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Tissue Engineering in Oral and Maxillofacial Rehabilitation—Current Status and Future Prospects

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Abstract

Purpose of Review The objective of this review is to provide a comprehensive overview of the existing literature pertaining to the principles and techniques utilized in tissue engineering for the purpose of rehabilitating oral defects that may involve tissues such as bone, cartilage, oral mucosa, periodontal ligament, nerve, and muscle.

Recent Findings Tissue engineering represents a cutting-edge area of research within the field of regeneration. Its potential application in the restoration of oral and maxillofacial tissues has emerged as a viable alternative to the traditional use of autologous bone grafts for reconstructing bone defects. In recent times, the field of tissue engineering has made significant progress in tissue regeneration through the utilization of cutting-edge technologies. Tissue engineering has facilitated tissue regeneration through the replication of stem cells, cytokines, and growth factors.

Summary Tissue engineering is definitely the future of reconstructive surgery that facilitates the regeneration of tissues that have been compromised by various dental pathologies. To date, significant progress has been made in the field of tissue regeneration, particularly in the restoration of simple tissue defects. However, the restoration of complex tissue structures and their corresponding functionality remains a formidable challenge that continues to be actively researched.

Keywords Tissue engineering · Bone grafts · Scaffolds · Bone regeneration · Stem cells · Maxillofacial rehabilitation

Introduction

Tissue engineering is a new frontier in the field of regeneration of tissues, and its approach in the oral and maxillofacial tissues is multidisciplinary through integration of various aspects of bio-engineering [1]. The morphology, appearance, and function of the maxillofacial tissues are distorted due to the loss of natural teeth and the supporting bone/tissue complex. The standard management for such conditions is the replacement of the missing teeth with denture or fixed prosthesis like fixed partial denture and implant. However, the challenges lie when the maxillofacial tissue are severely distorted or destroyed due to various causes like trauma, soft and hard tissue tumors, and congenital defects [2].

Oral and maxillofacial rehabilitation is the main challenge for the maxillofacial surgeon following ablative surgery or trauma. Though various treatment approaches are followed in reconstructive surgery, the use of autogenous grafts and osteo-cutaneous free flaps for the replacement of the tissues lost or damaged remains the standard measure [3]. Grafting procedure involves significant surgical effort as well as morbidity. The rehabilitation of maxillofacial defects has many challenges such as high possibility of bacterial contamination due to proximity to paranasal sinuses and oral cavity as well as mechanical loading during mastication [4]. The recent advances in biotechnology have enabled to cultivate the damaged or lost parts which can substitute the autogenous grafts [3, 5]. The tissue engineering has enabled the regeneration of tissues by recapitulating the stem cells, cytokines and growth factors [5].

Stem cells are the unspecialized cell that can renew and differentiate into a cell or tissue lineage with specialized functions. The embryonic or adult-derived mesenchymal

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stem cells have the potential to differentiate into mesodermal lineages such as osteocytes, hepatocytes, neurons, adipocytes, and chondrocytes. The mesenchymal stem cells are isolated from various tissues such as tonsil, adipose tissues, and bone marrow [6]. The embryonic stem cells need to be isolated from the human embryo and hence are associated with ethical issues which is hindering its clinical application [6]. Biobanking is an emerging business which offers collection and storage of the dental stem cells by many laboratories worldwide [7]. Hence, a paradigm shift has taken place in utilizing tissue engineering for regeneration of the maxillofacial structures. Tissue engineering can be used for the regeneration of various prototypes of oral and maxillofacial structures such as tooth structures, periodontium, temporomandibular joint (TMJ), condyle, and cranial sutures. Thus, this review provides an insight into principles, techniques for regeneration of various tissue components, and recent advances in tissue engineering oral and maxillofacial rehabilitation.

Materials and Methods

Search Strategy We searched various databases such as Scopus, PubMed, and Google Scholar with the following search algorithm: "Tissue Engineering" AND "Maxillofacial Rehabilitation." The articles published after the year 2000 were considered to review the contemporary advancements in the field.

Multiple reviews on the topic were analyzed, each reporting on different themes concerning maxillofacial rehabilitation and tissue engineering. Recent in vitro, in vivo, and preclinical animal studies were analyzed which presented data on rehabilitation of maxillofacial defects through tissue engineering. The presented findings are organized under the following subheadings: bone regeneration, nerve regeneration, cartilage regeneration, muscle regeneration, oral mucosa regeneration, and recent advances.

Results

Oral and maxillofacial reconstruction entails the restoration of significant tissue defects, necessitating the transplantation of cells due to the limited availability of suitable cells within the local tissue environment. The procedure involves obtaining a biopsy from a donor site, from which the cells are isolated and cultured. Subsequently, these regenerated cells are surgically implanted into the site of the defect. This therapy facilitates the regeneration of various types of soft tissue, including fat, nerves, blood vessels, bone, and cartilage [8].

Bone regeneration

Mesenchymal stem cells are the stem cells used in regeneration of bone due to their potential to differentiate into bone forming cells. Bone restoration is achieved by implantation of the cultivated autogenous bone cells, osteogenic growth factors, and scaffold that substitute the bone matrix. The mesenchymal stem cells of different origin has been used in stem cell therapy for bone generation [9]. The stem cells derived from amniotic fluid are seen to undergo osteogenic differentiation by activation of Wnt signaling pathway. The mesenchymal stem cells derived from dental tissues such as tooth germ progenitor cells, human exfoliated deciduous teeth, periodontal ligament, apical papilla, dental follicle progenitor cells, alveolar bone, and gingiva show potential and effective capacity to differentiate into bone forming cells [10, 11]. The amniotic membrane mesenchymal stem cells and umbilical cord mesenchymal stem cells are also known to show good osteogenic differentiation [12].

Scaffold is an essential factor in tissue regeneration. Scaffolds are implemented with the purpose of triggering the local environment. The various functions of scaffold in bone regeneration are to (i) provide mechanical support and fill the void caused due to bone loss, (ii) promote growth and adherence of precursor cells and provide platform for extracellular matrix deposition (osteoconduction), (iii) elicit the blood vessels and bone growth into porous scaffold, (iv) promote osteogenic differentiation and new bone formation (osteoinduction), (v) stimulate cell activity and support the integration with adjacent tissue (osteointegration), and (vi) release bioactive molecules to accelerate healing [13]. Scaffolds of synthetic origin such as aliphatic polyesters such as poly (lactic-acid), poly(glycolic-acid), and poly(caprolactone) are commonly used in bone tissue engineering due to their good mechanical, biocompatible, biodegradable properties [14]. Natural polymeric scaffolds are made up of extracellular biomaterials such as proteins (collagen, gelatin, fibrinogen, elastin, keratin, silk, etc.), polysaccharides (glycosaminoglycans, cellulose, amylose, dextran, etc.), and polynucleotides (DNA, RNA) [14]. Although natural polymers are biocompatible and undergo biodegradation, they have poor mechanical properties [14]. Ceramic scaffolds are also used as they mimic bone and provide better adherence and proliferation. Bioceramics like calcium silicate and calcium phosphate in combination with collagen has been used to stimulate the inorganic compartment of bone [15].

Cellular and molecular signaling pathways play important role in bone regeneration [16]. Wnt/β-catenin signaling pathway promotes osteoblastogenesis, controls the osteoblasts following its differentiation from stem cells,

and enhances the adult bone mass [17]. Further, Notch signaling via Notch 2 and Jag-1 promotes the differentiation of mesenchymal stem cells to osteoblast and also has osteoinductive effects [18]. Bone morphogenic protein and transforming growth factor β play important roles in the osteogenesis. Bone morphogenic protein 2 (BMP-2) has been extensively studied in clinical experiments of bone regenerative medicine. Bone morphogenic protein induces the formation of new bone by acting on cells at different stages of osteogenesis, from the differentiation of the immature mesenchymal stem cells to forming mature osteocytes. Bone morphogenic protein 2 also promotes the differentiation of mesenchymal stem cells into osteoblasts by upregulating vascular endothelial growth factor. The use of rhBMP-2 has been approved by the US Food and Drug Administration (FDA) in maxillofacial reconstruction [5, 16]. The other signaling pathways such as PI3K/Akt/mTOR, mitogen-activated protein kinase, insulin growth factor, platelet-derived growth factor, and fibroblast growth factor have been also studied to be having important role in the bone regeneration [16].

Various sources to obtain the growth factors have been tested in preclinical models. Platelet-rich plasma has extensively been used in combination with autogenous or allogeneic grafts. Platelet-rich plasma results in activation and degradation of platelets to induce the release of growth factors in turn promotes angiogenesis, tissue repair, and stem cell activity [5]. Platelet-rich fibrin is a second-generation autologous platelet concentration. Platelet-rich fibrin releases transforming growth factor-β, vascular endothelial growth factor, platelet-derived growth factor, glycoproteins, including fibronectin, thrombospondin-1, and vitronectin [19]. Bone marrow aspirate concentrate has also been used in orthopedic procedures. Bone marrow aspirate concentrate serves as the source of the mesenchymal stem cells and in addition consists of cytokines and growth factors important for tissue generation. Bone marrow aspirate concentrate has been used in the repair of cleft lip and palate. FDA has approved obtaining of bone marrow aspirate concentrate from the anterior or posterior iliac crests, tibia of the patient to deliver the mesenchymal stem cells for patient's own repair [5].

Cartilage Regeneration

Cartilage regeneration was one of the first tissues, which was addressed in tissue engineering. One of the approaches to repair cartilage defects is the use of tissue engineered cartilage. Cartilage tissue has an advantage over bone for being avascular, serving as the crucial factor in success of the tissue engineered cartilage [3]. However, the healing of cartilage is delayed due to this limited blood supply [20]. In oral and maxillofacial surgery, development of the nasal cartilage using the cartilage cells in polymer scaffold, implanted into the back of nude mice, has given promising results. Injecting the preparations of chondrocyte macroaggregates with fibrin sealant, or gelatinous mass of autogenous auricular cartilage cells, has been explored to develop nasal cartilage structures [21, 22]. FDA has approved the direct delivery of autologous chondrocytes into the area of defect called autologous chondrocyte implantation. The procedure includes the initial surgical removal of cartilage from the non-weight bearing area of the joint and then cultured ex vivo for four passages. The defect area is covered by periosteal layer of bone, and then cultured chondrocytes are injected into the defect arthroscopically [20]. In the repair of nasal deformity seen in cleft lip and palate, there has been an extensive use of three-dimensional scaffold materials to reinforce the mechanical strength of regenerated cartilage. On the other hand, the conventional periosteal layer is replaced with biomaterials such as collagen film or porous material made up of collagen and hyaluronic acid to overcome the adverse periosteal thickening [23]. The recent advances in cartilage tissue engineering are directed towards replacement of the structures associated with TMJ such as condylar cartilage and TMJ disc. The construction of TMJ cartilage endures several challenges due to the nature of TMJ condylar cartilage being an intermediate between fibrocartilage and hyaline cartilage [24]. Also the amount of glycosaminoglycans in TMJ disc is half of the usual articular cartilage and the tensile modules is six times higher [25]. Hence, the research on the tissue engineering of condylar cartilage and TMJ disk is still in infancy stage as there is requirement of several structural modulations to withstand the masticatory forces.

Oral Mucosa Regeneration

A stratified epithelium with fibrous connective tissue and a continuous basement membrane having a three-dimensional stability and functional properties during handling and healing is brought about by tissue engineering. This bioengineered full thickness oral mucosa is commonly called as ex vivo produced oral mucosa equivalent (EVPOME) [26]. These tissue-engineered oral mucosas have been used for intraoral applications such as restoration of defects following surgical resection of tumor, major trauma, maxillofacial pre-prosthetic surgery, and periodontal treatments [27–29]. The EVPOME are cultured from the primary human oral keratinocytes. The cultured oral keratinocytes are seeded on an acellular dermal matrix. AlloDerm is the acellular dermal matrix used, which on one side attracts the epithelial cells to grow on it and on other side has the porous dermal matrix with polarity for fibroblast ingrowth and cells inducing angiogenesis [30]. The procedures are based on the guidelines proposed by the cell-based products developed by the Center for Biologics Evaluation and Research, unit

of FDA [28]. The recent studies are focused on shortening the time of EVPOME fabrication for reconstructive surgery and also explore the ability of these cells in release cytokines and growth factors for extended period of time to facilitate the functioning [30].

Nerve Regeneration

Trigeminal nerve and facial nerve dysfunction are commonly seen following an injury or trauma in the maxillofacial region [31]. Bone marrow-derived mesenchymal stem cells can differentiate into myelinating cells and support nerve fiber regeneration. Adipose stem cells have also been shown to physically engraft and myelinate regenerating axons in in vivo studies. Bone marrow-derived mesenchymal stem cells can be induced to express neural stem cell markers. Studies utilizing pre-differentiated stem cell transplantation showed that they accelerated the regeneration of transected axons and achieved improved myelination as comparable to the Schwann cell transplantation. Additionally, they synthesize myelin proteins that serve to enhance the myelination and function of the regenerated nerves [31]. Dental pulp stem cells are also widely recognized for their exceptional capacity in nerve regeneration due to their remarkable ability to adapt to adverse metabolic conditions and produce a diverse range of neuroprotective and immunomodulatory factors [32••]. The transplantation of stem cells derived from human exfoliated deciduous teeth into a severed spinal cord has been observed to effectively preserve the myelin sheath and facilitate the differentiation of these cells into mature oligodendrocytes, which are crucial for the formation of the central nervous system myelin sheath [33].

Muscle Regeneration

Several research groups have directed their attention towards investigating the properties of oral stem cells related to muscle regeneration. The progenitor cells employed need to possess the essential characteristics of expandability, culture viability, and the ability to differentiate into both muscle and facial tissue cell types. The mesenchymal stem cells have the myogenic potential. Myoblasts are derived from mesenchymal stem cells with a high level of efficiency. The fusion of myoblasts results in the formation of myotubes, which undergo differentiation into muscle fibers. Additionally, myotubes possess a significant capacity for proliferation and self-renewal, making them highly suitable as progenitor cells for the engineering of skeletal muscle tissue [34]. Further, identification of a three-dimensional scaffold that meets the requirements of biocompatibility, elasticity, and stability is a critical concern for the successful clinical implementation of tissue engineered muscle [35]. In addition, it is crucial to consider the utilization of muscle progenitor cells that exhibit a strong inclination towards muscular differentiation, while also retaining the same characteristics and contractility as the donor muscle. For instance, satellite cells are a noteworthy option to be considered in the engineering of facial muscles [35]. Satellite cells exhibit a response to hypoxic and ischemic muscle damage in vivo by undergoing differentiation into myotubes, which are immature muscle fibers, and subsequently maturing into muscle fibers [36]. In addition, fibroblasts are other cell populations that can facilitate the self-assembly of tissue engineered muscle [37].

Periodontal Regeneration

The presence of bony defects in the oral cavity can exhibit considerable variation, encompassing smaller intrabony lesions caused by periodontal or peri-implant diseases, as well as larger osseous defects that extend through the jaws due to trauma, tumor resection, or congenital defects [38]. The variation in size and location of these alveolar defects is further complicated by patient-specific and environmental factors that contribute to the difficulties in achieving periodontal regeneration, peri-implant tissue regeneration, and alveolar ridge reconstruction [38]. Periodontal regeneration is an area of research that is experiencing significant growth and development. Several novel biomaterials, methodologies, and technological advancements have been devised in the last decade to enhance regenerative periodontal therapy [39].

There are two primary strategies employed in the field of periodontal regeneration: guided tissue regeneration and tissue engineering approaches [38]. The use of guided tissue regeneration has been extensively employed in clinical practice for several decades for the purpose of periodontium regeneration. The regenerative surgical technique involves the meticulous process of raising a mucogingival flap around the affected teeth, followed by the precise scaling and planning of the root surfaces. Additionally, temporary barrier membranes are strategically placed beneath the gingiva during the procedure. The biological principle of inhibiting the apical growth of epithelium over the denuded root surface is to promote the formation of periodontal ligament tissues and alveolar bone by facilitating the activity of periodontal ligament cells and osteoblasts [40••].

The tissue engineering strategy employs stem/progenitor cells, scaffolds, and bioactive molecules to construct biomimetic systems that facilitate the development of new tissue formation. The tissue engineering strategy for periodontal regeneration can be classified into two main approaches: scaffold-free and scaffold-based, depending on the utilization of biomaterials. In the scaffold-free approach, cells or cell aggregates are transplanted to a defect area in the absence of a cell carrier. There are various types of cells, such as bone marrow-derived mesenchymal stem cells, adipose-derived stem cells, and periodontal ligament stem cells which are

used [39]. In scaffold based, the scaffolding materials should replicate the compositions of the extracellular matrix found in periodontal tissues. Given that the periodontal ligament is composed of fibrous tissue, it is imperative that any scaffold designed for periodontal regeneration effectively promotes the formation of soft tissue while simultaneously preventing mineralization. Hence, polymeric biomaterials are extensively employed for periodontal ligament regeneration [39].

Recent Advances in Tissue Engineering

As tissue engineering is an emerging technology, recent advances aim at isolation of stem cells and differentiation of stem cells into specific cell types through modulation in cell signaling. Genetic modification of cells or genome editing are done using CRISPR/Cas system which systematically dissect the functional effect of genetic variants [41]. These technologies will address the difficulties encountered in isolation of sufficient amount of autologous cells [42]. Newer technologies, such as microfluidics and 3D printing, have been adopted in construction of scaffolds [41]. Microfluidics, a remarkable biotechnological innovation, possesses the extraordinary capability to intricately engineer droplets and fibers with intricate structures through the precise control and manipulation of fluids at the micro-scale [43••]. Functional structures or materials can be fabricated from microfluidics by solidifying the droplet/fiber templates. Microfluidic technology has emerged as a promising and versatile method for bio-scaffold construction due to its numerous advantages, including low cost, enhanced safety, and precise controllability [44]. Microfluidic systems often use single-phase continuous flow systems and segmented flow systems. A microfluidic droplet is formed when a single fluid or a continuous laminar flow consisting of multiple fluids passes through a microchannel [43••]. There are several parameters that can be utilized to modify the size and structure of droplets. These parameters include the microchip structure, solution properties, and flow rate. Both natural and synthetic materials are used for construction of scaffold; however, synthetic are better candidates for microfluidic scaffolds due to their stiffness and stretchability [45]. Microfluidic devices are used to fabricate spherical macro-porous beads made of polylactic-glycolic acid. These beads are intended to serve as carriers for cell transportation. The presence of a substantial pore size facilitates the provision of nutrients and oxygen during cell culture, thereby promoting the viability of the encapsulated cells. The cells are seeded on the surface of the droplet scaffold and incorporated within the hydrogel precursor prior to its emulsification and polymerization. This approach renders the scaffold suitable for three-dimensional (3D) cell culture, providing a conducive environment for cellular growth and development [46]. Similarly, microfluidic fibers are also used in scaffolds. Different fiber materials need various curing and molding techniques, namely ion cross-linking, photopolymerization, and solvent exchange. Cross-linking and solidification take place at the point of convergence when two-phase fluids meet in a single microfluidic channel. To produce microfibers, glass capillary-based device with modifications are usually employed [43••].

Conclusion

Tissue engineering exhibits significant potential for the future, as this pioneering approach is expected to enable the restoration of tissues that have been compromised by diverse oral and maxillofacial pathologies. Significant advancements have been achieved in research endeavors aimed at enhancing the properties of materials in this field, owing to the emergence of various materials and fabrication techniques. To date, significant progress has been made in the field of tissue regeneration, particularly in the restoration of simple tissue defects. However, the restoration of complex tissue structures and their corresponding functionality remains a formidable challenge that continues to be actively researched. It is advisable for maxillofacial surgeons and tissue engineers to engage in a collaborative effort, wherein the former communicate their functional needs and the latter apply the principles of tissue engineering.

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SBV: Literature search, manuscript writing and editing

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Declarations

Competing Interests The authors declare no competing interests.

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•• Of major importance

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