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REVIEW

Cartilage and facial muscle tissue engineering and regeneration: a mini review

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Abstract
Cartilage and facial muscle tissue provide basic yet vital functions for homeostasis throughout the body, making human survival and function highly dependent upon these somatic components. When cartilage and facial muscle tissues are harmed or completely destroyed due to disease, trauma, or any other degenerative process, homeostasis and basic body functions consequently become negatively affected. Although most cartilage and cells can regenerate themselves after any form of the aforementioned degenerative disease or trauma, the highly specific characteristics of facial muscles and the specific structures of the cells and tissues required for the proper function cannot be exactly replicated by the body itself. Thus, some form of cartilage and bone tissue engineering is necessary for proper regeneration and function. The use of progenitor cells for this purpose would be very beneficial due to their highly adaptable capabilities, as well as their ability to utilize a high diffusion rate, making them ideal for the specific nature and functions of cartilage and facial muscle tissue. Going along with this, once the progenitor cells are obtained, applying them to a scaffold within the oral cavity in the affected location allows them to adapt to the environment and create cartilage or facial muscle tissue that is specific to the form and function of the area. The principal function of the cartilage and tissue is vascularization, which requires a specific form that allows them to aid the proper flow of bodily functions related to the oral cavity such as oxygen flow and removal of waste. Facial muscle is also very thin, making its reproduction much more possible. Taking all these into consideration, this review aims to highlight and expand upon the primary benefits of the cartilage and facial muscle tissue engineering and regeneration, focusing on how these processes are performed outside of and within the body.

Keywords Soft tissue regeneration · Cartilage tissue engineering · Muscle tissue engineering · Facial regeneration

Introduction

The primary focus of cartilage and facial muscle tissue engineering and regeneration is on cranio-maxillofacial engineering in dentistry, and the scaffold design and eventual formation of these scaffolds [1,2]. Craniofacial muscle tissue engineering is essential to the human body's ability to facilitate movement and internally transport materials in response to internal and external stimuli as well [3]. As a result, the components of craniofacial muscles such as the skeletal muscle itself, salivary glands, and adipose tissue all need to be properly created and formed in order for the body to maintain its basic capabilities, mainly in regard to homeostasis and basic bodily functions necessary for survival [4]. Due to the emphasis on both the proper form and function of salivary glands, two different techniques are used to accomplish this, the first of which is inductive gene therapy [5], and the second of which is cell transplantation. Within cell transplantation, salivary epithelial cells have been cultured successfully in vitro on 2-dimensional polymer films [6]. Another critical aspect of these craniofacial muscles is the ability of their cells to form from the natural pace of generation. Within craniofacial muscles, the majority of their structures are made up of mesenchymal stem cells (MSCs) that originate from the neural crest, allowing them to migrate, differentiate, and sub-

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sequently morph into virtually all craniofacial structures such as cartilage, bone, ligaments, cranial sutures, musculature, tendons, the periodontium, and the teeth [7]. Mesenchymal stem cells are also self-renewable, making them very preferable for this purpose as well. Dental pulp stem cells are also used, serving as a source of reparative dentin which is used as a protective barrier for the pulp [8]. Stem cells from human exfoliated deciduous teeth and periodontal ligament stem cells can also be used in order to create nearly identical forms of their naturally formed structures [9]. Tissue engineering of the temporomandibular joint from stem cells is also possible [1,7,10–13] as a result and takes place in a similar manner to that of the aforementioned tissues and muscles, with more of an emphasis on cell density in order for the tissues to be properly formed. Another important aspect of craniofacial muscle tissue engineering is gene delivery, which is possible through periodontal tissue engineering, having a primary focus on gene transfer and its main benefits such as stimulation of the tissue engineering of periodontal defects. Focus on the calvarial osteoblast, similar to the focus on the neural crest in order to form multifunctional mesenchymal cells, is necessary in order to generate natural cranial skeletal repair and the specific molecular structures needed to achieve this cranial skeletal formation [4]. Craniofacial tissue engineering is not yet used in contemporary, non-cell-based dental practice therapies, making it an opportunity that will greatly benefit dentistry [7].

Although craniofacial tissue engineering practices are not yet used in contemporary dentistry, a form of muscle tissue engineering that has a more readily accessible application to dental practices is maxillofacial tissue engineering [7]. This is due to the fact that there are great similarities between the skin and oral mucosa, allowing the structure of already existing skin substitute products to be used as templates for oral mucosa applications [14]. These preexisting products have a focus on keratinizing colonies from in vitro cultured epidermal keratinocytes, beginning with the development of an epithelial sheet. Tissue-engineered oral mucosa has already been attempted to be produced, resulting in further improvements in both intraoral and extraoral usages [14]. Plastic compressed collagen has served as the most recent and extensively investigated potential scaffold for skin and oral mucosal grafting, ultimately serving as a template for the unique anatomical and fiber composed characteristics of facial muscles compared to other skeletal muscles. With enough research and testing, the hierarchical structures formed from "ultra-rapid plastic compression" could mimic the complexity stratification and mechanical properties of the natural tissues. Another focus of maxillofacial tissue engineering, similar to that of craniofacial, is the engineering of the temporomandibular joint [14]. Autogenic periosteal cells-seeded polymer fleeces augment the floor of the maxillary sinus prior to implants being inserted, providing beneficial results through histological and radiographical examinations [14]. In addition to this, the most beneficial cell source used for maxillofacial tissue regeneration is autogenic cells; however, it is very difficult to obtain cells from the deceased [14]. Due to the importance of the proliferation and maturation of osteoblasts that are derived from mesenchymal stem cells, autologous platelet gel is used in reconstructive oral and maxillofacial surgery, as well as an adjunctive procedure in the placement of osseointegrated titanium implants. PRP has been successful in maxillary sinus augmentation while inserting endosseous implants, while also producing new bone in as early as 2 months. Bone remodeling is also involved, creating a balance between osteoclasts' ability to resorb, and the osteoblasts' capacity of matrix generation. After these structures are created, the resulting secretions such as osteoprotegerin inhibit and absorb membrane receptors, causing knockouts and stimulating necessary activities such as osteoblast replication and bone collagen degradation [15].

The third essential component of both craniofacial and maxillofacial muscle tissue engineering and regeneration is the formation of the scaffolds used to implant the new cells and structures into the patient. In regard to tissue engineering of a particular cartilage, although implanting artificial matrices, growth factors, perichondrium, and periosteum can initiate the formation of cartilaginous tissue in osteochondral and chondral defects in synovial fluids, the results vary considerably from patient to patient [16]. A successful scaffold is one that fits the anatomical defects defined from clinical imaging data, while also having a design that is porous and that can balance load bearing and biofactor delivery requirements [17–30]. For these designs, the global image design database is created from a computed tomography (CT) or magnetic resonance (MR) image of a patient. The image from the global image design database is necessary in order to create a plan for how to design the porous microstructure of the scaffold to the needs of the body and system that it is entering [31]. An solid freeform fabrication (SFF) system is preferable to have when creating a scaffold [32]; however, polycaprolactone (PCL) scaffolds created directly in a selective laser sintering (SLS) system was created in which the SLS system sinters the PCL particles together [33]. After all of this has been completed and the scaffold has been created, it is important to make sure that the fabricated scaffold matches the designed architecture before testing the permeability and load-bearing capabilities. From here, many hybrid scaffold/biofactor variables can be tested. If the tests are successful, carriers can transport necessary materials and allow bone and muscle tissue regeneration in the patient [34]. As a result, this chapter uses an understanding of facial muscle characteristics, progenitor cells, scaffolds, and vascularization in order to then expand upon the importance of the maintenance of these aspects of cartilage and facial muscle

tissue when they are engineered and regenerated, while providing the optimal biomaterials and techniques necessary to engineer and regenerate these vital components of the mouth.

Facial muscle characteristics

Facial muscle is highly responsible for performing functions such as facial expression. When facial muscle experiences paralysis, the facial expression is impaired which results in physical deformations and distress, as well as social and psychological distress due to the physical deformations and consequent inability to perform basic human facial processes [35]. Facial muscle also works to house salivary glands and adipose tissue. Facial muscle, therefore, aids in energy homeostasis, sexual maturation, and steroid conversion [10]. This muscle also allows the human body to create movement, which is necessary to facilitate the internal transport of materials and reaction to environmental and internal stimuli. This facial muscle within the craniofacial area also works to generate eye and jaw mobility [36]. Going along with this, as a result of housing salivary glands, facial muscle also functions to produce and secrete saliva so that overall oral health can be properly maintained through the functions of the salivary glands [6,37]. Expanding upon this primary function of facial muscle, the production and secretion of saliva play many roles in correspondence with general health and disease prevention. These include dental remineralization, mucosal repair, physical protection, lubrication, mechanical cleansing, and digestion [6]. Facial muscle also assists with innervation and vascularization. This is important to basic human function due to the fact that if a patient has a deformed or injured facial nerve, there is often a fully functional facial nerve that performs the same function on the contra-lateral facial side. The human face contains 23 paired facial muscles and 1 unpaired, the orbicularis oris, which are all unique from other skeletal muscles in that they attach at least one side to the skin, making facial expression possible through this skin movement [38]. Each facial muscle consists of 75–150 muscle fibers [39] arranged in parallel bundles running from origin to insertion [40] and allowing for Type I (slow twitch) and Type II (fast twitch) muscle fibers to be distinguished as well [41]. Slow twitch muscle fibers are able to work for a long time without getting exhausted due to their ability to produce large amounts of energy at a slow pace. Fast twitch muscles have different characteristics than slow twitch, which allow them to perform rapid movements while becoming easily fatigued. The primary characteristic responsible for this is the ability of these fibers to produce small amounts of energy very quickly. Facial muscles are made up of both Types I and II muscle fibers, making their requirements for a proper function different from each muscle as well. The muscles that consist of primarily Type I fibers contain many capillaries and therefore are well perfused and red, making them highly dependent on a rich supply of oxygenated blood. As for muscles made up of primarily Type II muscle fibers, they are highly dependent on anaerobic metabolism, resulting in no rich blood supply being necessary for proper muscle function, making them more white colored as a result as well. An example of such a primarily Type II facial muscle is the zygomaticus minor, which also consists of an intermediate fiber between Type IIA and Type IIB (a subtype II fiber). These oxidative Type IIAB fibers provide a high resistance to fatigue, acting in accordance with the lacking of a firm insertion that is characteristic of facial muscle tissues, allowing for static contraction and a prevention of the development of high tension. This allows blood circulation to not be prevented and for fatigability to be postponed even further [42].

Progenitor cells

Progenitor cells are often used in tissue engineering due to the fact that they harbor a high diffusion capacity. Attesting to their functionality, progenitor cells of skeletal muscle show a high possibility of being able to perform muscular differentiation [43], making them very useful in restoring the highly specific forms and functions of facial muscle. Although they show a high proneness to perform muscular differentiation, the appropriate progenitor cell must be used, especially in muscles such as tissue-engineered facial muscles, which have a great fiber and anatomical composition compared to other skeletal muscle. With any progenitor cell being used for engineering, the cell must be expanded, cultured, and capable of differentiating into the cell types of muscle and facial tissue [43,44]. One of these progenitor cells is the mesenchymal stem cell, which comes from several different sources, each working to harbor myogenic potency. Myoblasts derive from these mesenchymal stem cells (MSCs) with high efficiency. The myoblasts fuse with each other to form myotubes, differentiating into muscle fibers while also consisting of a high proliferation capacity and being capable of self-renewal, making them very suitable as progenitor cells for skeletal muscle tissue engineering [45]. MSCs, besides being self-renewable, have been reported to differentiate into hepatic, renal, neural, and cardiac cells [46–50]. This is significant because stem cell populations that generate native craniofacial structures are heterogeneous and therefore most likely contain mesenchymal and hematopoietic stem cells [51]. Size-dependent sieving of a cell population from MSCs acquired from human bone marrow through a porous membrane has resulted in a mostly homogeneous population, which has the ability to perform multi-lineage differentiation and self-renewal. Necessary host cell invasion and stem cell homing are very likely inevitable when applied to porous

biomimetic scaffolds being used as carriers for delivering stem cells [7]. Although MSCs acquired through bone marrow are beneficial for the previously mentioned reasons, the fact that myogenic lineage induction in MSCs is an additional differentiation step, as well as the fact that it is a relatively invasive procedure for the patient [52]. By comparison, skeletal muscles harbor their own endogenous organ-specific MSCs (satellite cells). These satellite cells are already prone to myogenic differentiation and are more suitable for skeletal muscle TE as a result [52]. These are also very beneficial due to the fact that myogenic satellite cells start to proliferate in response to specific local challenges such as muscle damage [52]. The myogenic satellite cells migrate through the basal lamina sheets to the areas of injury and then differentiate into myoblasts and fuse with the preexisting damaged fibers or with each other in order to differentiate into muscle fibers. Failure to fuse either to the damaged fibers or to each other results in dedifferentiation back to quiescent satellite cells [45]. Muscle tissue is propagated in vitro, making the harvesting of myogenic satellite cells from this tissue accessible and consequently easy. Differentiation processes toward myofibers are difficult to control and induce in vitro, while the predetermination of satellite cells is also preserved in vitro. Facial muscles contain satellite cells with unique abilities such as resistance to apoptosis, while also being present in a higher quantity. The resistance to apoptosis makes facial muscles more favorable for TE than other derived satellite cells as well [53].

Scaffolds

The most important part of a scaffold being used for any tissue engineering and regeneration is the design [54–61]. One of the most guaranteed ways to ensure that the design of the scaffold will fit the needs and anatomical design of the affected area is to use clinical imaging data that will define the shape of the anatomical structure in combination with a global and local image database that consists of many different templates for the scaffold design [62,63]. Within the database is different structures for each porous scaffold design, varying from the nanometer to the centimeter scale [64,65]. The patient-specific images are taken from either a CT or MR image of the individual and the local image design is then determined. The density of the region is determined on a scale ranging from 1 to 255. Once the density and image design are gathered, the reconstruction region and a heterogeneous region intended for the purpose of designing a proper microstructure are designated. After this, load-bearing demands are determined and taken into consideration for the design along with porosity [34,66]. In addition to all of this, scaffolds must also contain a high elastic modulus in order to properly regenerate and fix ductile and hard tissues, while also being able to maintain the space that they were designed for and allowing enough room for growth [67]. Going along with the previously mentioned load-bearing capabilities of a scaffold, scaffolds must be designed so that if it is intended to be used as a temporary load-bearing device, that its properties must be so that the scaffold shows no signs of failure, degeneration, or fatigue before the required load-bearing time has expired [16]. Another highly important aspect of scaffolds is the way in which they are fabricated. Scaffolds are very complex 3-D structures, and therefore require materials that have a largely varying range of material properties [27,68–71]. The image-based design technique is too complicated for the scaffolds to be made by polymer processing techniques or machining, so one method of fabricating these scaffolds is either direct or indirect Solid Free-Form Fabrication (SFF) [72,73]. Direct SFF fabricates its scaffolds by using an additive layer-by-layer process to build either a mold for a biomaterial casting or the biomaterial scaffold itself [73]. Indirect SFF is simply taking the fabricated mold and casting a biomaterial into it [73]. The most commonly used biomaterials for this purpose and throughout these two different types of SFF is PCL, polyglycolic acid (PGA), HA/TCP composites, polylactic/polyglycolic acid copolymers (PLGA), polycaprolactone (PCL), and polypropylene fumarate/tricalcium phosphate (PFF/TCP). These biomaterials have been used to build composite material and local/global porous scaffolds, as well as optimized designs [34]. Whatever process is used to fabricate a scaffold, it must be able to process bioresorbable and biodegradable materials so that they can form a scaffold with a large surface area and high porosity. 3-D printing (3-DP) and fused deposition modeling (FDM) are two examples of rapid prototyping technologies that allow for the creation of scaffolds that are porous and are able to copy living tissue's microstructure [23]. 3-DP allows for the processing of bioresorbable scaffolds for applications relating to tissue engineering specifically [74]. The FDM process is nearly identical to the SFF process, with the addition of toolpaths and extrusion heads that work on a platform working in the X and Y axes with a platform lowering in the Z axis so that layer-by-layer formation is possible [75].

The design and fabrication of scaffolds are highly specific processes, but for a very good reason. The reasoning derives from the fact that the extracellular matrix (in vivo) of muscles is what allows muscle fibers to have the architecture, which makes it possible for them to aid in function and support. The extracellular matrix (ECM) therefore must be able to be mimicked by a scaffold when repairing damaged areas in the mouth so that differentiation and proliferation of progenitor cells can be supported properly [76]. This is all so that the tissue engineering of functional skeletal muscles can be properly formed. As it was previously mentioned, different scaffolds with different functions require different physio-

chemical compositions and features. In addition to this, their biological characteristics must also be taken into consideration in regard to their specific form and function as well. Although non-biodegradable scaffolds are considered to be optimal by some, biodegradable scaffolds are much more practical in regard to facial muscle tissue and repair due to the fact that their degradation allows for the natural muscular ECM to be almost exactly remodeled [77]. Although many polymers have been used in the creation of synthetic biodegradable 3-D scaffolds, the most useful polymer seems to be polylactic-co-glycolic acid (PLGA) [78]. This is used to make fiber mesh sheets that have been proven to provide appropriate connection and strength to withstand the different needs and loads that the scaffolds need to bear, while also allowing for progenitor cells to proliferate properly, contributing to the mimicking of the ECM and eventual formation of the tissue engineering of functional skeletal muscles [79]. Microscale and nanoscale topographic features allow for alignment of myoblasts and cytoskeletal proteins, promoting myotube assembly following the microgrooves and nanofibers to mimic myotube organization in muscle fibers. This allows the functional skeletal muscle to form. Myoblast proliferation during cell fusion and differentiation is also prevented as a result, myotube striation is enhanced, and cell spreading is restricted [80]. Natural biodegradable 3-D scaffolds are less preferable due to the fact that they are extremely fragile and difficult to handle, especially when made of acellular muscle ECM. Natural biodegradable scaffolds (such as collagen) also have aligned myoblasts and cytoskeletal proteins resulting from aligned topographic features [35].

Although they are not preferable, naturally degradable scaffolds still have their benefits. When fibrin is used in combination with a growth medium as a natural biodegradable scaffold, fibrin and thrombin form a fibrin gel. ECM proteins are then formed by muscle progenitor cells and replace the original fibrin matrix in 3–4 weeks [81]. This is significant because myoblasts grow and spread more readily in fast degrading gels [82]. The fibrin forms a scaffold that temporarily facilitates tissue regeneration, making this process very similar to wound healing. After this wound healing process is complete, the physiological ECM replaces the fibrin. Differentiation into muscle fibers is enhanced by the in vitro seeding of myogenic progenitor cells on a scaffold as well [81], making any of the aforementioned scaffolds beneficial in this regard. Taking all of this into consideration, it is reasonable to conclude that by combining parallel alignment, fibrin, and cell sheet techniques, the ideal scaffold for skeletal muscle can be formed and the in vitro seeding of progenitor cells can be applied to these scaffolds, resulting in an ideal formation of facial muscle tissue [83].

Vascularization

Making sure that the created tissues have proper vascularization is a very important step when planning cartilage and tissue generation since the mucosa of the mouth has mare blood vessels and is thinner than external skin. This mucosa of the mouth is also required to provide an atmosphere that is constantly moist on its surface with the help of salivary and mucous glands, while also lacking hair, sebaceous glands, and sweat glands [84]. Blood vessel ingrowth and the extent and optimization of its rate is also very important when planning out tissue regeneration techniques and methods as well. Angiogenesis is the optimal method for ensuring that the formed blood vessels are identical to the original or nonexistent, natural blood vessels. Vascular endothelial growth factor (VEGF) has been tested and observed to be potentially angiogenic in vivo, making it an ideal candidate to be delivered in a controlled manner to the oral cavity and its affected tissues through scaffolds [85]. This delivery would greatly influence angiogenesis [86]. Proper vascularization is vital to the formation as well as the maintenance of the bone, cartilage, and tissues within the oral cavity [1]. Being highly specific and vital to the growth and survival of bone and bone tissue, vascularization of implanted scaffolds is a process that has already undergone extensive research. Vascularization is especially necessary when planning the creation of skeletal muscle from tissue engineering since the myoblasts can neither differentiate nor proliferate when greater than 150 μm from both an oxygen supply and a nutrient source [87]. This is significant considering that the efficient transport of nutrients, waste products, oxygen, and carbon dioxide through being connected to a muscle construct takes place in muscle that is thicker than 300 μm [35]. Therefore, the integration of a vascular system is necessary in order to create a functional tissue that is inherently thicker. Pre-vascularized skeletal muscle constructs from cultures of myoblasts, implantation in vivo of muscle constructs, engineered skeletal muscle constructs, and fibrin gel being placed around a preformed ectopic arteriovenous are all techniques that have been tested and proven as successful in rats [88], making it apparent that the previously mentioned cell sheet practice over scaffolds holds a large amount of potential in relation to the concerted vascularization of muscle constructs. It was found that if neovascularization does, in fact, result from this process, new cell sheets can be applied in layers after neovascularization has already occurred on the previous layers of cell sheets [89]. After this, the required thick muscle tissue with vessels that are able to connect is formed. Although this process has not been used to create skeletal muscle, the aforementioned combination of techniques together with a layer-by-layer polysurgery technique and a fibrin coating would make its creation possible for human use in the development of skeletal/facial tissue [89].

Conclusion

Taking all of this into consideration, one can see how when the proper technique is used in combination with the most advantageous biomaterials, cartilage, and facial muscle tissue engineering and regeneration become possible and highly beneficial processes that will allow individuals to live healthier and more practical lives. This is due to the fact that the most properly functional biomaterials and techniques mentioned in this chapter, work in combination with each other in order to allow homeostasis of the oral cavity to be maintained through proper engineering and regeneration of cartilage and facial muscle tissue. The proper engineering and regeneration of these materials result from a complete understanding of facial muscle characteristics, progenitor cells, scaffolds, and vascularization, both for these aspects individually as well as when they are working in coordination with one another. Among the four aforementioned points of focus of this paper, there is not one point of focus that outweighs any of the others due to the fact that all must be replicated and reproduced in a way that allows for a function that is identical to that of the natural cartilage and facial muscle tissue of humans. All must properly work in concert with one another in order for homeostasis to be maintained, for nutrients, waste products, oxygen, and carbon dioxide to be transported efficiently, and for overall oral health and function to be completely restored to the patient. This all becomes possible when the proper biomaterials are used alongside the proper techniques in order to ensure exact replication, function, and overall health within the previously damaged part(s) of the mouth.

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