Advances of adipose-derived mesenchymal stem cells-based biomaterial scaffolds for oral and maxillofacial tissue engineering

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\textbf{ABSTRACT}

The management of oral and maxillofacial tissue defects caused by tumors, trauma, and congenital or acquired deformities has been a major challenge for surgeons over the last few decades. Autologous tissue transplantation, the gold standard of tissue reconstruction, is a valid method for repairing the oral and maxillofacial functions and aesthetics. However, several limitations hinder its clinical applications including complications of donor sites, limited tissue volume, and uncertain long-term outcomes. Adipose-derived mesenchymal stem cells (ADMSCs) widely exist in adipose tissue and can be easily obtained through liposuction. Like the bone marrow-derived mesenchymal stem cells (BMSCs), ADMSCs also have the multi-pluripotent potencies to differentiate into osteoblasts, chondrocytes, neurons, and myocytes. Therefore, the multilineage capacity of ADMSCs makes them valuable for cell-based medical therapies. In recent years, researchers have developed many candidates of ADMSCs-based biomaterial scaffolds to cater for the needs of oral and maxillofacial tissue engineering due to their superior performance. This review presents the advances and applications of ADMSCs-based biomaterial scaffolds, and explores their tissue engineering prospects in oral and maxillofacial reconstructions.

\section{Introduction}

Defects of the soft and hard tissues in the oral and maxillofacial region severely impair oral functions and cosmetic appearance, thereby causing several dilemmas in treatment [1–4]. Over the past few decades, autographs have been considered as the gold standard for tissue reconstruction [2]. However, drawbacks such as the morbidity of the donor site and the limited number of transplanted tissues, have contributed to its limited clinical application [3–7]. This has led to numerous attempts such as allografts, xenografts, and synthetic substitutes, being investigated by researchers and clinicians. Nevertheless, none of these methods can solve the problem due to various limitations associated with the methods. Therefore, tissue engineering, which provides an alternative approach, has continued to draw the researchers’ attention.

Current tissue engineering strategy utilizes living cells, biomaterials, and appropriate biochemical, physical factors, and the combinations to create tissue-like structures. The ultimate goal of the method is to incorporate these tissue-like structures into the body in order to repair the damage or replace dysfunctional organs [2]. Early tissue engineering application involved the use of mesenchymal stem cells (MSCs) for tissue homeostasis and the regeneration in oral and maxillofacial regions due to their self-renewal ability and pluripotent differentiation [4]. Bone marrow-derived mesenchymal stem cells (BMSCs) are considered to be the most frequently studied MSCs in tissue engineering. However, their clinical application is limited by the low extraction yield and number of BMSCs, the need for in vitro culture expansion, sensitivity to senescence, cost, and the loss of proliferative and differentiation ability during cell culture.

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expansion [8,9]. When compared with the BMSCs, evidence from both in vitro and in vivo studies have suggested that adipose-derived mesenchymal stem cells (ADMSCs) have the potential to differentiate into mesenchymal (such as adipocytes, osteocytes, and chondrocytes) and non-mesenchymal (such as neuron-like cells) cells [4,5]. With regards to the growth cycle of ADMSCs, despite their low proliferation and apoptosis rates in vitro, it is easy to obtain a high stem cell-to-volume ratio, low sensitivity to aging, and easy harvesting. Previous studies have reported that the content of ADMSCs is highly abundant in the stromal vascular fraction (SVF) [10–12]. In addition, ADMSCs within the SVF show high attachment rate to scaffold material, proliferate rapidly, and could differentiate into the osteogenic lineage [11]. In recent years, the application of biomaterial scaffolds based on ADMSCs has gradually become a hot topic.

The main aim of this review is to present and discuss the advancement of the application, vascularization, and tissue regeneration of ADMSCs in the oral and maxillofacial region. Moreover, we propose functional design and development of ADMSCs-based biomaterial scaffolds in oral and maxillofacial tissue engineering, which could lead to a feasible clinical application.

2. Adipose-derived mesenchymal stem cells

ADMSCs are multipotent stem cells which have an undifferentiated immunophenotype, with the potential for self-renewal and multipotency properties [13–16,25]. Therefore, ADMSCs can differentiate into several cell types including osteoblasts, chondrocytes, neurons, myocytes, endothelial cells, fat precursor cells, and myocardial cells [17–20]. In addition, ADMSCs can secrete a large number of anti-inflammatory proteins in response to inflammatory reactions including tumor necrosis factor-α (TNF-α), interleukin-4 (IL-4), IL-6, IL-10, and IL-1 receptor antagonist. These cells ADMSCs can also produce a variety of growth factors such as transforming growth factor-β1 (TGF-β1), hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), and stromal cell-derived factor-1 (SDF-1), which contribute to tissue remodeling, angiogenesis, and antiapoptotic events [18–22]. Moreover, ADMSCs could modulate immune response by preventing the immune cells from proliferating and functioning, such as T cells, B cells, macrophages, monocytes, and natural killer cells [21].

The study of ADMSCs in tissue engineering field has yielded promising results. In recent decades, Marta et al. [14] and Mario et al. [23] demonstrated that ADMSCs could be applied in musculoskeletal disorders and cartilage disorders such as osteoporosis, osteonecrosis, fractures, osteoarthritis, and cartilage lesions. On the other hand, Yang et al. [13] preclinically assessed the safety and efficacy of ADMSCs in vitro and in BALB/c-nu nude mice models. On this basis, this led to the application of ADMSCs to patients with knee osteoarthritis, where they improved the knee joint pain, function, and cartilage volume in the recipients. Meenakshi et al. [24] reported that ADMSCs could be used to treat what disorders, combat aging through dermatological rejuvenation and promote wound healing. Furthermore, Maryam et al. [26] showed regulatory effects of the ADMSCs on inflammatory responses and effective control over the immune response in treating colitis of a murine model. In the treatment of renal lesions, Wang et al. [15] reported that ADMSCs could restore the impaired cell regeneration and remodeling, which prevent further worsening of renal disease and even block or reverse renal fibrosis processes. In the oral and maxillofacial region, Massoni et al. [22] demonstrated the osteogenic differentiation potential of ADMSCs and applied ADMSCs/Hydroxyapatite-collagen hybrid scaffold to patients who wanted to optimize facial esthetics. All the above-mentioned studies indicate that ADMSCs, as pluripotent stem cells, has been widely used to address several medical issues and have so far yielded satisfactory therapeutic effects to an extent, especially in the oral and maxillofacial regions. The application of ADMCS in the oral and maxillofacial regions would be introduced in detail as follow.

3. Biomaterial scaffolds combined with ADMSCs for oral and maxillofacial regeneration

Soft and hard tissue defects in the oral and maxillofacial region severely impair oral functions and cosmetic appearance, thereby causing several dilemmas in treatment [27,29]. Tissue engineering is an alternative approach which has been the subject of growing interest from researchers due to the limitations of autologous tissue transplantation. Although the function of ADMSCs has been widely proven, ADMSCs alone cannot achieve good results in tissue engineering [30–32]. Previous studies have reported that random cell migration reduces the concentration of cells at target site, thereby hindering the efficacy of cell-based tissue regeneration [31,32]. The other aspect of tissue engineering involves scaffolds, a cell attachment skeleton structure. Scaffold influences the effect of ADMSCs in tissue engineering based on their strength, porosity, biodegradability, biocompatibility, and support for cell adhesion, differentiation, proliferation, and growth [33]. A recent study reported that 3D structured scaffolds can be tailored with specific porosity, surfaces, and pore connectivity to optimize the cellular adhesion and migration, and nutrient transportation [34]. These 3D scaffolds could provide physical, chemical, and mechanical maintenance for extracellular matrix (ECM) formation in vitro, and control degradation, reabsorption, and metabolism in vivo [36–38]. Moreover, scaffolds with open and interconnected pores are conducive to the growth, proliferation, and migration of cells. They also promote tissue vascularization and the formation of new tissues to some extent. Scaffolds play an important role in tissue engineering because they are used as carriers for the transport, enrichment, and maintenance of ADMSCs [33–35]. Moreover, cells-based biomaterial scaffolds show a cooperative relationship and are currently the mainstream in tissue engineering. In this review, we summarized the biomaterial scaffolds that have been combined with ADMSCs in oral and maxillofacial regeneration (Table 1). In oral and maxillofacial regeneration, these biomaterials could be used independently with severe complications, while they are more widely used in the form of composite materials through specific integration. These composites are designed to achieve synergy by combining the corresponding properties. The application of bioactive materials which combined with ADMSCs in oral and maxillofacial regeneration would be introduced in detail as follow.

3.1. Bioceramics

Bioceramics includes tri-calcium phosphate (TCP), hydroxyapatite (HA), and their composites. Besides, the combination of bioceramics and natural or synthetic polymers extensively exists. Generally, in the oral and maxillofacial region, bioceramics is commonly used in the engineering of bone tissues such as in orthopedic and oral and maxillofacial surgery [36–39]. TCP is characterized by its biocompatibility, compressive mechanical property, and degradation when compared with other bioceramics, which makes it quite distinct for hard tissue regeneration [40]. However, pure bioceramics is brittle and the structure lacks interconnected pores, which are required for a better cell proliferation and migration. Thus, the application of pure bioceramics is relatively limited [40,41]. Nevertheless, bioceramic scaffolds containing natural or synthetic polymers are more desirable because their improved mechanics with osteoinductive properties are more conducive for oral and maxillofacial regeneration [41].

3.2. Non-collagenous proteins

Previous study reported that growth factor delivery (GFD) is important in mediating the micro-environment of scaffolds and subsequent cellular responses [42]. Growth factors (GFs) are soluble polypeptides that affect cellular function and bind to cell membrane receptors. Several studies have used osteo-inductive-/conductive factors (BMP, TGF-β, etc.) to guide cell differentiation and tissue formation in
bone regenerative therapies [43–47]. Similarly, vascularization is critical for the sustainability of newly formed tissues, and it requires the addition of angiogenic GFs, such as platelet-derived growth factor (PDGF), VEGF and so on [48]. Different from injecting therapeutic factors into the defect site, scaffold-based GFD has several advantages including improved control over GF release kinetics and localization factors into the defect site, scaffold-based GFD has several advantages addition of angiogenic GFs, such as platelet-derived growth factor (PDGF), VEGF and so on [48]. Different from injecting therapeutic factors into the defect site, scaffold-based GFD has several advantages including improved control over GF release kinetics and localization of new tissues, and it requires the addition of angiogenic GFs, such as platelet-derived growth factor (PDGF), VEGF and so on [48].

3.4. Natural and synthetic polymers

To date, several researches have focused on the design of implantable scaffolds consisting of synthetic or natural polymers with predefined shapes and volumes [64]. Cellulose and its derivatives, alginates (such as poly(anionic co-polyacrylamides), agarose derivatives, etc.), chitosan, hyaluronate, fibrin, fibronectin, collagen, gelatin, and its derivatives are mainly used in the bone regeneration of natural polymeric materials [65–70]. The biological agents can be added through gel formulation because natural scaffold materials are commonly used in gel-like phases [71]. Among them, collagen is the most widely used in tissue engineering. Collagen is the main structural protein in mammals which is widely distributed in the body, and is one of the main components of the ECM [72]. Collagen exhibits high tensile strength, which makes it an essential structural factor in providing mechanical strength to hard tissues [73]. In addition, it contains ligands that promote cell attachment and thus it influences cell migration and differentiation [74].

On the other hand, synthetic polymers are an attractive alternative

### Table 1

| Study, Year | Target Tissue | Cells | Material of a Scaffold | Types of materials |
|-------------|---------------|-------|------------------------|------------------|
| Tobita et al., 2009 | Periodontal | ADMSCs | platelet-rich plasma (PRP) | Biologicals |
| Tobita et al., 2013 | Periodontal | ADMSCs | platelet-rich plasma (PRP) | Biologicals |
| Wu et al., 2016 | Periodontal | ADMSCs | Amniotic membrane (AM) | Biologicals |
| Requicha et al., 2014 | Periodontal | ADMSCs | The double-layer scaffolds were prepared from a blend of starch and poly (ε-caprolactone) (SPCL). | Biologicals |
| Sun et al., 2011 | Facial nerve | ADMSCs | Decellularized artery allograft | Biologicals |
| Ghoreishian et al., 2012 | Facial nerve | ADMSCs | Gore-Tex tube | Polymers |
| Watanabe et al., 2014 | Facial nerve | ADMSCs | A silicone tube with a type I collagen scaffold | Polymers |
| Han et al., 2015 | Adipose tissue | ADMSCs | Decellularized adipose tissue (DAT) scaffold | Polymers |
| Venugopal et al., 2017 | Adipose tissue | ADMSCs | bovine type I collagen sponge | Polymers |
| Mauney et al., 2007 | Adipose tissue | ADMSCs | Aquous (AR) and 1,1,3,3,5,5-hexafluoro-2-propanol (HFIP)- based silk fibroin 3-D scaffolds | Polymers |
| Lin et al., 2008 | Adipose tissue | ADMSCs | The scaffold was made of gelatin sponges, polyglycolic acid meshes, and polypropylene mesh. | Polymers |
| Probst et al., 2020 | Bone | ADMSCs | TCP-PLGA scaffolds | Bioeramic |
| Metim et al., 2009 | Bone | ADMSCs | microvascular flap, beta-tricalcium phosphate and bone morphogenic protein-2 | Bioeramic |
| Kang et al., 2011 | Bone | ADMSCs | a mixture of fibrin and hyaluronic acid (HA) and BMP-2 | Bioeramic |
| Lendeckel et al., 2004 | Bone | ADMSCs | autologous fibrin glue | Polymers |
due to the risks of immune rejection, clotting, or tissue hypertrophy, which are as a result of tissue-derived products. The molecular weight, molecular weight distribution, mechanical properties, and other physical properties can be customized. However, the major challenge is designing 3D architectures with clear porosity and customized surfaces to fit specific requirements for cell adhesion [75]. The synthetic scaffold materials for bone tissue engineering are mainly polyesters, with the most common being polyactic acid (PLA), polyglycolic acid (PGA), and polycaprolactone (PCL) [76–78].

Ceramic-polymer composites are synthesized by embedding ceramic particles into the polymer matrix and exposing them to the surface to enhance the bone conduction effect. The mechanical properties are mainly affected by the particle size of calcium phosphate and its distribution in the polymer matrix. One study reported that the stiffness of the composite increases as the particle size decreases [79]. Bioceramic scaffolds composed of biodegradable polymers such as poly (lactic acid-glycolic acid) (PLGA) have recently been developed with the overarching goal of improving the mechanical stability and tissue interaction [80]. In addition, recent studies have combined electrophoretic spinning with melting to generate a hierarchical PCL/HR-TCP scaffold embedded with collagen nanofibers [80,81]. The scanning electron micrograph of the obtained structure indicated that there are evenly distributed polyacrylamide (PCS) particles in the polycrylamide (PCL) struts, and the collagen nanofibers between the composite struts were well layered. Thus, the combination of collagen nanofibers and TCP provides a synergistic cell-related effect.

The polymers are usually biocompatible and most are bioresorbable. The development of injectable biomaterials such as hydrogels, particles, and microcarriers, which can provide more minimally invasive strategies for strengthening hard and soft tissues in the clinic, is also included in this application [84].

Recently, scholars have also made significant progress in the research of biomaterial scaffolds in order to adapt to the rapid development of tissue engineering. As mentioned above, numerous attempts such as mechanically-competent, tissue-specific, and multiphasic 3D scaffolds have been utilized in tissue engineering [39].

4. **ADMSCs-based biomaterial scaffolds for oral and maxillofacial tissue engineering**

ADMSCs are characterized by their highly homogeneous (high purity) cell population which is highly proliferative. In addition, ADMSCs have a multilineage potential under appropriate in vitro and in vivo conditions to differentiate into different cell types including osteoblasts, chondrocytes, neurons, and adipocytes. The advantage of using ADMSCs in vivo for bone, periodontal tissue, tooth, peripheral nerve, and soft tissue regeneration has been documented in several animal models (Table 2). Therefore, the use of ADMSCs seems to be a promising cell source for oral and maxillofacial tissue engineering. Fig. 1 illustrates the isolation of ADMSCs from adipose tissue and the development of ADMSCs/biomaterial for repairing oral and maxillofacial soft and hard tissue defects.

4.1. **ADMSCs-based biomaterial scaffolds in the treatment of cranio-jaw regeneration**

The basic requirement for tissue-engineered bone graft is the ability to integrate with the host organization, as well as provide and reconstruct bearing capacity. The ideal scaffold-stem cells compounds should simulate the induction of the natural bone structure or bone formation, and should include a variety of growth factors and cytokines in order to provide space for blood vessel formation. In addition, the transplantation of metabolites, degradation products, and harmless products, and the release of bioactive substances in the face of the host are shown in Fig. 2.

Several studies have proved the in vitro osteogenic potential of ADMSCs in oral and maxillofacial regions [86]. Therefore, many laboratories have begun to seed osteogenic differentiated ADMSCs on different biomaterials and scaffolds in order to develop the potential for tissue-engineered bone repairs. Cowan et al. [49,50] investigated the in vivo osteogenic capacity of ADMSCs in the treatment of skull defects in rats. The obtained results indicated that the skull defects produced obvious intramembrane bone formation after two weeks through the implanted pure ADMSCs, apatite coating, and ADMSCs/PLGA scaffolds. Moreover, X-ray examination, histology, and live micromolecular imaging results indicated that the bone bridges were completely formed at 12 weeks. The ADMSCs/biological scaffolds have since been used by another laboratory for clinical applications. Lendeckel et al. [76] combined ADMSCs with autologous fibrin glue and used it in a 7-year-old girl suffering from extensive cranial defects to repair skull defects. The postoperative course was uneventful, and the obtained CT-scans revealed new bone formation and near-complete continuity of the skull three months after the reconstruction.

In addition to repairing skull defects, there are many instances where ADMSCs/biological scaffolds have repaired maxillary and mandibular defects. Mesimaki et al. [74] completed maxillary reconstruction with a vascular flap using auto ADMSCs, TCP, and BMP-2. The donor flap had developed new bone structures and vasculature after eight months of follow-up, and was transplanted into the defect area. On the other hand, Mehrabani et al. [78] subsequently combined ADMSCs with fibrin glue scaffold and applied it to repair mandibular defects in rabbits. The obtained results indicated that the therapeutic effect of ADMSCs in conjunction with fibrin glue was similar to those of autologous bone graft, and the effect of ADMSCs/fibrin glue on bone formation was greater than that of fibrin glue alone. In addition, ADMSCs with TCP are widely used in bone regeneration to facilitate the formation of the bone extracellular matrix, thereby promoting reparative osteogenesis. Probst et al. [86] reported that ADMSCs seeding on ceramic and polymer composite scaffolds improves bone regeneration in large mandibular defects.

The oral and maxillofacial region is a complex system with the mutual attachment of hard and soft tissues. The displacement of the remaining jaw bone wound leads to facial deformities and dysfunction due to muscle contraction. As mentioned above, the ADMSCs used for the reconstruction of oral and maxillofacial hard tissue are usually combined with biomaterials possessing good mechanical properties such as bioceramics or bioceramics-collagen composites. Therefore, they can integrate ADMSCs with the host organization and fight with the pressure from muscles.

4.2. **ADMSCs-based biomaterial scaffolds in the treatment of periodontal tissue regeneration**

As the supporting tissue of teeth, the periodontal tissue is composed of the pericementum, alveolar bone, and gingiva. The gingival connective tissue is attached to the upper part of the alveolar bone, while the root of the tooth is connected to the alveolar bone through the periodontal ligament. Therefore, excessive growth of gingival fibroblasts can easily lead to defect of the periodontal tissue [45]. Traditional treatments for periodontal tissue regeneration include bone grafting, guided tissue regeneration, and the application of enamel matrix derivatives through basic research and clinical experience. However, it is difficult to completely reconstruct the periodontal tissue due to the limited regeneration ability once damaged [92]. Therefore, the application of ADMSCs-based biomaterial scaffolds for guided periodontal tissue regeneration is considered as the treatment of choice due to the excellent characteristics of ADMSCs (Fig. 2).

The application of ADMSCs-based PRP composite material has been reported in periodontal tissue engineering. Many scholars have applied ADMSCs/PRP in vivo to demonstrate that PRP could be a promising component for tissue engineering. Tobita et al. [83,99,100] applied ADMSCs/PRP to rat and canine periodontal defect models and
Tobita et al., 2008  
ADSCs isolated from Wistar rats  
platelet-rich plasma (PRP)  
48 10-week-old inbred male Wistar rats in two groups: controls and PRP groups  
Periodontal tissue defects were created with a 1/101 mm defect, respectively.  
PRP gels containing stem cells such as ASCs could be useful clinically for periodontal tissue regeneration.  

Tobita et al., 2013  
ADSCs isolated from inguinal fat pads of beagle dogs  
platelet-rich plasma (PRP)  
9 or 10 months old beagle dogs (mean weight 8–10 kg) (n = 8) in three groups: ASC/PRP gel or PRP gel alone was implanted into the periodontal tissue defect in each dog bilaterally. Non-implantation sites were also prepared.  

Wu et al., 2016  
Human ADSCs were isolated from infrapatellar fat pad  
Amniotic membrane (AM)  
Male Sprague-Dawley rats (body weight 80–100 g) were divided into four groups, including control, ADSCs, AM, and ADSCs and AM ocular system groups.  
Extract the right maxillary first molar (M1) and fill with newly formed bone. 3 weeks after M1 extraction in terms of creating a two-wall intrabony defect (2.0 ± 0.2 mm) / AM was used to reconstruct ocular surfaces or cover the wounds clinically. The strong elastic properties make it an ideal scaffold for surgical repair of a bone defect and tissue engineering.  

Requicha et al., 2014  
ADSCs were isolated from subcutaneous abdominal tissue of adult healthy dogs  
The double-layer scaffolds were prepared from a blend of starch and poly(E-caprolactone) (SPCL).  
Four groups: APL membranes with non-patterned (SPCL-NP) or patterned (SPCL-P). SPCL wet-spin fiber mesh used non-functionalized with silanol groups (SPCL-WS) or functionalized with silanol groups (SPCL-WS-Si).  
The method achieved satisfactory regenerative outcomes approaching those achieved with SC-seeded artery conduits at week 8  

Sun et al., 2011  
Autologous transdifferentiated ADSCs from visceral fat in rats  
Decellularized artery allograft  
60 young female Sprague-Dawley rats (weighing 100–120 g) randomly divided into 6 groups: artery conduit, artery + ADSCs, artery + dADSCs, artery + SCs, nerve autografting, sham operation  
under a surgical microscope the shaved facial skin was opened with a presaccular incision on the left side to expose the buccal branch of the facial nerve hair over zygomatic arches and presaccular area of the 2 sides was shaved; after pepping and draping, an incision 4 cm long was made over the midportion of the arch; the frontal branch of facial nerve was transected; gap size 7 mm  

Ghorbani et al., 2012  
Undifferentiated MSCs extracted from autogenous adipose tissues from mongrel dogs  
Gore-Tex tube  
7 mongrel dogs subjected to nerve bilateral transaction; in 4 animals the left nerve was repaired using ADSCs in 3, stem cells were used on the right side  
Addition of stem cells in Gore-Tex tube enhanced neural repair from a functional standpoint; for better functional and histologic results, differentiated SCs and other mediators may be warranted.  

Watanabe et al., 2014  
ADSCs were isolated from Lewis rats and were cultured into uADSCs and dADSCs  
A silicone tube with a type I collagen scaffold  
Male syngeneic Lewis rats aged 8 weeks were divided into five groups: Undifferentiated ASCs (n = 16), dADSCs (n = 16), SCs (n = 16) and collagen gel alone as a negative control (n = 16) were transplanted into the gap in the buccal branch of the left facial nerve. Autologous nerve graft transplantation (n = 13) was used  

Han et al., 2015  
ADSCs were isolated from male Wistar rats  
Decellularized adipose tissue (DAT) bioscaffold  
In each rat, one seeded and one unseeded DAT scaffold was carefully inserted and the small incisions (~1 cm) were made on the back of each rat and two separate subcutaneous pockets  
Adipose-derived ECM bioscaffolds provide an interesting model system for probing cellular interactions (continued on next page)
PRP prevented gingival invasion when compared with the control two months of implantation. The obtained results indicated that the group. The biological effects of activated PRP may also influence

| Study, Year | Cell Source and Type | Biomaterial Scaffold | Donor and Host Animal | Site of Injury | Regeneration Advantage Conferring Over Vehicle |
|-------------|----------------------|----------------------|-----------------------|---------------|------------------------------------------------|
| Venugopal et al., 2017 | ASC’s were isolated from the subcutaneous fat pad of male Sprague Dawley rats | bovine type I collagen sponge | Sprague Dawley rats (n – 6) of weight 190–210 g for a period of 21 days | Two separate small skin incisions on the dorsal side were making in each rat. | bovine type I collagen provides its physicochemical properties and cyto-compatibility |
| Mauney et al., 2007 | hMSCs and hASCs were obtained from male donors ≤ 25 years of age. | Aqueous (AB) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP)-based silk fibroin 3-D scaffolds | Athymic nude male rats (RI-mu, 300 g each) for a period of 4 weeks | Scaffolds were individually implanted into bilateral muscle pouches within the rectus abdominus muscles of athymic nude male rats (RI-mu, 300 g each) and maintained there for 4 weeks. None of the scaffolds served as negative controls and were treated similarly. | The slow degradation and mechanical integrity of silk scaffolds in comparison with other conventional biomaterials such as collagen and PLA, especially for long-term in vivo studies, suggest that silk fibroin-based scaffolds would be an efficient biomaterial for long-term adipose tissue growth and function. |
| Lin et al., 2008 | hAD-MSCs were isolated from abdominal subcutaneous adipose tissue excised from the transverse rectus abdominis myocutaneous flap for breast reconstruction | The scaffold was made of gelatin sponges, polyglycolic acid meshes, and polypropylene mesh. | Female immunodeficient mice (4 weeks of age). Group I (n = 2) was injected with MSCs only, Group II (n = 2) was implanted with scaffolds only, and Group III (n = 8) was implanted with scaffold-MSCs treated in adipogenic medium for 2 weeks. | Scaffolds were implanted individually into the subcutaneous pockets in the backs of female immune-deficient mice. | All of the successfully harvested scaffolds were filled with newly formed adipose tissue and had retained their predetermined shape and dimensions. |
| Probst et al., 2020 | ASCs were isolated from pigs | TCP-PLGA scaffolds | Sixteen skeletally mature miniature pigs were divided into two groups: Control group and scaffolds seeded with osteogenic differentiated pADSCs (n = 8/group). | mandibular critical size defects | Tri-calcium phosphate (TCP) bioceramics are quite distinct for hard tissue regeneration due to their biocompatibility, degradation and new bone formation. |
| Mesim et al., 2009 | autologous ASCs | microvascular flap, beta-tricalcium phosphate and bone morphogenetic protein-2 | The patient underwent a hemimaxillectomy | maxilla | The heming capacity of the ASCs and the osteoconductivity of the betaTCP act synergistically towards producing a well-osseified construct |
| Kang et al., 2011 | Human ASCs were obtained by liposuction from informed and consenting patients | a mixture of fibrin and hyaluronic acid (HA) and BMP-2 | Six-week-old female athymic mice were divided into four groups: Undifferentiated ASCs were inoculated on uncoated scaffolds (group 1), fibrin/HA-coated scaffolds without BMP-2 (group 2), fibrin/HA-coated scaffolds injected once with BMP-2 (group 3), and BMP-2-loaded fibrin/HA-coated scaffolds (group 4) (n = 6/group) | Transplanted into the dorsal subcutaneous sites of the mice | The fibrin/HA-coated and BMP-2-loaded scaffolds fabricated using MHDS would be useful for bone regeneration from undifferentiated ASCs |
| Lendeckel et al., 2004 | autologous ASCs | autologous fibrin glue | A 7-year-old girl suffering from widespread calvarial defects | Multi-fragment calvarial fractures with a 120 cm² defect | It showed no inhibition of stem cell proliferation; it is highly biocompatible and biodegradable. Fibrin glue can also serve as a biological vehicle for cell transplantation |

The table represents various studies that have investigated the use of different cell sources and types, biomaterial scaffolds, donors and host animals, sites of injury, and the regeneration advantages conferred over the vehicle. Each study highlights different aspects such as cell isolation, scaffold composition, animal models, treatment procedures, and the observed outcomes in terms of tissue regeneration. The table suggests a comprehensive approach to understanding the potential of using stem cells and biomaterials in regenerative medicine, particularly in the context of adipose tissue regeneration.

demonstrated the significance of PRP for periodontal tissue reconstruction. Pure PRP, non-implantation, and autologous ADMSCs-based PRP were respectively implanted into receptors with the defects of periodontal tissue. Histologic, immunohistochemical, and x-ray tests were then used to analyze tissue sections for the amount and scale of newly formed bone in the periodontal tissue defect region within one to two months of implantation. The obtained results indicated that the implantation of ADMSCs facilitated periodontal tissue regeneration and PRP prevented gingival invasion when compared with the control group. The biological effects of activated PRP may also influence periodontal tissue regeneration by ADMSCs because the ADMSCs-based PRP composite material could significantly enhance periodontal tissue regeneration. Furthermore, Kolaparthi et al. also applied ADMSCs/PRP to the rat periodontal defect model and yielded similar results [72].

In addition to the combination of growth factors and ADMSCs in periodontal regeneration, researchers have also applied ADMSCs in combination with other biomaterials in the last five years. One example is the amniotic membrane (AM), which is a biofilm that is the innermost layer of the fetal membrane surrounding the developing fetus. A previous study reported that the AM has good physicochemical and biological implications in the fields of obesity and diabetes research.
Fig. 1. Strategy for oral and maxillofacial regeneration based on ADMSCs from adipose tissue. The cells are grown in vivo by exposure to various factors and finally seeded onto the biomaterial scaffolds, which are implanted into the oral and maxillofacial soft and hard tissue defects. (A) Isolation of ADMSCs from adipose tissue and construct ADMSCs/biomaterial scaffolds which are prepared for implantation. (B) ADMSCs/biomaterial scaffolds are implanted into oral and maxillofacial soft and hard tissue defects.

Fig. 2. ADMSCs/biomaterial scaffold applying to jaw defect. (A) Schematic picture of the implantation of the ADMSCs/biomaterial scaffold in a jaw defect. (B) Repaired jaw tissue. ADMSCs in the construct regenerate jaw tissue at the implanted site.

Fig. 3. ADMSCs/biomaterial scaffold applying to periodontium. (A) Schematic picture of the implantation of the ADMSCs/biomaterial scaffold in a periodontal defect. (B) Repaired periodontal tissue. ADMSCs in the construct regenerate periodontal tissue at the implanted site.
properties, and is rich in collagen type I-VII, elastin, laminin, and fibronectin [102]. Considering the excellent properties of AM, Wu et al. used an ADMSCs-based AM co-cultured system to study periodontal regeneration in vivo in rat periodontal defect models. The results obtained in the study demonstrated the potential of using stem cells in combination with appropriate scaffolds for periodontal disease in clinical periodontology [102]. In addition, Requicha et al. [67,68] combined a three-dimensional (3D) fiber mesh functionalized with membrane and silanol groups, both made of starch and poly-E-(-caprolactone) (SPCL). The study further carried out corresponding in vitro experiments for the periodontal regeneration by co-culturing ADMSCs on the scaffold material. The scaffold consists of an osteo-conductive wet-spin fiber mesh and a solvent casting membrane, which could further be enriched with ADMSCs. The main aim of combining the two was to achieve two main functions in the implantation of periodontal defect, thereby inducing the formation of new alveolar bones and guiding tissue regeneration as a barrier, respectively.

Beta-TCP is a bioceramic osteoinductive material which has been reported to induce osteogenic differentiation of ADMSCs. Sadeghi et al. seeded ADMSCs into beta-TCP and implanted the ADMSCs-beta-TCP composite materials into the periodontal defects of Wistar rats with the goal of observing the regeneration of periodontal tissues in vivo [88]. This attempt also opens up new possibilities for periodontal tissue engineering.

Clinically, periodontal disease is still a major problem which causes many patients to lose teeth and related functions. The application of ADMSCs-based biomaterials in the clinical treatment of periodontal disease has a broad prospect and important significance.

4.3. ADMSCs-based biomaterial scaffolds in the treatment of dentine-pulp complex regeneration

Dental pulp necrosis which caused by infection, periodontal disease or trauma is treated conventionally by pulpometry and root canal treatment (RCT). Although RCT is a currently available therapy, it carries the risk of reinfection and root fracture [114]. As an alternative method, the application of ADMSCs-based biomaterial scaffolds for guided dentine-pulp complex regeneration was considered the treatment of choice.

In the last decade, the research on tooth-derived stem cells (TDSCs), including dental pulp stem cells (DPSCs), periodontal ligament stem cells (PDLSCs), stem cells from human exfoliated deciduous teeth (SHEDs), dental follicle progenitor stem cells (DFPCs), and stem cells from apical papilla (SCAPs), is still the mainstream in this field [115–118]. Due to the limitation of pulp tissue and in order to explore the feasibility of ADMSCs, Hung et al. [119] conducted a controlled trial between ADMSCs and DPSCs. Hung et al. implanted autologous ADMSCs and DPSCs with BMP-2 into adult rabbit extraction sockets, respectively, and both groups grew assembled new teeth which were living with nerves and vascular system. Besides, Ishizaka et al. [110] established an experimental dog model with whole pulp removal and transplanted autologous PDSCs, BMSCs and ADMSCs with stromal cell-derived factor (SDF)-1, respectively. Through the detection of the corresponding markers and genes, Ishizaka et al. demonstrated that ADMSCs could enhance matrix formation and induce pulp/dental regeneration.

As stated above, ADMSCs have ideal differentiation potential and could be an alternative cell sources for dental-pulp complex regeneration.

4.4. ADMSCs-based biomaterial scaffolds in the treatment of facial nerve regeneration

Clinically, the common causes of facial paralysis are inflammation, trauma, and facial nerve tumor. Facial nerve symptoms caused by facial paralysis can alter facial symmetry including loss of forehead lines, incomplete eyelid closure, shallow nasolabial groove, and angular mouth. Therefore, facial paralysis often causes a severe psychological blow to the patients. As a result, such conditions have serious consequences for the society and individuals, thereby requiring great efforts to try and understand the various factors which influence the damage, regeneration, and repair [54].

Peripheral nerve injury is a major challenge for nerve recovery, and the restoration of facial nerve function depends on the growth of new axons, myelin formation, and proper reconstruction of target organs. The myelin formation system of the peripheral nerve occurs when Schwann cells (SCs) spread their axons layer by layer, thereby ensuring a rapid conduction velocity. SCs are the main structural and functional cells of peripheral nerves, and play an important role in nerve regeneration and functional recovery after nerve injury [103,104]. Despite stem cells having matured as artificial nerve seed cells, some deficiencies have been reported including the limited source of autologous stem cells, the need for secondary surgery, and the immune rejection of stem cells. However, stem cells are still a promising choice for nerve regeneration. ADMSCs are pluripotent mesenchymal stem cells with the common characteristics of self-renewal and SC-like cell transformation, which can accelerate axonal regeneration and functional recovery [104,105]. ADMSCs may become better seed cells, which can transcend the limited use of SCs and provide a less invasive source of somatic cell transplantation to promote facial nerve regeneration. Fig. 4 displays the schematic diagram of facial nerve regeneration using ADMSCs/biomaterial scaffolds.

Sun et al., examined the effects of a decellularized allogeneic artery conduit containing autologous transdifferentiated ADMSCs (dADMSCs) on an 8-mm facial nerve branch in a rat model [91]. The study also compared cultures by immunohistochemistry using GFAP and S-100 markers and confirmed that the trans-differentiated effectiveness of dAMSCs was similar to that of SCs. The researchers segmented the abdominal artery of rats as an arterial catheter and wrapped it with dADMSCs to repair the facial nerve in vivo. The obtained results indicated that the peak amplitudes of the compound muscle action potential (CMAP) and nerve conduction velocity (NCV) values were significantly improved eight weeks after the operation when compared with the control group. Moreover, the amount of Fluorogold-labeled neurons were also significantly higher than those in the control group. The final results showed that dADMSCs-based biomaterial scaffolds can effectively promote facial nerve regeneration.

Although dADMSCs have been identified as SCs substitutes, Watanabe et al., distinguished the phenotypic and functional characteristics of undifferentiated ADMSCs (uADMSCs) from dADMSCs [70]. In addition, the silicone tubes of type I collagen scaffolds containing uADMSCs, dADMSCs, or SCs, respectively, were transplanted in vivo to study the effect of uADMSCs and dADMSCs as SC substitutes to repair the 7 mm gap in the facial nerve of rats. Their results suggest that uADMSCs and dADMSCs support axonal growth at the same level by optimizing SC phenotypic expression and cell transplantation into nerve channels. Moreover, their results support the idea that ADMSCs have a therapeutic effect on neuronal regeneration and may be a promising source of neuronal guided ducts, which are more abundant than autologous SCs to connect nerve gaps. Furthermore, biopolymer scaffolds with growth factors also provide the basis for facial nerve regeneration. Choresihan et al. used an uADMSCs-based expanded polytetrafluoroethylene tube encapsulated in alginate hydrogel to repair a 7 mm-gap facial nerve [57]. The obtained results indicated that the NCV and maximal amplitude of action potential were significantly improved in the experimental group than in the control group.

The above mentioned studies have shown that the features of ADMSCs are similar to those of SCs. Furthermore, the advancement of research has drawn further attention to the possibility of using polymer materials as biological scaffolds.
4.5. ADMSCs-based biomaterial scaffolds in the treatment of adipose tissue engineering

In the modern era of cosmetic and reconstructive surgery, tissue-engineered therapies for improving aesthetic appearance continue to be the focus of attention. Besides restoring normal tissue contours, augmentation therapy may affect a person’s overall health. According to the American Society of Plastic Surgeons (ASPS) survey, millions of prosthetics and reconstructive operations are performed worldwide each year. The main focus of the operations is on tumor resection, laceration repair, and scar revision, which are the major challenges faced by plastic and reconstructive surgeons [98]. In recent years, facial reconstruction surgery has received significant attention and improvement in the field of augmentation therapy. In addition, facial reconstruction is a routine cosmetic surgery in China [99]. From the beginning, tissue engineering has focused on modifying traditional augmentation therapies using the concept of bioengineered structures [86] - the combination of cells and scaffolds that achieve a normal aesthetic. Currently, several prototypes of different tissues and organs have emerged in the field of biomedicine. However, recent research has focused on adipose tissue engineering (ATE) to repair soft tissue defects (Fig. 5).

In the development of engineered tissue construction, ADMSCs with proven multilineage differentiation potential are expected to be an ideal cell source. A previous study reported that the easy isolation, abundant stem cell population, and high differentiation potential of ADMSCs makes them to be an important candidate cell for adipose tissue engineering [95]. Meanwhile, a large number of synthetic and natural materials are being used for adipose tissue engineering, which can simultaneously perform regulated non-toxic degradation of host tissues occupying the tissue voids.

Collagen, a special ECM element, is a widely proven scaffold for ATE. Cells differentiating towards the adipogenic lineage secrete collagen, which is a marker of adipogenesis, and emphasizes the role of collagen in adipogenesis [88]. Therefore, the use of collagen as a scaffold is expected to promote cell anchoring [90] with the overarching goal of ensuring their differentiation in vitro and in vivo, while filling defective sites at the same time. Some researchers have studied the regeneration of adipose tissue by collagen scaffolds [97]. In situ regeneration of adipose tissue was achieved using various forms of collagen scaffolds. It is worth noting that the ADMSCs are multipotent and collagen type I is a natural extracellular matrix component. Because of this situation, Venugopal et al., attempted to apply ADMSCs-based type I collagen sponge, an established ATE scaffold, in vivo [69]. They observed the formation of the reticular meshwork of adipoid cells after 21 days of implantation of the constructed cell seed collagen into the rat dorsal muscle model, and histological characterization was performed using a variety of staining techniques. In addition, the retrieved samples showed fat formation in situ within 21 days.

Several studies have used decellularized biomaterial scaffolds in tissue engineering because of their potential to enhance the regeneration and repair of damaged tissues [100–105]. Ideally, the decellularization process should be designed to gently extract cellular components while retaining the complex structure and composition of the extracellular matrix (ECM) [106–110]. These strategies can be used to create ready-made biomaterial scaffolds enriched with collagen and other ECM structural components, which can conduce to cell attachment and infiltration both in vivo and in vitro [106–108]. Han et al. [60] investigated the in vivo effects of ADMSCs-based decellularized adipose tissue (DAT) on adipose tissue engineering using an immunocompetent rat.

Fig. 4. Clinical scenario for ADMSCs/biomaterial scaffold-based therapy for facial nerve injuries. (A) Schematic picture of the implantation of the ADMSCs/biomaterial scaffold in a facial nerve injury. (B) Repaired facial nerve. ADMSCs in the construct regenerate facial nerve injury at the implanted site.

Fig. 5. Clinical scenario for ADMSCs/biomaterial scaffold-based therapy for oral and maxillofacial adipose tissue. (A) Schematic picture of the implantation of the ADMSCs/biomaterial scaffold in a soft tissue injury. (B) Repaired facial soft tissue. ADMSCs in the construct regenerate facial soft tissue at the implanted site.
model. The obtained results indicated that the host significantly improved the ability of angiogenesis and adipogenesis through the implantation of ADMSCs/DAT. In addition, Pati et al. [82] constructed a composite that used DAT matrix bioink encapsulating ADMSCs to detect the expression of standard adipogenic genes and then applied it to mice in vivo. The study found that the printed DAT gels were more likely to express adipogenic genes than non-printed DAT gels. Similarly, adipose tissue formation and constructive tissue remodeling was observed in vivo. Furthermore, the decellularized tissue biomaterial scaffolds could also simulate the tissue-specific biochemical and biomechanical properties inherent in the cellular microenvironment, which are considered to be important mediators for various functions such as cell proliferation and differentiation [110,111].

5. Conclusion

Allogeneic ADMSCs based regeneration therapy may be the potential direction of future research because the ADMSCs have a low immunogenicity. For practical application, the osteogenic potential of ADMSCs decreases with age. On the other hand, the immunoregulation and angiogenesis characteristics of ADMSCs promote tumor cell growth, thereby making safety assessment a necessity.

Composite scaffolds should be the main direction of scaffold development in the future. It is worth noting that even modern methods such as inducing tissue regeneration, using bioactive proteins alone or loading bioactive proteins on scaffolds, and alternative materials with or without cells, are only moderately effective. Therefore, we must develop specific stem cells and innovative scaffolds to solve the above problems. In addition, clinical management and surgical techniques should be considered for potential inclusion in future oral and maxillofacial surgery.

Author contributions

Tong Liu was responsible for the design of the work, and undertook the implementation of the study and drafting of the manuscript; Huixiu Xie and Xiaoyi Wang revised the manuscript and conducted final approval of the version to be published; Xun Pan and Zhangfan Ding contributed to quality assessment of the work and offered intellectual content to the manuscript.

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Declaration of competing interest

The authors declare that there are no conflicts of interest.

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