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Regenerative Technologies for Craniomaxillofacial Surgery

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Regenerative medicine has recently enjoyed a tremendous amount of basic and translational research activity. A convergence of technologies is occurring that has afforded opportunities previously not possible with conventional surgical reconstructive techniques. These discoveries are making their way into current surgical practice. Patients requiring complex reconstructive surgery in the craniomaxillofacial region typically benefit from local or regional flaps, nonvascularized grafts, microvascular tissue transfer, and substitute alloplastic materials to restore function and form. In these clinical situations, grafting procedures or alloplastic substitute materials serve as best-case replacements for resected, injured, or congenitally missing tissues. However, in many cases, ideal reconstructive goals, such as a complete return to original form and function, are not completely achieved. Regenerative techniques, currently in clinical use and at the translational research stage, hold the promise of custom-tailored constructs that have the potential to regenerate tissue in the host without major donor-site morbidity. These techniques can provide better structure, esthetics, and function compared with the best of currently available options. This article presents the most recent concepts in craniomaxillofacial regenerative medicine and reviews the multiprong approach to restoring architecture using novel "smart" multifunctional scaffolds, cellular technologies, growth factors, and other novel regenerative strategies.

There is a need for predictable reconstructive techniques for surgeons to use in patients with complex injury, congenital malformation, or defects from ablative surgery. Reconstructive goals have not been entirely met using current techniques—even by the best of reconstructive surgeons using the most recent techniques.[1] Traditional techniques focus on providing tissue from the local anatomic region to compensate for the lost tissue or providing tissue from another region of the body and retrofitting this anatomy to yield the desired form. The craniofacial region has different specific functional demands, such as protection of the brain and optic tracts, breathing, mastication, speech, and hearing. In addition, the craniofacial region is important for social acceptance and self-esteem.[2] A surgeon must plan for reconstructions and be mindful of the functional and esthetic requirements to achieve success.

Regenerative medicine and tissue engineering aim to provide custom constructs that become integrated fully in the local anatomy and provide ideal form and function once they are in the host. Regenerative medicine can be used to recruit local tissues to produce the desired tissue—ideally in a manner in which the structure and form are esthetically and functionally useful. The use of commercially available recombinant bone morphogenic protein (BMP) products serve as an example of this concept.[3] Currently, proteins can be delivered to "grow" bone at a given site and regenerate lost bony tissue.[4] However, the field is taking these concepts several steps further. Examples of current strategies consist of a biodegradable scaffold embedded with stems cells to produce bone

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regeneration after mandibular resection or use of advanced calcium phosphate-based cements that are biomimetic and tailored with nano-functional attributes offering the capability to temporally release proteins, medications, or genes that drive the regenerative process locally.[5-9]

The growth in technologies related to this field has propelled the possibilities forward and new reconstructive options are becoming a reality. The convergence of different technologies has been instrumental in contributing to recent developments in this area. This article discusses these advances, including the basic concepts of regenerative medicine for the craniomaxillofacial region.

Regenerative Medicine: An Interdisciplinary Field

The basic premise of regenerative medicine or tissue engineering is that a practitioner can provide a new construct to replace lost tissue—whether that tissue be bone, skin, mucosa, tendon, cartilage, heart muscle, liver, entire solid organs, or composite tissues.[10,11] Different terms have been used to describe activities involved in repairing and regenerating tissues, in whole or part by using cells, proteins, matrices, signaling molecules, or other strategies. *Regenerative medicine, reparative medicine*, and *tissue engineering* have been used, somewhat interchangeably, to describe these activities. As with many advances, the process of defining these efforts is more accurately described as incremental process and systematic discovery, rather than a specific sentinel event or seminal published work. Many discussions, articles, and symposia have contributed to the current understanding of the field. However, one can point to several areas of discovery to explain the current direction in the area of craniofacial regeneration.[12-14]

Thus far, biomaterials have been used as replacement tissues, and grafting is performed to reconstruct defects in the craniofacial region. Synthetic vascular grafts, resorbable collagen matrix, synthetic bone cements, and allogeneic transplants have been used to serve as replacement tissues for those that were diseased, lost to injury, or lacking in some way owing to deformity or defect.[10,12-16] In some cases, autogenous grafts can be used to replace lost tissue. These techniques have worked reasonably well, but have considerable downsides. When Urist[4] first produced exogenous bone with the help of BMP, it became clear that it was possible to engineer a process within tissues using the local milieu and its complex cellular signaling environment to produce a desired tissue response. Although these attempts have been directed at producing only some bone at a few select locations, they have been some of the first successful attempts at tissue engineering in the craniofacial region. Other tissues have been repaired or regenerated, including skin and bone, using different techniques, such as expanded neonatal cell lines or stem cell transplants[17] (Fig 1). The challenge of late has been to combine different technologies to control the response in a particular defect. Currently, a collision of bioscience, bioengineering, biomaterials science, and clinical surgery is occurring in an attempt to find workable constructs or bioreactors using the body's ability to recapitulate itself to produce the desired regenerated tissue.

Basic Principles of Regenerative Medicine

Regenerative medicine or tissue engineering is an interdisciplinary, translational field that applies the principles of bioengineering to the development of biological substitutes that restore, maintain, or improve tissue function.[10] To regenerate new tissues within a specific environment, 3 basic tools are essential—cells, a scaffold, and signaling molecules. Some or all of these can be provided by the engineered construct. In some instances, proteins, signaling molecules, and matrices can be used to drive the body's response in the desired direction for regeneration. Concerted efforts in the craniomaxillofacial region are being explored using different techniques, such as bone regeneration with proteins, cellular technologies, synthetic matrices, and vascular biomimetic systems.

BONE REGENERATION

The area of regenerative medicine that has received the most attention for the craniomaxillofacial region is bone regeneration with cellular techniques, biomaterial replacement, and signaling molecule use. Autogenous grafting has been considered the standard for bone replacement in the craniomaxillofacial region. Surgical specialists have been looking for bone substitutes to avoid donor-site morbidity and provide a more convenient way to regenerate defects whether they are from congenital deformities, acute trauma, chronic nonunion, or resection of pathology. Allogeneic bone grafts are suitable, to some extent, for more simple defects but still have drawbacks, such as cost, less than ideal mechanical properties, risk of disease transmission, and the need to procure the material from limited cadaveric specimens. For most serious craniomaxillofacial defects, allografts and xenografts have a small role if one compares outcomes with autogenous sources. For example, grafting a maxillary or alveolar cleft site is typically performed with autogenous bone from the iliac crest. Previous attempts to use allogeneic