Soft Tissue Regeneration Incorporating 3-Dimensional Biomimetic Scaffolds

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KEYWORDS

• Soft tissue engineering • Computer-aided design/computer-aided manufacturing
• 3-dimensional printing • Scaffolds

KEY POINTS

- Soft tissue regeneration in the craniomaxillofacial region is a burgeoning field of study. With the loss of skin, muscle, oral mucosa, or the neurovascular bundle, the predominant approach for closure has been to harvest local, regional, or distant flaps. Regenerative medicine and tissue engineering hope to provide custom constructs that become integrated fully in the local anatomy and provide ideal form and function once they are fully integrated into the host.
- Soft tissue regeneration has found momentum in reconstructing skin, oral mucosa, muscle, fat, and other soft tissue structures.
- By combining soft tissue cell lines, growth factors such as platelet-derived growth factor and transforming growth factor β1 found in sources like platelet-rich plasma, and scaffolds by virtue of 3-dimensional printing have shown promise in the field of soft tissue regeneration to develop constructs that not only obturate defects but also restore form and function.

INTRODUCTION

Soft tissue regeneration in the craniomaxillofacial region is a burgeoning field of study. Over the last 20 years, success at various centers across the world in craniomaxillofacial allotransplantation has led to more interest in developing a hybrid model of allotransplantation with tissue engineering models consisting of cell lines, biomimetic scaffolds, and biochemical signals.[1] With the loss of skin, muscle, oral mucosa, or the neurovascular bundle, the predominant approach for closure has been to harvest local, regional, or distant flaps—this technique may accomplish the closure of dead space but still lacks providing good facial function and esthetics in complex regions such as the lips or eyelids.[2] As with bone regeneration, specialists are looking for substitutes to flap reconstruction to avoid donor site morbidity in the setting of trauma, deformities, or pathologic conditions.[3] Major obstacles in soft tissue regeneration include developing and sustaining a vascular supply to the engineered construct[2] as well as immunosuppression and tissue interactions.[1] Regenerative medicine and tissue

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engineering hope to provide custom constructs that become integrated fully in the local anatomy and provide ideal form and function once they are fully integrated into 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 useful both aesthetically and functionally.

Three-dimensional scaffolds provide an environment for cells and biomolecules to interact in a specific environment aided by the architectural design of the scaffold.[3] The use of advanced printers for scaffolds has helped overcome challenges in regenerative medicine by enabling the precise positioning of cells and biomaterials in a finely tuned manner.[4] Scaffolds add a welcome layer of complexity to tissue engineering because of the varied styles of 3-dimensional printing and the intricacies of their internal and external architecture.

SOFT TISSUE REGENERATION

Combined techniques of allotransplantation and tissue-engineered constructs has gained some momentum in recent years; rat models in which a rotational latissimus dorsi muscle flap was augmented with in vitro engineered oral mucosa to recreate a functional orbicularis oris complex have been shown.[2] Furthermore, advances have been made in overcoming volumetric deficiency from the loss of fat and muscle. The adipose-derived stem cells are of mesenchymal lineage with characteristic multipotent tendency, which makes their use heterogeneous for not only cell-enriched fat grafting[5] but also restoring volume loss by bony regeneration when coupled with materials such as recombinant human bone morphogenetic protein-2.[6]

The development of tissue-engineered skin has been documented for more than 20 years and has garnered success in the commercial market for grafting and wound repair.[7] Initially, engineered skin was processed neonatal foreskin coupled with bovine type I collagen providing a bilayered skin construct for the use in venous ulcers.[8] Recent techniques have been reported to use mesenchymal stem cells because of their ease of harvest from many sources (bone marrow, adipose tissue, umbilical cord blood, dermis); their inhibitory properties of the inflammatory process; and their ability to synthesize tissue with higher amounts of growth factors, collagen, and angiogenic factors than native fibroblasts.[9]

Advances have also been made in engineering oral tissue constructs by isolating oral fibroblasts and transfecting the cells with a viral carrier to deliver transcription factors to reprogram the cellular microenvironment to create tissues such as mucosa, dental pulp, and oral hard tissues.[10] Tissues engineered or processed that are used as oral mucosa are steadily becoming commercially available with products such as ex vivo–produced oral mucosa equivalent EVPOME and AlloDerm (LifeCell, NJ).[11] Furthermore, the development of highly specialized scaffolds with various cellular and biomolecular approaches has aided in the development of oral tissues such as salivary glands[11] and pulpodentin complexes in a sophisticated and elegant manner.[12]

GROWTH FACTORS IN SOFT TISSUE ENGINEERING

Much of what is known about growth factors in clinical soft tissue engineering comes from studies on platelet-rich plasma (PRP). PRP is a common approach to tissue regeneration strategies in the craniomaxillofacial surgery practice for general improvement of soft and hard tissue healing in the postoperative period.[13] Multiple clinical investigators describe sequestering and concentrating autologous platelets in plasma to serve in surgical sites as grafts to bolster healing responses by the work of primarily 3 growth factors: platelet-derived growth factor (PDGF), transforming growth factor β1 (TGF-β1), and transforming growth factor β2 (TGF-β2).[14] An initial study by Marx and colleagues[14] on bone regeneration focused on describing the potential clinical use and biologic nature of PDGF and TGF-β growth factors. PDGF is a glycoprotein that is secreted by degranulating platelets and endothelial cells that, in turn, activate cell membrane receptors on target cells that subsequently induce mitogenesis, angiogenesis, and macrophage activation. TGF-β is part of the same superfamily as bone morphogenic protein—they are proteins synthesized by platelets and macrophages and secreted in paracrine fashion to exert effects on neighboring fibroblasts, marrow stem cells, and preosteoblasts.[14] Marx[15] later made the case that PRP may have many clinical uses including not only bone augmentation but also in the preparation and treatment of split-thickness skin grafts (**Fig. 1**).[15] Despite the initial enthusiasm, harnessing the use of this technique has been difficult and this technique has not proven effective in follow-up studies for bone or soft tissue regeneration in a predictable and repeatable way.

PRP has also been used as an adjunct in autologous fat grafting. Liao and colleagues[16] state that although fat grafting aids in reestablishing volumetric soft tissue deficiency, its use is often marred by a 40% to 60% reabsorption rate and