Basic Principles of Bioengineering and Regeneration

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KEYWORDS

• Autogenous grafts • Allografts • Osteoinductive • Osteoconductive • Scaffolds • Stem cells • Growth factors • Angiogenesis

KEY POINTS

- Research into fabricating allografts may potentially reduce the need for autografts, thus reducing donor site morbidity.
- Different systems of delivery of stem cells have been explored with varying results.
- The use of growth factors along with stem cells and scaffolding systems has been shown to aid in grafting procedures.

INTRODUCTION

Although wound healing in the oral cavity occurs with minimal scarring, and oral tissue repair can take place in conditions of dental disease and infection, complex hard and soft tissue defects pose major challenges to clinicians and researchers.[1] Current methods range from simple autogenous or alloplast bone grafting to the use of growth factors with stem cells supported by biodegradable scaffolds to create elaborate 3-D constructs for tissue regeneration.[2–6] Although autogenous bone is the gold standard grafting material due to its osteogenic, osteoinductive, and osteoconductive properties, it has significant drawbacks, including a second surgical site with associated morbidity and resorption over time.[7–10] Bone graft substitutes, such as allografts, xenografts, and alloplasts, are a constant source of investigation with the goal of retaining the favorable characteristics of autogenous grafts without donor site morbidity.[11–13] Unfortunately, bone substitutes lack significant osteoinductive properties and autogenous bone grafts often create unacceptable donor site morbidity to reconstruct large or challenging craniomaxillofacial defects. Therefore, the search for methods to repair and regenerate missing or damaged craniofacial structures rather than grafting or reconstructing them is the ultimate goal of current and future research.

It is widely known that the human body has the capacity to regenerate certain tissues, such as the liver, which can regain function after significant loss.[14] Hepatocytes and liver parenchyma replicate and repopulate the missing area, restoring it to full function.[15] Unfortunately, this process of regeneration does not occur in the oral cavity or elsewhere in the body. If any oral soft or hard tissue is lost, it does not return to its original form. Instead, repair occurs, where damaged tissue is replaced by a fibrous network, without restoration in form or function.[16] Therefore, regeneration must take place by grafting hard and/or soft tissue.

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Currently, more than 1 million bone grafts are performed each year in the United States,[11] which puts a large economic burden on the health care system. Decreasing invasiveness of the procedures and eliminating the need for harvesting donor tissue, while continuing to improve outcomes are major goals for tissue engineering. As researchers become more successful with stem cell isolation and differentiation, developing improved scaffolds that are able to stimulate multiple tissue types while supporting vascularity and producing growth factors that can attain Food and Drug Administration (FDA) approval, the field of tissue engineering will continue to advance and tackle new challenges in tissue repair and regeneration.

BIOLOGICAL MECHANISMS OF WOUND REGENERATION AND REPAIR

The process of regeneration and repair begins with the formation of a wound. This leads to an inflammatory cascade that activates hemostasis. Platelets help to form an initial barrier from the outside environment and secrete growth factors from their α-granules.[17] Fibrinogen, a soluble protein, is converted into fibrin, an insoluble protein that creates a solid clot and provides a scaffold for further inflammatory cells.[18] Various cells in the environment, after being stimulated by injury, secrete chemotactic factors, such as platelet-derived growth factor (PDGF), epidermal growth factor, histamine, and von Willebrand factor.[19] The combination of these signals attracts macrophages and other leukocytes to the area, which destroy bacteria and decontaminate the area, ending the inflammatory portion of the process.[16]

The proliferation phase is marked by angiogenesis and the formation of fibrous tissue during this process; the tissue volume is re-established by fibrous repair.[20] Growth factors released from early cells in the healing wound, such as PDGF, transforming growth factor β-1 (TGF-β1), vascular endothelial growth factor (VEGF), insulin-like growth factor, basic fibroblast growth factor, and epidermal growth factor from macrophages and platelets, are responsible for beginning angiogenesis and vasculogenesis.[21,22] New blood vessels form in the granulation tissue and begin the reconstruction of the area.

After this proliferative phase, the wounded tissue undergoes remodeling and maturation. Myofibroblasts, a combination of smooth muscle cells and fibroblasts, contract to close the wound. Collagen fibers become more organized and the epithelium over the area is regenerated.[2,23] Current methods used to regenerate tissue target various portions of this pathway to achieve a desirable result, yet unfortunately the tensile strength of the healed tissue is not equal to the uninjured tissue.[24,25]

BASIC PRINCIPLES OF BONE HEALING

Missing hard tissue in the craniofacial region or oral cavity can be augmented through various procedures, each of which has benefits and pitfalls. Regardless of the material or method used, all these techniques have a few basic principles that must be followed. Many of these techniques are based on cell exclusion and cellular proliferation.[26] Cell exclusion involves the use of a resorbable or nonresorbable membrane to limit the ingrowth of epithelial cells. Cellular proliferation is the differentiation and growth of cells in response to a certain stimulus. The success of regeneration is greatly dependent on the vascular supply available in the area. Because of this, biomaterials are frequently combined with angiogenesis stimulators.[27]

Bone augmentation is an attempt to preserve or regain bone in preparation for a prosthesis, whether an implant or denture. Various techniques are currently reported in the literature, but they all follow the same principles.[28] After extraction, it is a widely known fact that alveolar bone undergoes marked atrophy. Approximately 3.8 mm of bone is lost horizontally, whereas 1.2 mm is lost vertically.[29] To prevent this resorption, extraction socket augmentation or preservation is often performed. This procedure is generally simple and only requires particulate grafting material to serve as a scaffold to prevent soft tissue ingrowth and significantly reduces the horizontal and vertical resorption compared with tooth extraction alone.[30] Biomaterials include autografts, allografts, xenografts, and synthetic alloplasts.[31] The most commonly used materials are bovine-derived xenografts, which have proved clinically effective.[32]

Bone augmentation relies on 3 mechanisms: osteogenesis, osteoinduction, and osteoconduction. Osteogenesis involves the transplantation of osteocompetent cells to the recipient site. Only autogenous bone has osteogenic properties, especially trabecular bone with more bone marrow and increased cellularity. This is why the iliac crest is a preferred site for large craniofacial defects. Both anterior and posterior approaches provide cortical and cancellous bone and have been successful for continuity defects, alveolar clefts, and severe alveolar atrophy.[3,4,13] Osteoinduction involves chemotaxis of undifferentiated mesenchymal stem cells to the recipient site and stimulates them to become osteoblasts and form bone. Autogenous bone and specific bone morphogenic proteins (BMPs) possess osteoinductive properties.