Guest Editorial  From Passive to Active: Will Recombinant Growth Factor Therapeutics Revolutionize Regeneration?

The demand for predictable treatment modalities in regenerative medicine continues to escalate as researchers seek to gain a better understanding of the cellular and molecular mechanisms involved in regeneration and as clinicians seek more predictable outcomes and user-friendly techniques. We are now entering the era of recombinant protein therapeutics. Long viewed as the technology holding the greatest promise for predictable and successful clinical outcomes, recombinant tissue growth factors provide highly purified, concentrated bioactive proteins with well-characterized cell-stimulating activities to enhance regenerative outcomes. Further development of these powerful protein therapeutics has been achieved by combining them with tissue-specific biomaterials to provide a substrate for new tissue regeneration as well as an ability to attenuate release of the recombinant growth factor. To appreciate the significance of this new class of regenerative therapeutics, it is helpful to understand the basis for their emergence.

Regenerative treatment modalities in all areas of medicine have historically used three-dimensional biomaterial scaffolds, or matrices, to support the regeneration of tissues lost to disease, trauma, or congenital deformity. Autogenous bone grafts, used in craniomaxillofacial and general orthopedic grafting procedures, are considered the gold standard because they provide an osteoconductive matrix in addition to cells and growth-stimulating molecules, but they require a second surgical site for harvest. In osteopenic and osteoporotic patients or patients with a compromised healing response (eg, patients with diabetes), autogenous grafts present no real advantage and actually may be contraindicated because of an increased risk of morbidity. Even in healthy patients, the disadvantages of limited supply, increased postoperative pain, and risk of morbidity at the harvest site often outweigh the advantages provided.

Additional matrices, including those made from allogeneic, xenogeneic, and synthetic materials, are available for use in oral surgical and orthopedic procedures and function primarily by passively guiding or "conducting" cell migration through the matrix to repair the defect. While these options are useful for maintaining space and providing a framework for tissue deposition, results obtained with passive therapeutic matrices have been variable, depending upon their inherent physical and chemical properties as well as the patient's individual healing response.

The desire to increase the predictability of successful outcomes when using osteoconductive matrices has led to the development of regenerative treatments designed to stimulate the cells responsible for regeneration. The use of cell-stimulating proteins in combination with osteoconductive scaffolds and cells in periodontics and oral surgery is based on the principles of tissue engineering.1 This approach combines three key elements to enhance regeneration: (1) conductive scaffolds, (2) signaling molecules, and (3) cells.

A variety of naturally occurring potent bioactive (cell-stimulating) proteins called growth factors and morphogens are known to be present in bone, platelets, and a number of other cells and tissues. These growth factors and morphogens have been extensively studied in the periodontal, craniomaxillofacial, and orthopedic fields; the two types of molecules that have received the greatest attention are growth factors that are primarily mitogenic (cell proliferative) and chemotactic (cell recruitment) agents and morphogens that act by osteoinduction (ie, by causing the differentiation of stem cells into bone-forming cells).

Growth factors such as platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β), contained in the α-granules of blood platelets and released at sites of injury, have been shown to be important in the normal healing of bone, gingiva, and skin.2 However, the ability to use concentrated forms of these proteins for routine oral surgical treatment was not presented until 1998, when Marx and coworkers3 introduced the technique of platelet concentration to dental surgeons. These factors, when applied to the treatment site, provide the signal to local mesenchymal and epithelial cells to migrate, divide, and increase collagen and matrix synthesis. However, studies evaluating the effect of platelet gel concentrate alone, or in combination with osteoconductive matrices, have demonstrated somewhat variable outcomes4 because of differences in platelet concentration as well as individual patient healing responses.

The need to provide growth-modulating molecules (growth factors and morphogens) in a highly concentrated form is believed to be important in order to increase the predictability of regenerative procedures.5 With advances in recombinant technology, proteins may now be synthesized and subsequently concentrated and purified in large quantities, allowing for the development and commercialization of recombinant growth factor–matrix combination products in all fields of medicine. Combination products represent an emerging new trend in regenerative therapeutics and have gained increasing attention from pharmaceutical and medical device (matrix) companies as a strategy to optimize tissue regeneration. These products combine tissue-specific matrices with highly concentrated bioactive proteins to actively recruit progenitor cells to the treatment site in order to significantly expand cell numbers. The ability to combine highly concentrated forms of signaling proteins allows clinical researchers to develop improved regenerative products that have the physical and chemical characteristics required for specific cell attachment, growth, and differentiation and optimal binding with ideal release of bioactive proteins. To date, only three recombinant growth factor products have been commercialized for use in tissue regeneration.
The first recombinant protein therapeutic approved by the US Food and Drug Administration (FDA) was recombinant human platelet-derived growth factor-BB (rhPDGF-BB) in 1997. The product, Regranex (Ethicon), provides rhPDGF-BB in a gel formulation for the treatment of recalcitrant neuropathic dermal ulcers in patients with diabetes. This product, with an estimated 17 million applications, has been shown to be safe and effective in a series of well-controlled human clinical trials as well as in patient use for nearly 10 years since approval.

The second FDA-approved recombinant protein therapeutic is a bone morphogenetic protein (BMP). BMPs are growth and differentiation factors originally isolated from bone matrix based on their ability to induce ectopic bone formation.6 BMPs function by inducing the differentiation of cells of mesenchymal origin into osteoblasts that have developed through the endochondral (cartilaginous) or intramembranous pathway. These proteins are able to induce bone formation at non-bone-forming sites (i.e., ectopic bone formation). Demineralized freeze-dried bone allograft (DFDBA) has been shown to contain BMPs; however, the concentration of BMPs compared to the concentration of other growth factors present in allograft, such as insulin-like growth factor II (IGF-II) and TGF-β, is very low,7 and the amount of BMP within quantities of DFDBA typically used in periodontal and craniomaxillofacial procedures may not be sufficient to elicit an inductive response.6 Recombinant human bone morphogenetic protein-2 (rhBMP-2; INFUSE Bone Graft, Medtronic Sofamor Danek), was approved in combination with a type I bovine collagen sponge by the FDA for use only in combination with a titanium cage for spinal fusion procedures in skeletally mature patients. Evaluation of this recombinant therapeutic has also been performed in a variety of dental surgical applications, although no recombinant BMP has been approved for any dental indication by the FDA as of the writing of this editorial.

Recently rhPDGF-BB, in combination with a synthetic calcium phosphate carrier (beta tricalcium phosphate, β-TCP), was the first recombinant protein therapeutic approved by the US FDA for treatment of periodontal defects (GEM 21S Growth factor Enhanced Matrix, BioMimetic Therapeutics). Development of rhPDGF-BB within the fields of periodontics and oral surgery gained significant momentum when pilot human histologic studies evaluating rhPDGF-BB in combination with DFDBA for the treatment of severe periodontal intrabony and class II furcation defects provided the highest level of proof for regeneration—human histologic evidence.8,9 These studies demonstrated that the use of purified rhPDGF-BB mixed with bone allograft results in robust periodontal regeneration in both class II furcations and interproximal intrabony defects. Subsequently the effectiveness of rhPDGF-BB was demonstrated by the results of a pivotal clinical trial required for approval by the FDA.10 The results showed that moderate to severe periodontal intrabony defects treated with 0.3 mg/mL rhPDGF-BB + β-TCP (GEM 21S) had significantly greater clinical attachment level (CAL) gains and less gingival recession at 3 months with significantly greater radiographic bone fill at 6 months compared to sites treated with the β-TCP matrix alone. This product is commercially available and provides approximately 1,000 times greater concentration of rhPDGF-BB than that which is commonly obtained through platelet concentration.11–14

A recently published case series15 reporting patient follow-up for up to 24 months for representative cases from the large-scale pivotal clinical trial demonstrated maintenance of clinical outcomes with substantial increases in radiographic bone fill compared to results obtained at the original 6-month conclusion of the trial. Another case series16 evaluating rhPDGF-BB and β-TCP (GEM 21S) for the treatment of recession defects compared the product used in combination with a resorbable barrier membrane to the standard of care, a subepithelial connective tissue graft. The recombinant therapeutic, rhPDGF-BB/β-TCP provided comparable results to the standard of care, without the need for a second surgical site (harvest site).

Finally, in the recent proof-of-principle study17 reported in this issue, which evaluates vertical ridge augmentation in a standardized dog model using rhPDGF-BB in combination with block form anorganic bovine bone, the authors report results demonstrating the potential to regenerate significant amounts of new bone around dental implants placed in severely atrophic mandibular ridges. The results demonstrate the advantage of bioactive recombinant therapeutics over GBR techniques that rely on passive wound healing.

Regenerative therapeutics for use in periodontal, craniomaxillofacial, and orthopedic indications will continue to evolve as our understanding of the physical and biologic requirements for regenerative cells in specific tissue locations (bone, cartilage, tendon, and ligament) are further elucidated and optimal binding and release characteristics for the bioactive proteins are established. However, the availability of recombinant therapeutics represents a major evolution in our regenerative therapies. Dental surgeons who skeptically approach new regenerative therapeutics as “promise without predictability” at long last have access to pure recombinant tissue growth factors. This advancement from previously passive therapies to new active treatments enhances the opportunity for bone and tissue regeneration and provides faster and more predictable outcomes for patients.

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References


