



Tissue Engineering: Emerging Concept in Oral Maxillofacial Reconstruction-A Review Article

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Introduction

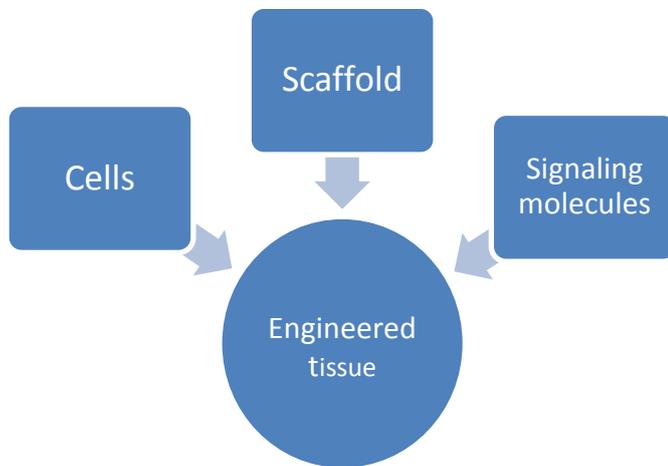
Tissue engineering or tissue regeneration is a multidisciplinary field with the perspective to replace tissue loss as a result of the traumatic defect, oncosurgery, or organ damage.⁽¹⁾ As an alternative to current surgical techniques developments in tissue regeneration using the gene therapy and stem cell research endeavor to develop cells, scaffolds and cell signaling molecules to rejuvenate large oral and maxillofacial tissue defect with accurate reproduction of normal tissue. One of the major challenges in front of maxillofacial surgeon is reconstruction of large tissue defect. A tissue engineering approach provides numerous prospective benefits, including a declination in donor site morbidity, a decrease in procedural sensitivity of the repair, and the capacity to intimately ape the *in vivo* tissue environment into recapitulate normal craniofacial development.⁽²⁾

Principles of tissue engineering

The general principles of tissue engineering involve combining living cells with a natural/synthetic support or scaffold to build a three-dimensional living construct that is functionally, structurally and mechanically equal to or better than the tissue that is to be replaced. The development of such a construct requires a careful selection of four key materials: 1) scaffold, 2) growth factors, 3) extracellular matrix, and 4) cells.⁽³⁾ Regeneration of tissues is a complex and process that proceeds along a pathway including the three well known steps of inflammation, proliferation, and remodeling. During this process biological signals accomplish the increase in cell numbers that fill the defect or cover the wound. At the same time, specialization of the newly formed tissue-occurs through morphogenic signals which induce the tissue specific differentiation.⁽⁴⁾

The three components i.e. cells, scaffold and signaling molecules when transferred to the *in vitro* environment of tissue-engineered constructs,

the extracellular matrix is replaced by synthetic or natural scaffolds which are used to accommodate and arrange the cells in a three-dimensional fashion. The triad of cells, signals, and scaffolds thus makes up the “classic” Tissue engineering triad ⁽⁵⁾



Stem cells

A stem cell is defined as an unspecialized cell that can renew and maintain itself for a longer period of time with the potential to commit to a cell or tissue lineage with specialized functions. The cell-based approach is based on strategy to obtain a small number of cells or a small tissue portion through a minimally invasive procedure. These cells are expanded *ex vivo* to a volume that is expected to form desired amount and type of tissue.

- i. **Mesenchymal stem cells:** are immature and undifferentiated cells that are commonly obtained from bone marrow aspirates but can also be retrieved from fat tissue and periosteum.
- ii. **Induced Pluripotent stem cells (iPSC's):** Mature skin cells transformed into pluripotent cells by inserting 4 genes, Oct3/4, Klf4, Sox2, and c-Myc, into the cell nucleus. These cells are called “induced pluripotent stem cells”.
- iii. **Recombinant cells:** Gene transfer have been used to the seeded cells that would allow for overexpression of the required growth factors which make them less dependent from the level of host tissue factors. Thus, the functionality of the

implanted devices could be increased and the therapeutic outcome improved.

- iv. **Differentiated Osteoblasts:** These cells are committed mesenchymal cells that have been directed down the osteogenic lineage to push the cell type closer to the final type desired. ^{(5) (9) (10)}

Scaffold

A scaffold is a permanently or temporarily placed three-dimensional porous and permeable natural or synthetic biomaterial that is biocompatible. It can be natural or synthetic. It consists of a matrix and various cell types.

The matrix represents a 3D structure for cells, which provides them a specific environment and architecture for a given functional purpose.

The function of the scaffolds is to provide structural support to cells and to provide flexible and physical environment for remodeling. It also acts as a reservoir for growth factors. ⁽⁶⁾

Signaling molecules

Growth factors are soluble peptides that are capable of binding cellular receptors and producing either a permissive or preventive cellular response toward differentiation and/or proliferation of tissue ⁽⁷⁾. Various growth factors and cytokines are mixed to the ECM, like bone morphogenetic proteins (BMP), fibroblast growth factor-2 (FGF-2), interleukin-6, insulin-like growth factor (IGF), platelet-derived growth factor (PDGF), etc. ECM must be capable of providing the optimal conditions for cell adhesion, growth, and differentiation within the construct by creating a system capable of controlling environmental factors such as pH, temperature, oxygen tension, and mechanical forces ⁽⁸⁾

Steps of tissue regeneration and implantation ⁽¹¹⁾

- 1) Cell harvesting from body
- 2) Isolation, cultivation, and proliferation of cells into scaffold in presence of growth factors or signaling molecules (*in vitro*)
- 3) Implantation of the tissue regenerate.

Tissue engineering in oral and maxillofacial reconstruction

Growth factors used in oral and maxillofacial reconstruction: ⁽¹⁶⁾

- Platelet-Derived Growth Factor (PDGF)
- Basic fibroblast Growth Factor (bFGF)
- Insulin-Like Growth Factor (IGF)
- Transforming Growth Factor Beta (TGFβ)
- Vascular Endothelial Growth Factor (VEGF)
- Bone Morphogenetic Proteins (BMPs)

For Craniofacial and dental tissue regeneration there are 3 major approaches;

- ✚ Recombinant protein therapy
- ✚ Cell-based therapy
- ✚ Gene therapy.

- 1) **Recombinant protein therapy:** consists of delivering the appropriate growth factor on a scaffold in order to stimulate certain cells in the target site. Application of this approach may help to reduce or even eliminate the need for autogenous bone grafts. ⁽¹⁷⁾
- 2) **Cell-based therapy:** involves direct contribution to tissue regeneration, genetic modification of cells to act as vehicles for gene therapy and differentiation into various tissue types ⁽¹⁸⁾.
- 3) **Gene therapy:** is a relatively new pattern in medicine with tremendous therapeutic potential where specific genetic information is delivered to the cells directing them to secrete a certain protein product ⁽¹⁹⁾.

Application of tissue engineering in oral and maxillofacial surgery:

- Bone regeneration
- Cartilage regeneration
- Soft tissue regeneration
- Salivary gland regeneration
- Fat, muscle, and nerve regeneration

Bone: Mesenchymal stem cells are considered best cells for bone regeneration as they can convert into osteoblasts and osteoclasts. ⁽¹²⁾ BMP

are the widely used growth factors for bone regeneration by osteoinduction and osteogenesis. BMP 7, BMP 2, PRP, and platelet-derived growth factors are currently researched growth signaling molecules. ⁽¹³⁾

In bone tissue engineering, periosteal cells from the mandibular ramus and bone-derived cells from the maxillary tuberosity have been used to produce bone in sinus lift procedures and lateral rim augmentations in preimplant surgery. ⁽¹⁴⁾

Cartilage: Cartilage tissue engineering in oral and maxillofacial surgery is limited very much to the temporomandibular joint. Recent studies have dealt with tissue engineering of nasal and ear cartilage. Cartilage present in the articular disc of temporomandibular joint, nasal septum, and ear gives physical and functional support to these parts. Cells with chondrogenic potential like bone marrow-derived mesenchymal cells, and periosteum-derived mesenchymal cells used in concurrence with a diversity of scaffolds such as carbon fiber pads, decalcified bone fibrin glue, collagen gels, and alginate hydrogels in the presence of FGF2, FGF-β, bFGF. ⁽¹⁵⁾

Soft tissue

Skin Skin is composed of superficial epidermal and deeper dermal layer. To generate complex skin grafts poised of both an epidermal and a dermal layer, fibroblasts and keratinocytes have been planted into various scaffolds. ⁽¹⁸⁾ The research to achieve versatile and universal engineered skin tissue is oriented to add vascular endothelial cells (angiogenesis), melanocytes (Melanin pigments) sweat glands, and hair follicles.

Oral mucosa Oral mucosa is thin and more vascular than skin with the absence of hair follicles and sweat glands. Clinical tissue engineering of epithelium using EVPOME (ex vivo produced oral mucosa equivalent) preparations has been employed in intraoral applications such as vestibuloplasty, repair of superficial postablative mucosal defects, and for prelamination of free radial forearm flaps with

subsequent transfer to the oral cavity. Clinical results have shown a good to excellent take rate with vascular in growth from the recipient bed. ^(19, 20)

Salivary Glands

Salivary gland hypofunction, also known as xerostomia, occurs as a result of radiation therapy for head cancer, Sjogren's syndrome or aging, and can cause a variety of problems, including dental decay, bacterial infection, mastication dysfunction, swallowing dysfunction and reduced quality of life. Gene therapy which uses adenoviral vector, has been used to increase salivary flow at the irradiated areas. ^(21, 22)

Muscles, fat and nerves

Muscles for facial expressions maintain the facial contour and tone. Fat or adipose tissue gives support to the facial muscles. All the muscles have innervations from the nerves. All the 3 components are required to reconstruct facial defects. Muscle has the low regenerative capacity⁽²³⁾. Adipose tissue, myotubes, and nerves have been regenerated in laboratories with relevant signaling molecules and scaffolds, but motor end plate is must for a muscle to contract and retract. Research is going on to produce such functional muscles ⁽²⁴⁾

Advancements in tissue engineering

In bone tissue engineering, fibrin has been introduced as an excellent scaffold, because of its biocompatibility and biodegradability, and the initial stability of the grafted stem cells. It promotes cell migration, proliferation, and matrix making through acceleration in angiogenesis. Growth factors in fibrin glue can stimulate and promote tissue repair. ⁽²⁵⁾

Various studies have been done on autologous fibrin glue, which shows it is promising scaffold in regenerative maxillofacial surgery. Study done by Lee et al. showed that, when a combination of autogenous bone and platelet-enriched fibrin glue is used for maxillary sinus grafting with simultaneous implant placement, the volume of the formed new bone is significantly greater than

that of when treated with autogenous bone alone. ⁽²⁶⁾ In a study by Giannini et al. in 2004, reduced infections and length of hospital stay of patients treated by fibrin-platelet glue, were observed. ⁽²⁷⁾

Conclusion

Stem cell therapy has got a paramount role as a future treatment modality in dentistry and maxillofacial reconstruction. Tissue engineering is a highly active field to develop products and devices with all the needful components and following all principles of regenerative medicine. With advancements in the tissue engineering, many clinical problems related to maxillofacial reconstruction can be overcome. The real challenge of tissue engineering in clinical treatment is the reduction of surgical morbidity by the application of biological signals or bio-artificial components cultivated from the patient's own cells. The areas of new and expanding research demonstrate the field of tissue engineering has become multidisciplinary and while the challenges are vast, the opportunities for improving human health in a whole variety of areas are immense.

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