scaffold chemistry could also potentially contribute to enhanced wound healing. A final fourth factor that plays a key role is vasculature, which provides angiogenic elements to the regenerating wound and provides a transport mechanism for participating biochemical constituents (Polson and Proye 1983, Wikesjö *et al* 1992). The presence or absence of periodontopathic bacteria also affects wound healing, often detrimentally (Selvig *et al* 1992). Undeniably, the elimination of infection is therefore key to achieving ideal regenerative results, even in the presence of all contributory factors.

Graft materials

The use of various graft materials as a part of regenerative periodontal therapy has become commonplace. These materials vary widely from autologous bone to human cadaver sourced allografts to animal sourced xenografts. The use of synthetic alloplasts is also very common (Reynolds *et al* 2003).

The first documented use of an autograft in periodontal therapy was by Hegedus in 1923 and their use in regenerative therapy in both periodontics and implantology is still apparently mandated.

The limited availability of autografts initially led to much interest in allografts and xenografts and their use was based largely on the fact that they were naturally derived and chemically identical. Cadaver sourced allografts have also been subjected to biochemical processes such as decalcification and freeze drying in order to enhance their osteoinductive potential, ostensibly by the exposure of bone morphogenic proteins (Urist 1965, AAP Position Paper, Pearson *et al* 1981). Several years of use have however brought into question the potential of these materials to consistently induce cellular differentiation of osteoprecursor cell lines. Variations in biologic activity as a result of differing processing

protocols have also been demonstrated and renewed standards for potency evaluation, a defined age/systemic status for cadaver donors and the development of assays for inductive capacity have all been suggested (Schwartz *et al* 1998, Schwartz *et al* 1996). Xenografts on the other hand are of questionable consistency in replicating the physical structure of human bone in order to act as a suitable scaffold, as most of these materials are classified as 'osteoconductive', in apparent recognition of their inability to actually induce new bone formation. The age and the systemic status of the source animal, as well as the actual osseous location from which the graft is harvested, are factors that affect the consistency of the physical structure of a xenograft. Allografts and xenografts have also frequently presented concerns about cross-infections and immunogenicity by virtue of a natural source (Sogal and Tofe 1999). Therefore, as a gold standard for grafts, cellular autografts seem to hold the most potential for use.

Signaling molecules

Several attempts have also been made to isolate various biochemical constituents of the wound healing process, with a view to providing them in the immediate environment and thereby presumably accelerate the rate of healing (Giannobile and Somerman 2003). Comprising largely of proteins that are derived from various cells (principally platelets and macrophages), these constituents function concomitantly and often upregulate individual function of respective constituents that are present in the environment (Sculean *et al* 2002, AAP Position Paper 1996). Their isolation and use in clinical therapy may therefore have limited application. Nevertheless, studies suggest that these attempts may be a step in the right direction with the documented clinical success of use of autologous plasma concentrates that provide higher concentrations of platelets and related growth factors (Camargo *et al* 2002). The ability to incorporate these techniques into a chairside procedure and the potential for use of autologous concentrates with graft materials is also appealing from the standpoint of ease of use. It must be emphasized however, that these molecules have a role to play only in the presence of cellular graft materials.

Initial studies with recombinant human proteins and matrix proteins are also encouraging, but there is very limited evidence from human clinical trials with these materials (Kinoshita *et al* 1997, King *et al* 1998). Similarly, the use of a new putative collagen binding peptide utilizing a combination of a bovine hydroxyapatite matrix and a synthetic clone of the 15 amino acid sequence of Type I Collagen, also has limited evidence (Yukna *et al* 1998, Qian and Bhatnagar 1996, Bhatnagar *et al* 1999).

Scaffold matrix and blood supply

The use of non-cellular grafts materials is primarily an attempt to provide a physical scaffold matrix for the regenerating wound. The physical importance of such a matrix comes into play in situations where the volume of osseous deficit extends beyond the regenerative capacity of surrounding or augmented tissue (Meffert *et al* 1985). In such situations the topography of the osseous defect, number of peripheral osseous walls and the proximity of normal bone, all play a role. The physical and chemical nature of the scaffold is nevertheless contributory and it is important to ascertain that this does not become a deterrent to the regenerative process (Le Geros 1990). The physical nature of the scaffold must provide for ideal inter- and intra-particular porosity to allow angiogenesis and osteoconduction of the regenerating fibroangiomatous elements of the wound (Kenney *et al* 1996). The nature of such

porosity should be interconnected and continuous in order to allow proper tissue ingrowth (Carranza *et al* 1987). In addition, the porosity of the scaffold has important implications for the rate of resorption of the graft material, thus allowing its replacement by natural bone (Surathu 1994). Given the same chemistry, a graft particle that is dense would resorb far more slowly than one that is porous, a phenomenon that is explained by increased vascular and cellular access to multiple surfaces of a graft particle that is porous.

The resorptive ability of a graft particle is in itself however dependent on the chemistry of the material that constitutes it. Depending upon the crystallinity, molecular structure and chemical constitution, alloplasts can vary between totally resorbable to totally non resorbable. In an ideal scaffold configuration, the material must eventually undergo complete replacement by natural bone. In implantology, the rate of such resorption and replacement may also be of some clinical consequence to the treatment plan. Alloplasts have been constituted by various calcium phosphate ceramics, bioactive glasses and the like and these materials have varying rates of resorption. It may be that biphasic calcium phosphate ceramics constituted in the right chemical ratio may hold promise for ideal resorption dynamics in the future (Daculsi *et al* 1989).

The use of a scaffold also mandates the use of guided tissue or bone regeneration techniques as there is ample evidence to suggest that failure to do so results in improper/ unproportional constitution of the wound by various tissue types (Nyman *et al* 1982). Guided tissue regeneration materials in use today are largely resorbable in nature, by virtue of the convenience that such a technique provides in terms of elimination of a secondary surgery for extrication of the material (Teparat *et al* 1998). Resorbable materials are largely constituted either by synthetic polymers (Caffesse 1997) or animal collagen (Black *et al* 1994, Blumenthal 1993), of which the latter seems preferable due to the fact that polymers tend to metabolize into end products that are acidic in nature (Mattson *et al* 1999). Current collagen materials also maintain their integrity for sustained clinical periods and offer the advantage of an ideal tensile strength that allows tacking or suturing to immobilize the material, since mobility may be detrimental to healing (Egelberg 1987). Collagen has also been demonstrated to possess a hemostatic function that may facilitate early clot formation and wound stabilization (Steinberg *et al* 1986), in addition to a chemotactic function for fibroblasts that may aid cell migration and to promote primary wound closure (Poslethwaite *et al* 1978).

Vascular supply to the healing wound is undoubtedly also important and emphasis continues to be placed on the formation of a stable blood clot with ideal fibrin linkages that enhance connective tissue matrix formation. Disruption of the fibrin linkages has been shown to promote long junctional epithelial healing as well (Polson and Proye 1983, Wikesjö *et al* 1992).

Periodontopathic pathogens

Favorable clinical results have most often been observed in healthy patients demonstrating good plaque control and compliance with recommended oral hygiene measures. Studies have also noted an inverse relationship between plaque contamination of retrieved membranes and clinical attachment gain. Colonization of membranes with black pigmented species and the presence of bacteria in samples treated with regenerative procedures has been shown to correlate with diminished healing response (Selvig *et al* 1992, Nowzari and Slots 1994).

Conclusion

The quest for techniques that make periodontal regeneration predictable continues. An amalgamation of all that we currently know seems to suggest that autologous grafts and signaling molecules will play a large role in the future. The use of alloplastic materials with ideal porosity and resorbability seems supportive at best, in combination with resorbable guided regeneration devices. The emphasis on prevention and maintenance however seems central to all attempts to regenerate tissue that is lost to disease. In the near future, we will possibly encounter enhanced clinical techniques that will employ advancements in material science and our improved understanding of wound healing biology, for greater success.

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