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REVIEW

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Advanced progress of adipose-derived stem cells-related biomaterials in maxillofacial regeneration

Lijun Zhang[1†], Zihang Yu[1†], Shuchang Liu[1†], Fan Liu[1], Shijie Zhou[1], Yuanyuan Zhang[1†] and Yulou Tian[1*†]

Abstract

The tissue injury in maxillofacial region affects patients' physical function and specific mental health. This decade, utilizing regenerative medicine to achieve tissue regeneration has been proved a hopeful direction. Seed cells play a vital role in regeneration strategy. Among various kinds of stem cells that effectively to regenerate the soft and hard tissue of maxillofacial region, adipose-derived stem cells (ADSCs) have gained increasing interests of researchers due to their abundant sources, easy availability and multi-differentiation potentials in recent decades. Thus, this review focuses on the advances of ADSCs-based biomaterial in maxillofacial regeneration from the progress and strategies perspective. It is structured as introducing the properties of ADSCs, biomaterials (polymers, ceramics and metals) within ADSCs and the latest applications of ADSCs in maxillofacial regeneration, including temporomandibular joint (TMJ), bone, periodontal tissue, tooth, nerve as well as cosmetic field. In order to further facilitate ADSCs-based therapies as an emerging platform for regenerative medicine, this review also emphasized current challenges in translating ADSC-based therapies into clinical application and dissussed the strategies to solve these obstacles.

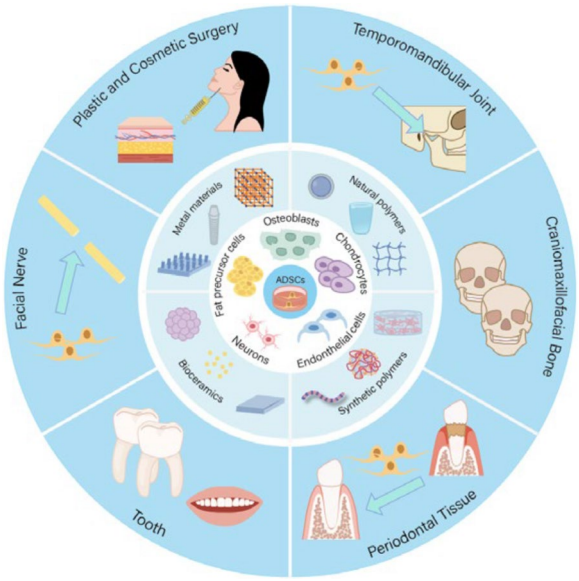
Keywords Adipose-derived stem cells, Regenerative medicine, Biomaterials, Maxillofacial regeneration, Extracellular vesicles

†Lijun Zhang, Zihang Yu and Shuchang Liu these authors contributed equally to this work.

†Yuanyuan Zhang and Yulou Tian are co-last authors.

*Correspondence:
Yulou Tian
yltian@cmu.edu.cn

Graphical abstract



Background

The maxillofacial region is comprised of various soft and hard tissues, including the maxilla, mandible, TMJ, teeth and surrounding periodontal tissues. Due to the unique characteristics of maxillofacial region that constant exposure to external environment, it is susceptible to be injured from endogenous and exogenous factors [1]. Although craniofacial tissue has intrinsic healing ability, due to the complexity of its structure, the damaged tissue cannot completely rebuild the intact matrix and regenerate the natural surface. Several strategies are performed to achieve basic functional restoration in clinic, such as autografting, allografting, and xenografting, however, it is far from enough to achieve tissue regeneration in maxillofacial region [2, 3]. For instance, autograft is widely regarded as the golden standard for various tissue reconstructions, nevertheless, it is constrained by factors such as limited availability of donor tissue, potential disease transmission at the donor site, and suboptimal functional recovery [4–9].

Regenerative medicine offers an innovative alternative that aims to regenerate, repair, or replace tissues and ensure the restoration of their impaired functions by integrating tissue engineering with the inherent self-repair ability of the human body [10]. In the last twenty years, the utilization of stem cells, scaffolds, and/or growth factors that constitute tissue engineering is increasingly used in maxillofacial reconstructive medicine, providing new options for the reconstruction of the TMJ, bone and cartilage, periodontal tissue, teeth, skin, nerves and blood vessels.

Various kinds of stem cells have been proved effectively to regenerate the soft and hard tissue of maxillofacial region, including dental pulp stem cells (DPSCs), periodontal ligamental stem cells (PDLSCs), bone marrow-derived stem cells (BMSCs) and ADSCs, due to their multidirectional differentiation potential [11–14]. Among them, ADSCs have gained increasing interests in recent years. In addition to their undifferentiated immunophenotype, self-renewal capacity, and ability to differentiate into multiple lineages [15, 16], it is generally accepted that ADSCs are obtained in large quantities from adipose tissue with minimal invasiveness [17, 18]. Especially, compared with BMSCs, ADSCs exhibit more favorable proliferation and differentiation capabilities [19, 20]. Moreover, the therapeutic potential of extracellular vesicles (EVs) secreted by ADSCs are close and even superior to that of ADSCs, suggesting a potential alternative treatment to solve limitations of ADSCs.

In the domain of regenerative medicine, biomaterials exhibiting biocompatibility and appropriate mechanical properties have been extensively utilized as scaffolds for the delivery of ADSCs. These scaffold materials serve as effective vectors, promoting the adhesion, proliferation, and differentiation of ADSCs by modulating the biomechanical and biochemical properties of the microenvironment [21]. Throughout the research process, either natural or synthetic

biomaterials may be selectively employed based on specific requirements for the fabrication of cell scaffolds. Furthermore, to improve the biological properties of biomaterials or to mitigate their potential limitations when used in isolation, researchers frequently integrate multiple biomaterials into composite scaffolds [22, 23]. Additionally, the incorporation of nanotechnology and other advanced methodologies in material processing further optimizes their capacity to support ADSCs, ultimately leading to superior tissue repair and reconstruction outcomes [24].

In this review, we provide a comprehensive overview of ADSCs-based biomaterials in maxillofacial regeneration. It covers the characteristics of ADSCs, the intrinsic/extrinsic properties of representative biomaterials within ADSCs for tissue engineering, and typical models and examples in maxillofacial applications. Additionally, we also prospect the future development direction to promote clinical transformation.

Adipose-derived stem cells

ADSCs are a population of pluripotent stem cells that are extracted from the stromal vascular fraction (SVF), that are derived from subcutaneous fat deposits in various regions [20, 25, 26]. In liposuction, approximately 1×10^7 ADSCs can be harvested from 300 mL of adipose tissue [27, 28]. The criteria that established by the International Society for Cellular Therapy in 2006 defined MSCs as the adherence to plastic in vitro, capacity for multilineage differentiation that can be identified by oil red staining, alizarin red staining, alcian blue staining, or immunohistochemistry staining [20, 29–31], and the expression of specific antigens including CD105, CD90 and CD73, and negative expression of CD14, CD19, CD34, CD45, CD79 and HLA-DR [32–34]. In 2013, the International Society for Cellular Therapy suggested that the surface markers of ADSCs should include $CD13^+$, $CD29^+$, $CD44^+$, $CD31^-$ and $CD235a^-$ [35]. EVs are known as nanovesicles with phospholipid double-layer membranes that are released by most cell types during physiological processes. Compared with stem cells, EVs are easily manufactured, processed and stored, and exhibit smaller sizes, lack of immunogenicity and non-tumorigenic properties that avoid rejection reaction by direct cell transplantation [36]. ADSC-EVs have been applied for the regeneration of bone defects, joint or muscle injuries and skin wounds [37–44]. Compared to EVs derived from BMSCs and synovial MSCs, ADSC-EVs demonstrate superior osteogenic and chondrogenic efficacy both in vivo and in vitro, as well as broader availability and enhanced safety in clinical applications [45].

Biomaterials within ADSCs for tissue regeneration

Enhancing the activity of ADSCs both in vivo and in vitro is pivotal for advancing the field of regenerative medicine. The incorporation of biomaterials in the culture and transplantation of ADSCs has been shown to significantly improve their viability and functional activity [46]. Biomaterials encompass any substance or combination of substances, excluding pharmaceuticals, that can be utilized to augment or replace tissues, organs, or bodily functions to enhance an individual's quality of life. Biomaterials can be broadly categorized into synthetic and natural biomaterials based on their origin. Natural biomaterials primarily consist of biopolymers such as proteins and polysaccharides, whereas synthetic biomaterials are predominantly composed of chemically engineered polymers, including polyesters, ceramics and similar materials (Table 1) [47]. By regulating the composition of synthetic materials, implants can be engineered and fabricated to fulfill specific clinical and research requirements.

Natural polymers

Natural polymers, referred to as bio-derived materials occur in nature and can be extracted by physical or chemical methods. Normally, natural polymers present three prominent characteristics: favorable biocompatibility, poor mechanical strength and rapid biodegradability. In the subsequent sections, an in-depth review of several representative natural polymers, including hyaluronic acid (HA), chitosan (CS), and alginate (Alg), is presented, focusing on their biocompatibility, biodegradability, structural stability, biological properties, and applications in tissue engineering and regenerative medicine.

HA is a naturally occurring polysaccharide renowned for its exceptional cytocompatibility and significant biological relevance, and it is commonly synthesized into hydrogels for loading ADSCs [64]. The functionality and bioactivity of ADSCs can be enhanced through interactions between cell surface receptors and HA-mediated motility receptors [65, 66]. HA can facilitate the regeneration of joint cartilage, expedite the healing of skin wounds and restore the function of salivary glands [67–71]. For example, HA within cellulose nanofiber microbeads, particularly at a molecular weight of 700 kDa and a concentration of 0.2%, was found to enhance the expression of stemness-related markers (*i.e.*, CD90, CD29) of ADSCs, indicating the composite material could significantly promote cell viability [72].

CS, a naturally derived polymer from chitin, has favorable biocompatibility, antibacterial properties and biodegradability, which has been well applied in many biomedical fields, such as bone, skin and cartilage repair. To be specific, the structural similarity to

Table 1 Analysis of natural and synthetic biomaterials along with their advantages and disadvantages

Biomaterials		Advantages	Disadvantages	References
Natural biomaterials	Protein-based biomaterials Polysaccharide-based biomaterials Glycosaminoglycan-based biomaterials ECM biomaterials	Biocompatibility Biodegradability Bioabsorbable Bioactivity Nonimmunogenicity Elasticity Variety of cell-adhesive/binding properties Delivery of drugs and bioactive molecules Accelerate tissue repair Ease of production Renewability Low cost	Poor mechanical strength and stability Quick rate of degradation	[48–52]
Synthetic biomaterials	Synthetic polymers	Biocompatiblility Cytocompatibility Nontoxic degradation products Wide range of degradation rates Low frictional properties Excellent processability Toughness	Low bioactivity Hydrophobicity Some problems related to withstanding mechanical loads Degradability over time	[53–55]
	Bioceramics	Biocompatibility Corrosion resistance High compressive strength Chemical inertness Low thermal and electrical conductivity	Poor fatigue resistance High brittleness Low impulsive tensile strength High specific weight Not easy to process	[56–59]
	Metals	Biocompatibility Corrosion resistance High mechanical properties Low friction High fatigue resistance Ductility	Low bioactivity Stiffness High specific weight	[60–63]

ECM extracellular matrix

glycosaminoglycans makes CS as a favorable candidate for cartilage regeneration [73–75]. It was demonstrated that porous CS/HA scaffolds could enhance chondrogenic differentiation of ADSCs, producing cartilage matrix [76]. Additionally, poly(lactic-co-glycolic acid) (PLGA)/CS hydrogel scaffolds featuring tubular pore structures have been shown to spontaneously induce the aggregation of ADSCs. The subsequent introduction of bone morphogenetic protein 2 (BMP-2) facilitates the differentiation of ADSCs aggregates into chondral tissue in vitro [77].

Alg, a hydrophilic polysaccharide predominantly sourced from brown seaweed and certain bacteria, represents one of the most abundant natural biomaterials globally. Owing to its high biocompatibility, low toxicity, and renewability, Alg has been extensively utilized in the fabrication of dressings, scaffolds and hydrogels for applications in regenerative medicine [78, 79]. Alg scaffolds demonstrate significant porosity, thereby promoting the diffusion of cytokines and nutrients. The encapsulation and culture ADSCs within Alg core–shell capsules or Alg microparticles proves advantageous for preserving ADSCs viability and augmenting their secretion potential, while maintaining their clonogenic properties [80, 81]. The Alg/gelatin (Gel) hydrogel provides a conducive environment for ADSCs, thereby enhancing the regeneration of joint cartilage injuries [82].

Synthetic polymers

Synthetic polymers are human-made polymers produced by chemical reactions with adjustable chemical structures and physical properties. Most synthetic polymers have more outstanding mechanical properties when compared with natural polymers. The tailored physical–chemical properties suit particular biomedical applications. The commonly used biodegradable synthetic polymers include polycaprolactone (PCL), PLGA and polylactic acid (PLA), which have taken a priority in hard tissue replacement [83, 84].

PCL, a polymeric material, exhibits exceptional biocompatibility and mechanical properties, including high tensile strength and elastic modulus. Furthermore, PCL possesses remarkable biodegradability, facilitating its hydrolysis into ε-caprolactone monomers, which are subsequently eliminated from the body through metabolic pathways [85]. Due to these properties, PCL has garnered

extensive applications as a scaffold material in diverse tissue engineering domains, including bone, cartilage and neural tissue engineering. Previous research indicated PCL nanofiber scaffolds with suitable pore sizes exhibited favorable biocompatibility, but lack of cell adhesion due to its hydrophobic property. Thus, the incorporation of natural polymers (*i.e.*, laminin, fibronectin, and fibrin) into PCL scaffolds is necessary to enhance physical–chemical properties including surface morphology, roughness and hydrophilicity [86–89]. Meanwhile, the combination of bioceramics and PCL was designed to improve the bioactivity and osteogenic differentiation of ADSCs [90, 91]. The ADSCs-loaded hydroxyapatite (HAp)/Alg/PCL scaffold exhibits superior flexibility, mechanical strength and osteogenic potential, thereby facilitating the regeneration of type I collagen (Col) in newly formed bone and periodontal ligament. Additionally, it enhances the immunoreactivity of vascular endothelial growth factor (VEGF) and osteopontin and expedites the healing process of class II furcation defects [92]. Furthermore, the integration of ADSCs with PCL/tricalcium phosphate (TCP) composite scaffolds, followed by implantation into an alveolar defect model, facilitates a uniform distribution of osteoblasts and mineralized tissue. This strategy also enhances scaffold integration with host tissue through immunomodulatory mechanisms, resulting in improved outcomes for alveolar regeneration [93].

PLGA is another commonly used synthetic polymer with outstanding hydrophilicity and biodegradability, which has been applied as implantable devices for tissue engineering [94, 95]. Similar to other synthetic polymers, bio-inert PLGA needs to be modified to improve its bioactivity. A typical example was the utilization of black phosphorus (BPs)/PLGA scaffolds coated with BMP-2-encapsulated PLGA microspheres. Under near-infrared irradiation, BPs-based scaffolds exhibited excellent antibacterial properties, as well as accelerating bone regeneration offering promising prospects for addressing infectious bone defects [96]. Besides, amorphous calcium-phosphate nanoparticles could enhance the surface roughness of PLGA scaffolds, facilitating the adhesion and osteogenic differentiation of ADSCs [97].

PLA is a biodegradable lactic acid derivative synthesized through the fermentation of carbohydrates, which can be decomposed into water and carbon dioxide. In addition, PLA exhibits excellent biocompatibility and flexibility, and does not induce corrosion of bone tissue following implantation in the human body [98]. The osteogenic differentiation of ADSCs can be effectively induced by PLA nanopillar arrays in the absence of osteogenic growth factors, with nanopillar arrays exhibiting a diameter of 200 nm demonstrating superior ectopic osteogenic capacity [99]. Nonetheless, PLA is associated with several limitations, including inadequate mechanical properties, high brittleness, and pronounced hydrophobicity. However, the incorporation of biomaterials such as HAp, calcium silicate, polyethylene glycol, and polyglycolic acid can yield composite scaffolds that exhibit enhanced elastic modulus and improved osteoinductive potential [100, 101]. The PLA/bioactive glass composite filaments exhibit superior wettability and osteoinductivity relative to pure PLA scaffolds, leading to an elevated expression of collagen and osteocalcin, which in turn promotes the osteogenic differentiation of ADSCs [102]. Moreover, the PLA/10 calcium silicate/10 dicalcium phosphate dihydrate scaffold has the capability to adsorb exosomes from ADSCs that persist on its surface, thereby enhancing the osteogenic potential of ADSCs and demonstrating significant promise in regenerative bone healing [103].

Bioceramics

Calcium phosphate-based bioceramics, such as HAp and TCP are commonly used in bone regeneration, owing to the similar composition with human nature bone tissue [104, 105]. HAp synthesized by different methods, such as sol–gel, hydrothermal and sono-chemical synthesis, exhibits diverse morphologies and particle sizes. The application of HAp as an implant material adaptable to various types of bone injuries facilitates optimal anatomical congruence and biological functionality [106]. Additionally, due to the capacity of HAp to generate mineral elements essential for osteoblast metabolism, its bioactive coatings have been extensively employed to enhance the bonding between implants and adjacent bone tissue [107]. For instance, the application of ADSCs in conjunction with HAp/silk fibroin (SF) scaffolds has been shown to yield superior reparative outcomes in mouse calvarial bone defects compared to the utilization of SF scaffolds alone [108]. TCP is an inorganic compound characterized by its high strength, toughness, wear resistance, and corrosion resistance, exhibits osteoinductive and biocompatible properties. These attributes render TCP conducive to creating an optimal growth environment for ADSCs, thereby facilitating fracture healing. Additionally, TCP has been found to modulate nerve conduction and alleviate inflammation associated with fractures and pain resulting from nerve compression [109].

Moreover, biphasic calcium phosphate (BCP), the mixture of HAp and TCP with proper proportion is well developed in bone tissue engineering. BCP could promote extracellular matrix (ECM) mineralization and accelerate bone formation [110–112]. Meanwhile, researchers indicated BCP was able to promote bone regeneration by enhancing vascularization through the

sustained release of Ca^{2+} ions, and sequentially activated the store-operated calcium entry and calcineurin pathways by up-regulating NFATc1 and VEGF expression in $CD301b^{+}$ macrophages [113]. However, bioceramic presents poor fatigue resistance and high brittleness, which is hardly used as scaffold in bone defect, especially load-bearing region. The incorporation of polymers including PLGA, PCL, Gel methacryloyl into bioceramic could enhance the mechanical and biological properties of composite scaffolds [90, 114–117].

Metallic materials

Compared with other materials, metallic materials are mostly used for hard tissue regeneration, especially for orthopedic and dental application. The requirements of implantable metallic materials include corrosion resistance, proper mechanical strength (specific strength, endurance strength and impact toughness) and high biocompatibility. Titanium (Ti), magnesium (Mg), zinc (Zn) and their oxides were found to improve the biocompatibility of ADSCs [118]. Nevertheless, the lack of biological activity of metallic materials limits their application. Ti is a lightweight metal characterized by exceptional strength properties and a modulus of elasticity ranging from 100 to 115 GPa. The porous architecture of Ti can reduce its elastic modulus to levels comparable to that of bone. Furthermore, the surface of Ti is susceptible to the formation of a thin oxide layer, which enhances its biocompatibility and stability [119]. Normally, inorganic particles including HAp, TCP or strontium were loaded into porous Ti scaffolds to promote the osteogenic differentiation of ADSCs [120–123]. Changing the surface structure is another effective approach to increase the bioactivity of ADSCs. It has been demonstrated that the bond strength between ADSCs and dental implants is improved by the increasing surface roughness of Ti implants. The rougher surface exhibited greater adhesion ability and proliferation rate, and sequentially enhanced osteogenic effects of ADSCs when compared to smooth surface implants [124].

Mg exhibits a relatively low elastic modulus of approximately 45 GPa, which enhances its compatibility with the deformation characteristics of human tissue when utilized in implant applications. Meanwhile, as a biodegradable metal possessing antibacterial properties, the degradation rate of Mg within the human body can be modulated through the manipulation of alloy composition and manufacturing processes. Mg and its oxides are frequently combined with other biomaterials in the context of ADSCs research. Mg^{2+} is regarded as an effective booster especially bone regeneration. Mg^{2+} loaded PCL scaffolds has been proven to enhance the expression of osteogenesis-related genes, alkaline phosphatase activity when compared to pure PCL scaffolds. In detail, the adhesion and proliferation ability of ADSCs are positively correlated with the Mg^{2+} [84]. Moreover, magnetite nanoparticles, which exhibit lower toxicity relative to cytotoxic gold nanorods and palladium nanoparticles, have the potential to substantially improve the biocompatibility, osteoconductivity, and osteoinductivity of Mg/HAp/type I Col scaffolds when stimulated by magnetic fields [125].

Zn, a novel biodegradable metal, exhibits an optimal degradation rate in vivo when used as an implant for tissue regeneration and therapy, aligning with the healing rate of local tissues and promoting tissue remodeling and formation [126]. Although pure Zn possesses relatively low mechanical strength, this can be substantially enhanced through alloying, thereby making it suitable for orthopedic implants. At the same time, Zn mitigates the risk of implant-related infections by inhibiting bacterial adhesion and proliferation [127]. Doping Zn on the surface of titania nanotube arrays markedly improves their antibacterial properties and biocompatibility, while exhibiting no cytotoxic effects on ADSCs [128]. Furthermore, the zinc oxide nanorods demonstrate an effective release of Zn^{2+} ions, which not only sustains the stemness of ADSCs but also promotes their proliferation and orientational differentiation [129].

The application of ADSCs in maxillofacial regeneration

Temporomandibular joint Regeneration

Temporomandibular disorder (TMD) is the abnormal structure and relative disfunctions of TMJ, which is composed of dense fibrocartilage between the mandibular condyle and the temporal bone. The incidence of TMD was in the range of 10.6—68.1% (male) and 21.2—72.4% (female) in China [130]. Generally, the therapies of TMD included non-surgical intervention that temporarily relieved from the pain, and surgical interventions based on the cartilage reconstruction. However, the inadequate ability of cartilage regeneration always impedes the healing process [131–133]. Given these limitations, there is an increasing interest in exploring innovative therapeutic approaches that not only alleviate symptoms but also promote true cartilage repair and regeneration.

Emerging treatments such as regenerative medicine techniques, including stem cell therapy, hyaluronic acid injections, and the application of growth factors, are being investigated for their potential to enhance healing outcomes in TMD patients [134]. Stem cell therapy, especially ADSCs, offers the possibility of leveraging the regenerative properties of stem cells to restore the damaged fibrocartilage in the TMJ [135]. These approaches aim to more effectively address the

root causes of TMD, potentially reducing the reliance on surgical interventions. Moreover, the integration of multidisciplinary care involving physical therapy, occlusal splints, and lifestyle modifications may provide a more holistic management strategy for those suffering from TMD [136].

In conclusion, while the current management of TMD presents challenges due to the limitations of existing treatments, ongoing research into regenerative techniques and the multidisciplinary approaches offer hope for more effective solutions that could alleviate symptoms and promote long-term joint health. In this section, we demonstrated the ADSCs-based therapy on TMJ regeneration.

ADSCs-EVs were developed as the novel delivery system within a SF. The up-regulation of miR-27b-3p in ADSCs-EVs/SF scaffolds reduced the level of colony-stimulating factor-1 (CSF-1), and promoted M2 macrophage polarization, which enhanced osteochondral regeneration (Fig. 1A) [137]. Another investigation reported that ADSCs and Ginsenoside Rg1 could be loaded into HA matrix, which effectively enhanced cell proliferation and development by regulating the expression of TIMP-1 and MMP-13 (Fig. 1B) [138]. Photobiological regulation was another effective treatment, which indicated that 660 nm laser with fibroblast growth factor (FGF) could promote the differentiation of ADSCs, facilitating chondrogenic regeneration in vitro [139].

Additionally, clinical trials illustrated the injection of autologous ADSCs into the TMJ led to an improvement of joint structure, reducing pain levels and increasing range of motion, stomatology function, and overall quality of life, without adverse event at six months of follow-up [140]. However, few studies have examined the long-term clinical efficacy of ADSCs injected into the TMJ. Existing literature indicates that intravarticular ADSC injection is a safe and effective treatment for knee osteoarthritis (OA) [141–143]. While some patients have experienced temporary joint pain or swelling post-treatment, these symptoms typically resolve with analgesia [144]. A clinical study demonstrated that ADSC injections improved chondropathy and bone marrow edema in knee OA patients over two years, outperforming sodium hyaluronate [145]. Given the similarities between the knee and TMJ in OA progression, advancements in knee cartilage regeneration may inform TMJ treatment [146]. Further clinical studies are needed to confirm safety and efficacy and to establish standardized protocols. See Table 2 for additional ADSC-based preclinical studies on TMJ regeneration.

Craniomaxillofacial bone regeneration

The hard tissues from craniomaxillofacial part protect the brain and sensory organs, and play important role in the functions including facial expression, mastication, respiration, and speech within facial soft tissues.

Differ from the abnormal deformities in other parts, cranial defects were more likely to occur, due to the exposure to external environment. During the last twenty years, bone grafts, including autogenous bone grafts, allografts, and xenografts have emerged as the solution for craniomaxillofacial defects [149]. Nevertheless, several limitations need to be carefully addressed: further surgical procedures, potential risks of disease transmission, unfavorable immune responses and religious concerns [150, 151]. As an alternative, ADSCs-related biomaterials have been widely applied due to their unique capacity to secrete growth factors and stimulate angiogenesis, enabling them to facilitate the provision of oxygen and nutrients to sites of bone regeneration [152].

Hydrogels are three-dimensional networks of crosslinked hydrophilic polymers that play an important role in facilitating tissue replacement, repair, and regeneration due to their biocompatibility, degradability, and tissue-mimicking water content [153]. The utilization of hydrogels within ADSCs in craniomaxillofacial regeneration was summarized in this part. A study showcased the promise of microbial transglutaminase (mTG) crosslinked Gel hydrogels in addressing craniofacial defects in diabetic rats through the delivery of self-assembled ADSC spheroids (ADsp). These spheroids, which maintain the properties of ADSCs within a 3D environment, were able to mimic natural cell morphology, facilitate cell–cell interactions, and promote cell-ECM interactions [154]. In order to overcome the challenges posed by the unfavorable osteogenic environment and lack of osteogenic signaling in diabetes, it is necessary for osteogenically pretreated ADsp-mTG to directly differentiate into bone [155]. Injectable scaffolds offer the advantage of facilely filling irregularly shaped bone defects with minimal invasiveness [156]. A study involved the construction of an injectable nHA/PLGAs/CS hydrogel as a carrier for delivering BMP-2, VEGF, and ADSCs, resulting in enhanced vascularization and new bone formation in critical size mandibular defects. Among them, BMP-2 and VEGF were loaded in PLGA microspheres, exhibiting sustained release and retained bioactivity. After that, CS, nHA and loaded PLGA were incorporated to form a 3D structure material for housing ADSCs (Fig. 2A) [157]. Furthermore, it was observed that structural units with fibrous and ribbon-like geometries are advantageous for promoting interconnectivity, as they offer a larger surface area and greater porosity compared to microspheres. Hence,

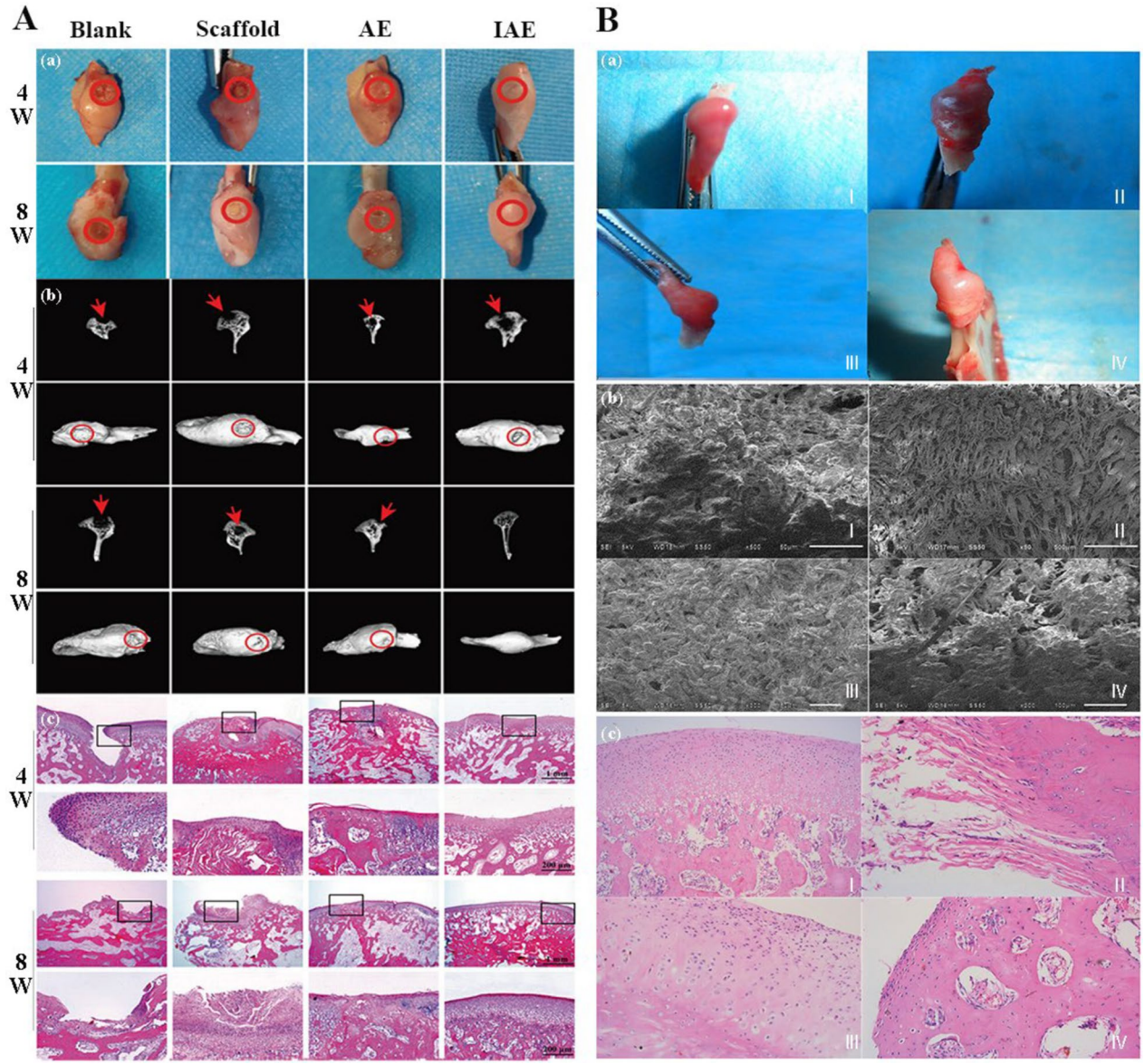


Fig. 1 The effects of ADSCs to repair TMJ in vivo [137, 138]. **A**. **a** Gross observation of the recovery condition of rabbit osteochondral defect. **b** Micro-CT demonstrated the osteochondral regeneration of condyle. **c** H&E staining of TMJ sections. Black boxes indicate the microscopic field of view illustrated below in the higher magnification panels. Reproduced with permission from Ref. [137] Copyright 2022 Wiley–VCH GmbH. **A**. **a** Gross observation of the smoothness of the cartilaginous surface of rabbit TMJ OA models. **b** The condition of cartilaginous surface by SEM. **c** H&E staining describes the structure of cartilage layers, tide line and matrix under the cartilage. (I), (II), (III), (IV) mean blank, model, experimental and control groups respectively. Reproduced with permission from Ref. [138] Copyright 2023 Informa UK Limited

given the scarcity of injectable scaffolds with large pores, a gelatin-based microribbon-shaped hydrogel was developed to facilitate the direct encapsulation of ADSCs. This hydrogel can be injected and subsequently form a macroporous scaffold in situ, thereby improving the survival and implantation of ADSCs and expediting bone formation in craniofacial defects. Furthermore, the co-delivery of BMP-2 and ADSCs has been proven to synergistically enhance bone regeneration and vascularization in vivo (Fig. 2B) [158].

The ECM serves essential roles in facilitating long-term cellular proliferation, differentiation, and the construction of a microenvironment characterized by cell–cell interactions [159]. Implantable scaffolds have been engineered to replicate the diverse physicochemical properties of the ECM found in the natural bone

Table 2 The in vivo trials of ADSCs in TMJ

Application	Source	Experimental subjects	Methods	Conclusion	References
TMJ	sEVs	Rabbit models with osteochondral defect	Inflammation-stimulated ADSC-EVs were attached to SF scaffold by TGase	Regulated differentiation of macrophages into M2 type by targeting CSF-1 to promote TMJ condylar regeneration	[137]
	ADSCs	Rabbit TMJ OA models	Re-suspensed ADSCs with RG1 and then injected with a 1:1 mixture of ADSCs and hyaluronic acid	Promoted chondrocyte activity and type II Col expression	[138]
	ADSCs	TMD adults	Injected 1 cc autologous ADSCs into the upper compartment of TMJ	Joints' construction, pain level, opening degree, stomatology function and living quality of these patients improved without causing adverse events	[140]
	ADSCs or their secretome	Rat TMJ OA models	Low-level laser (0.64 W/cm^2) irradiated ADSCs injection area	Recovery of joint structure, cartilage and disc thickness and suppression of inflammatory processes	[147]
	ADSCs	Rabbit models underwent TMJ disc discectomy	4000 TGF-β-treated ADSCs seeded on PLA disk (7 × 5 × 1.2 cm)	More regular morphology and increased calcification of the condyle	[148]

TGase transglutaminase, *SF* silk fibroin, *CSF-1* colony-stimulating factor-1, *HA* hyaluronic acid, *PLA* polylactic acid

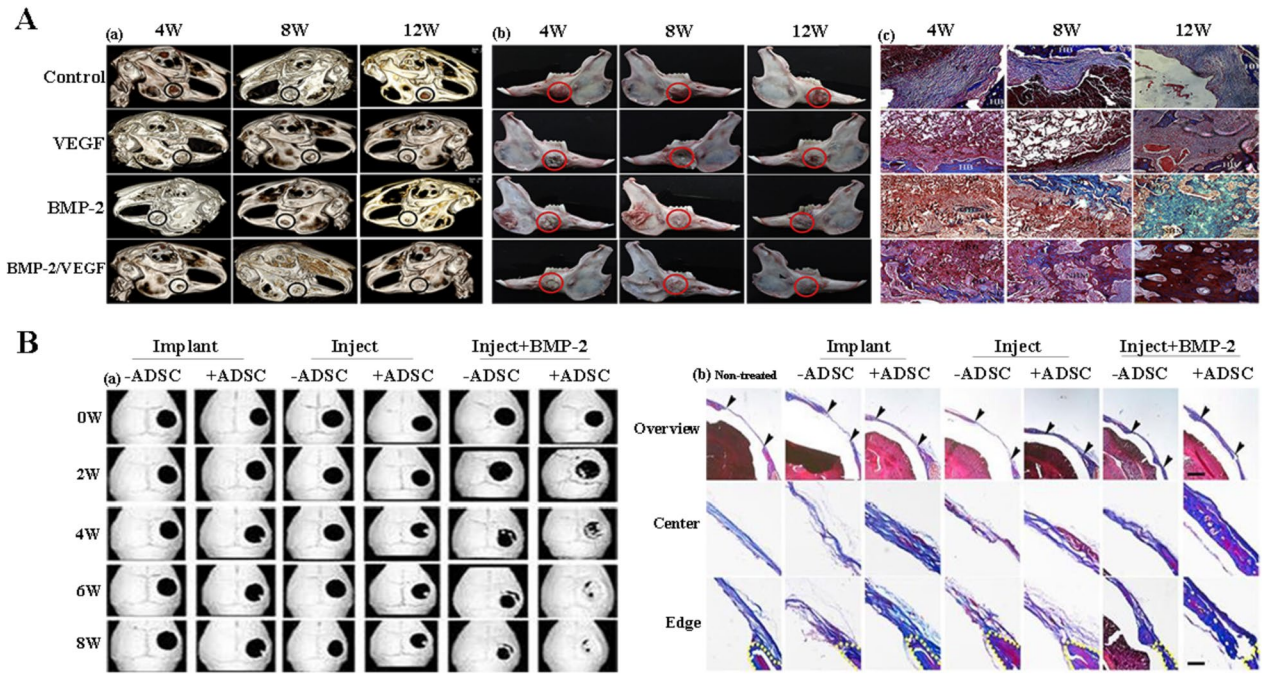


Fig. 2 The results of ADSCs to facilitate cranio-jaw regeneration [157, 158]. **A**. **a** Gross observation of mandibular defect rabbits. **b** 3D-CT images of the bone defect cavity. **c** Masson Trichrome staining of histological sections of the bone defect cavity. Reproduced with permission from Ref. [157] Copyright 2020 Elsevier. **B**. **a** micro-CT images of cranial defect mice. **b** Trichrome staining of the defect center and edge of cranial defect mice. Reproduced with permission from Ref. [158] Copyright 2020 Ivyspring International Publisher

matrix, offering tailored microenvironments for guiding osteogenic responses during stem cell transplantation. A novel chimeric mussel adhesive protein (MAP)-based sticky bone-specific artificial ECM (aECM) onto a Col sponge was fabricated to expedite ADSCs-based bone regeneration and establish a functional vascular network resembling that of the bone marrow in situ. Bioactive peptide sequences fused with MAP chimeras offer

a straightforward and adaptable method for coating surfaces with desired biological activity, eliminating the need for additional modification steps [160, 161]. In the present investigation, Alg-Gly-Asp and BMP-2 combined with MAP coating was employed to dual-functionalize 3D Col scaffolds, resulting in the promotion of skull defect healing [162]. Other researchers have innovatively utilized heparin-conjugated decellularized bone matrix (HC-DCB) particles as a biomimetic vehicle for delivering platelet-derived growth factor (PDGF) to ADSCs, drawing inspiration from the ECM to mimic its physiological conditions to facilitate growth factor delivery [163]. PDGF has emerged as a promising alternative to BMP-2, as it exhibits a lower incidence of adverse effects and directly promotes osteogenesis of ADSCs in higher efficacy by activating the PDGF β receptor (PDGFRβ) signaling pathway [164, 165]. Therefore, this team employed bionic tether to attach PDGF to HC-DCB particles, replicating the PDGF tethering mechanism in a bone fracture healing microenvironment and delivering colocalized synergistic osteogenic factors to enhance ADSCs-mediated bone regeneration in cranial defects. Furthermore, in a separate study, bone demineralized and decellularized ECM (bdECM) was incorporated onto 3D-printed PCL/TCP scaffolds, followed by the injection of ADSCs aggregates to increase cell density and paracrine effects. This strategy resulted in bone formation in mandibular defects in canines [90].

Preclinical studies utilizing ADSCs in bone tissue engineering have led to the initiation of several clinical trials. Beta-TCP (β-TCP) is a bioceramic material recognized for its osteoinductive and osteoconductive properties [166]. Under physiological conditions, β-TCP has the capacity to spontaneously mineralize, which is a prerequisite for osteoinduction and the occurrence of heterotopic ossification. Moreover, β-TCP is resorbed through cell-mediated processes rather than dissolving spontaneously in physiological environments [167]. Given that most bone is formed as lamellar bone—a process facilitated by osteoclasts—the combination of osteoclast-mediated resorption and bone conduction facilitates the rapid osteotransduction of the β-TCP scaffold into a trabecular structure [168, 169]. This phenomenon accounts for the microscopic invasion of bone into β-TCP, and when β-TCP is fully implanted, it results in increased bone production, making it a widely used and effective synthetic bone graft substitute. Studies have exhibited that β-TCP can promote the osteogenic differentiation of ADSCs, prompting researchers to combine these two elements in clinical trials aimed at bone regeneration.

One such trial involved the use of autologous ADSCs in conjunction with β-TCP granules in patients with large cranial defects, resulting in positive outcomes after 3 months follow-up assessments [170]. Clinically, the grafted area exhibits a hard texture upon palpation and reveal a grainy appearance. The bone density of the graft tends to increase over time. Although initial results were promising, the outcomes observed at a 6-year follow-up were not satisfactory [171]. While no significant adverse events were reported, the outcomes were deemed suboptimal as the clinical results did not surpass those attained through conventional skull repair techniques. Two cases demonstrated relatively positive outcomes: in one instance, the patient did not require reoperation, and the graft remained palpably firm despite radiological evidence of graft absorption. In another case, a patient underwent reoperation 2.2 years later due to the recurrence of meningioma; however, the graft was deemed successful as it ossified clinically, adhered well to the defect margin and remained intact during reoperation. Conversely, two cases necessitated reoperation due to significant graft absorption, likely attributable to inadequate ossification resulting from the excessive absorption rate of β-TCP. Consequently, inducing and enhancing ossification presents a significant challenge in improving graft efficacy. Identifying an optimal scaffold material to support ossification in the cranial region may offer a viable solution. While the use of absorbable mesh eliminates residual material at the graft site, it also compromises structural integrity over a short period, potentially increasing micromotion. This micromotion may hinder effective bone bridging by perpetuating the destruction of weak initial bone struts and impeding early blood vessel formation. The success observed in the aforementioned cases with relatively positive outcomes can be partially attributed to the utilization of stiffer titanium mesh as a scaffold material [172]. Additionally, the application of growth factors such as BMP-2 to facilitate reconstitution is another viable strategy. Various studies have suggested that the utilization of autologous ADSCs, β-TCP granules, and BMP-2 can enhance bone regeneration in patients undergoing segmental mandibular resection [26]. Furthermore, the defects in patients who underwent hemimaxillectomy were reconstructed with a microvascular flap utilizing the same scaffold [173]. However, the biosafety of BMP-2 remains a topic of debate [174]. In consequence, while certain animal studies have demonstrated the capacity of ADSCs to address craniojaw defects (Table 3), the limited number of corroborating clinical trials necessitates further exploration through larger-scale clinical trials to assess the effectiveness and safety of ADSCs-based therapies.

Periodontal tissue regeneration

The periodontal tissue is comprised of periodontal membrane, alveolar bone, cementum, and gingiva.

Table 3 The in vivo trials of ADSCs in cranio-jaw regeneration

Application	Experimental subjects	Methods	Conclusion	References
Cranio-jaw regeneration	Patients underwent segmental mandibular resection	Titanium mesh with 25–45 ml β-TCP, 12 mg rhBMP-2 and 4.7×10^6—1.6×10^7 ADSCs	Large mandibular defects averaging 8.2 cm were successfully closed, most implants achieved osseointegrated and supported masticatory function	[26]
	Dog mandibular defect models	0.1 μg ADSCs aggregate were added to 3D printed PCL/TCP/bdECM scaffold	Obvious ossification, higher bone density and no immune rejection	[90]
	Pig mandibular defect models	5.0×10^6 ADSCs were seeded to the 7.15 cm^3 3D TCP-PLGA scaffold	Improved the osteogenic capacity of TCP-PLGA scaffolds	[115]
	Rat cranial defect of diabetic models	Encapsulating ADsp in mTG at the density of approximately 3072 ADsp / 100 μL	Promoted diabetic calvarial osseous defect regeneration	[155]
	Rabbit mandibular defect models	BMP-2/VEGF-loaded PLGA microspheres (10 mg/mL) combined with nHA/CS solution (w_{CS}:w_{nHA} = 1:1) to form injectable hydrogel with ADSCs	Realized the sustainable release and bioactivity preservation of BMP-2 and VEGF and promoted the ossification and vascularization of bone defects	[157]
	Mouse cranial defect models	5%-7.5% (w/v) gelatin-based μRB hydrogel loaded with 20 million/ml ADSCs	Supported vascularization and enhanced bone regeneration	[158]
	Rat cranial defect models	30% (w/v) MAP-RGD or MAP-BMP-2 were coated on gelatin sponge (8 mm in diameter, 2 mm in thickness), then inoculated 5×10^4 ADSCs	Significantly accelerated the formation of bone tissue and facilitated the construction of functional vascular networks of bone marrow-like compartments	[162]
	Mouse cranial defect models	2×10^5 ADSCs and 200 ng PDGF connected by HC-DCB were injected into 3D PCL scaffold	Enhanced the osteogenic signaling of PDGF to ADSC-mediated bone regeneration	[163]
	Patients with large cranial defects in short term prognostic	60 ml β-TCP granules (porosity 60%, granule size 1.4—2.8 mm) seeded by 1.5×10^7 ADSCs with titanium screws or resorbable meshes	No complications on clinical examination, the skull was hard on palpation, CT scan showed a granular appearance and the bone density of the graft tended to increase	[170]
	Patients with large cranial defects for six years of follow-up	60 ml β-TCP granules (porosity 60%, granule size 1.4—2.8 mm) seeded by 1.5×10^7 ADSCs with titanium screws or resorbable meshes	No serious adverse events occurred, but the clinical results are not superior to those conventional skull repair methods	[171]
	patients underwent the hemimaxillectomy	1.3×10^7 ADSCs were combined with 60 ml BMP-2 treated β-TCP granules	Vascular system was formed, bone formation was similar to that of a mature maxilla and the implant was successfully integrated without adverse events	[173]
	Mouse cranial defect models	PLGA scaffolds treated by phenamil (100—1500 μM and BMP-2 (30—100 mg/mL)	Enhanced bone regeneration	[175]
	Rat cranial defect models	ADSC sheet (0.5 mm × 0.5 mm) mixed with CGF (0.5 mm × 0.5 mm × 0.5 mm particles) in a ratio of 1:4	Promoted the proliferation and osteogenic differentiation of ADSCs	[176]
	Rat cranial defect models	HA/Col scaffold (8 mm in diameter, 3 mm in thickness) seeded with 1×10^6 co-culture ADSC/EPCs	Facilitated vascularized bone regeneration	[177]
	Dog mandibular defect models	Commercial surgical gel foam seeded by 5×10^6 ADSCs	Higher bone regeneration in ADSCs group	[178]
	Rat congenital cleft-jaw models	vhEGCG sponge scaffold (5 mm in diameter, 3 mm in thickness) loaded by 3×10^4 ADSCs	Enhanced bone regeneration	[179]

PCL polycaprolactone, *TCP* tri-calcium, *bdECM* bone demineralized and decellularized ECM, *PLGA* poly (lactic-co-glycolic) acid, *ADsp* adipose-derived stem cell spheroids, *mTG* microbial transglutaminase crosslinked gelatin hydrogels, *HA* hyaluronic acid, *CS* chitosan, *μRB* the gelatin-based microribbon, *MAP* mussel adhesive proteins, *Col* collagen, *HC-DCB* heparin-conjugated decellularized bone matrix, *PDGF* platelet-derived growth factor, *CGF* Concentrated growth factor, *EPCs* endothelial progenitor cells, *PRP* platelet-rich plasma, *vhEGCG* gelatin sponges modified with epigallocatechin gallate

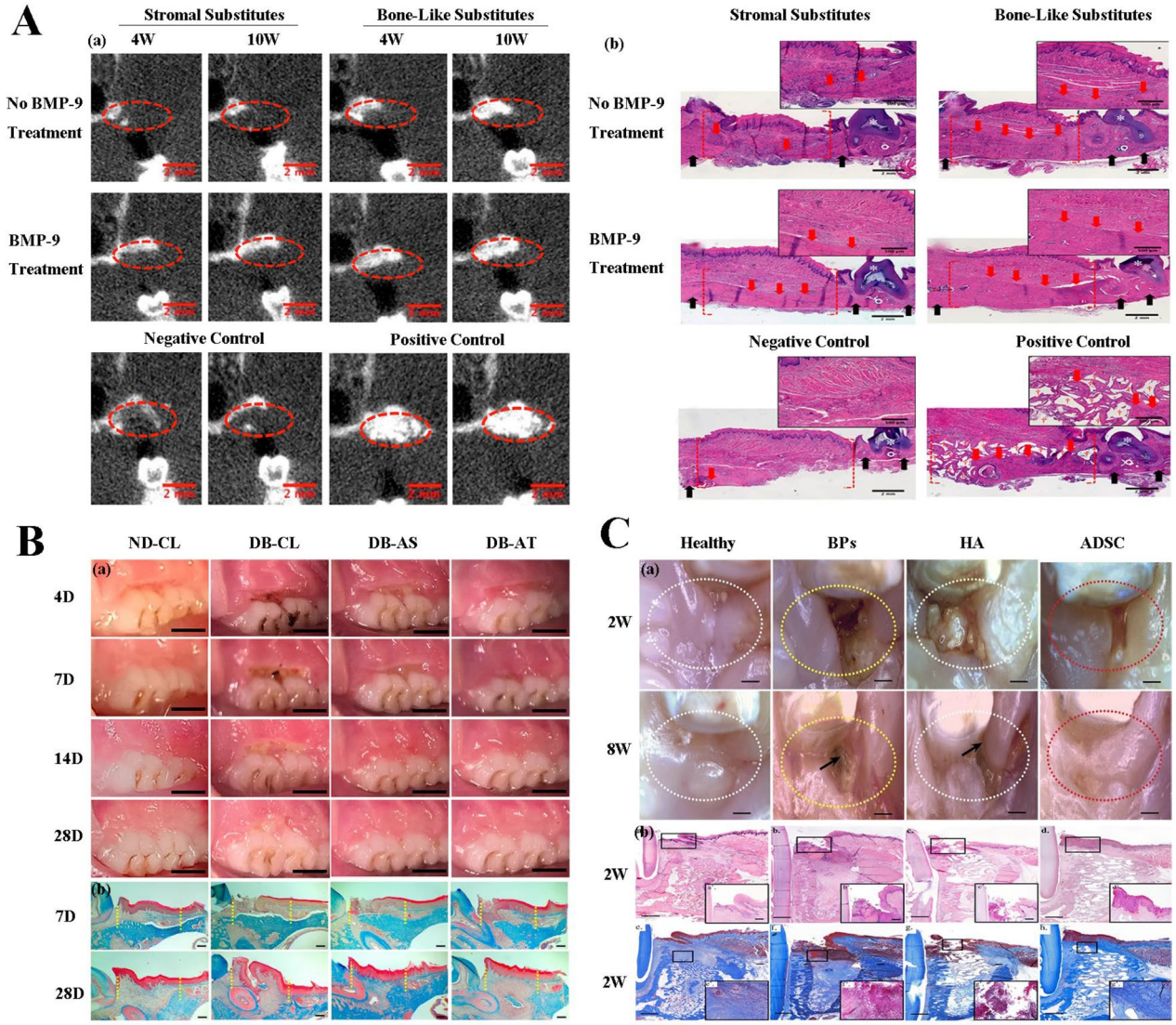


Fig. 3 The ADSCs' effectiveness of accelerate periodontal tissue formation [155, 188, 199]. **A**. **a** Micro-CT images of coronal plane of the implantation sites. **b** Representative histological observations of the grafting sites. The red arrows indicated bone regeneration. Reproduced with permission from Ref. [188] Copyright 2021 MDPI (Basel, Switzerland). **B**. **a** Gross observation of diabetic mucosal wound healing within 28 days. **b** Representative images of Masson's trichrome staining. Reproduced with permission from Ref. [155] Copyright 2023 BioMed Central Ltd. **C**. **a** Gross observation of gingival regeneration in BRONJ rabbits. **b** H&E staining and **c** Masson staining illustrated gingival regeneration and collagen deposition respectively. The rectangular line exhibits the magnified area. Reproduced with permission from Ref. [199] Copyright 2019 BioMed Central Ltd

Epidemiological data revealed the proportion of periodontal health among individuals aged 35–44 in China were only 9.1%, while ages from 55 to 64 decreased to 5.0%. Moreover, the prevalence of adult periodontitis ranges from 40 to 60% [180].

The process of healing following conventional treatment is characterized as periodontal repair, involving the migration of gingival epithelial cells to the apex of the defect area and the subsequent formation of a long connective epithelium on the root surface, hindering regeneration [181]. The limitations and challenges associated with conventional treatment have prompted interests in utilizing ADSCs as a potential solution to enhance periodontal tissue regeneration [182].

Alveolar bone regeneration

Alveolar bone serves as the support of dental and periodontal structures. Adequate alveolar bone volume, is

Table 4 The in vivo trials of ADSCs in periodontal tissue regeneration

Application	Source	Experimental subjects	Methods	Conclusion	References
Alveolar bone regeneration	ADSCs	Dog class II furcation defect models	PCL scaffold was cut into sheets (3×21 mm) and seeded by 1×10^6 ADSCs	Promoted the regeneration of alveolar bone dominated by type I collagen	[92]
	ADSCs	Pig models underwent tooth extraction and implantation surgery	3D-printed PCL-TCP (8×8×3 mm) loaded with stromal vascular fraction	Improved bone regeneration and reduced the possibility of scaffold fiber coating	[93]
	ADSCs	Rat alveolar bone defect models	Osteogenically induced ADSCs treated by BMP-9	Substitutes have similar or even better overall alveolar bone retention compared to clinical-grade biomaterials	[188]
	ADSC-EVs	Rat alveolar bone defect models	PLGA/pDA (4 mm in diameter, 2 mm in height) loads ADSC-EVs to deliver CGRP to promote PDLSCs osteogenesis	Promoted the osteogenic differentiation of PDLSCs and repaired alveolar bone defects through CGRP transfer	[190]
	ADSCs	Dogs class III furcation defect models	2% $CaCl_2$ activates the 1.5×10^7 cells/mL ADSCs and 1 ml PRP gel	Accelerated the regeneration of alveolar bone, cementoid structure and periodontal ligamentoid structure	[192]
	ADSCs	Patients with periodontal disease	2% $CaCl_2$ activates the 1.5×10^7 cells/mL ADSCs and 1 ml PRP gel	Be ongoing	[194]
	ADSCs	Rat alveolar bone defect models	3×10^5 ADSCs were co-cultured on 3×1.5 cm^2 AM	Accelerated alveolar bone regeneration	[205]
	ADSCs	Rat ZA-treated models	1×10^6 ADSCs with 25 μl PRP	Reduced Osteonecrosis, promoted alveolar bone regeneration and prevented BRONJ	[206]
	ADSCs	Rats ZA-treated models	1×10^6 ADSCs seeded on absorbable haemostatic gelatine sponge	Reactivation inhibited bone remodeling after tooth extraction and promoted bone regeneration	[207]
	ADSCs	Dog alveolar cleft models	5×10^6 ADSCs inoculation on HA/TCP scaffold (3×3×3 mm, 60% HA and 40% β-TCP)	The osteogenic effect of autogenous bone graft is better than that of ADSCs	[208]
	ADSCs	Dog models underwent tooth extraction and implantation surgery	1×10^6 ADSCs seeded HA scaffolds	Accelerated the healing of bone defects around the implant	[209]
	ADSCs	Dog buccal dehiscence defect models	Mixed 1×10^7 ADSCs with 1 mL PRP	PRP enhanced the osteogenic effect of ADSCs	[210]
	ADSCs	Dog alveolar defect models	PRP assisted 1×10^6 ADSC inoculation on HA/TCP granules (30% HA and 70% β-TCP)	Accelerated alveolar bone regeneration	[211]
	ADSCs	Dog alveolar defect models	ADSCs seeded on β-TCP (5×10^5 cells/1 g β-TCP)	Accelerated alveolar bone regeneration	[212]
Gingival regeneration	ADSCs	Rat stomatology mucosal wounds of diabetic models	Encapsulating ADsp in mTG at the density of approximately 3072 ADsp /100 μL	Facilitated diabetic periodontal wound healing and observed keratosis	[155]
	ADSCs	Rat alveolar bone defect models	Osteogenically induced ADSCs treated by BMP-9	Adequate gingival re-epithelialization	[188]
	ADSCs	Rabbit BRONJ models	5×10^6 ADSCs were inoculated per 40 mg of spheroidal HA	Promoted gingival healing by up-regulating the expression of TGF-β1 and fibronectin to prevent BRONJ	[199]
	ADSCs	Rat periodontal defect models	8 mm diameter DAM was loaded with 2.5×10^4 cells/cm^2 ADSCs	Support cementoid matrix deposition and periodontal ligament structure regeneration	[204]
	ADSCs	Rat periodontal defect models	ADSCs sheet	Effectively promoted periodontal tissue regeneration	[213]
	ADSCs-Exo	Rat periodontal defect models	Injected 80–150 μg ADSCs-Exo or 1×10^7 ADSCs into pocket	The tissue regeneration effect of ADSCs-Exo was better than that of ADSCs alone	[214]

PCL: polycaprolactone; CGRP: calcitonin gene-related peptide; TCP: tri-calcium; PRP: platelet-rich plasma; AM: amniotic membrane; HA: hyaluronic acid; PLGA: poly (lactic-co-glycolic) acid; ZA: zoledronic acid; ADsp: ADSC spheroids; mTG: microbial transglutaminase crosslinked gelatin hydrogels; DAM: decellularized human amniotic membrane;

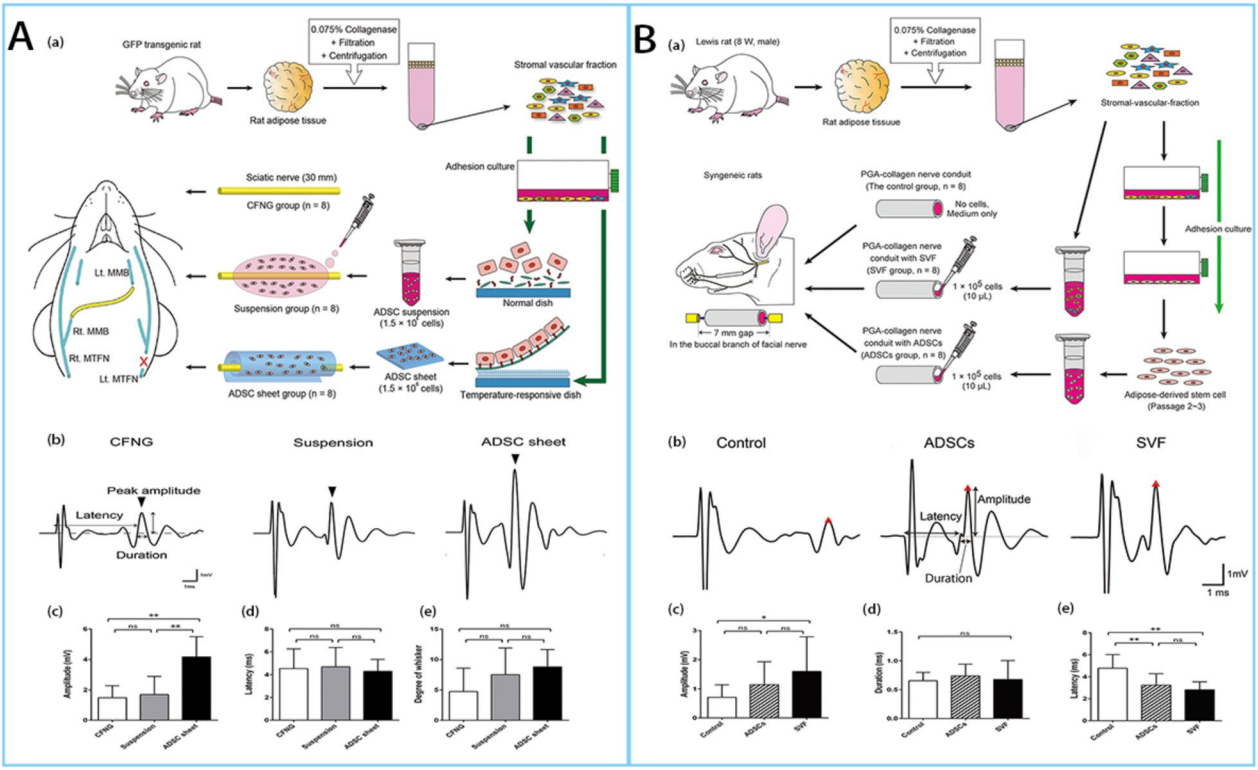


Fig. 4 The strategies and effects of ADSCs to promote facial nerve regeneration [228, 231]. **A**. **a** Schematic overview of the experimental procedures. **b** Compound muscle action potential (CMAP) analysis. **c**, **d**, **e** Illustrate CMAP amplitude and latency and the degree of whisker stimulation, respectively. Reproduced with permission from Ref [228]. Copyright 2020 John Wiley & Sons, Ltd. **A**. **a** Schematic overview of the experimental procedures. **b** CMAP analysis. **c**, **d**, **e** illustrate CMAP amplitude and duration and latency, respectively. Reproduced with permission from Ref [231]. Copyright 2018 Wound Healing Society. One (*) and two (**) asterisks represent probabilities less than 0.05 ($p < 0.05$) and 0.01 ($p < 0.01$), respectively

the prerequisite for dental implantation and orthodontic tooth movement [183, 184]. Oppositely the gradual reduction of the alveolar bone leads to tooth loosening and affects normal oral function, and the reabsorbed alveolar bone does not effective recovery function due to limited regenerative capacity [185]. Numerous studies have reported the application of ADSCs in alveolar bone regeneration, which could be introduced in this section.

Alveolar bone preservation is essential for tooth extraction. Cell-free biomaterials are commonly used after tooth extraction. Nevertheless, an inflammatory response was hardly avoided, which probably resulted in bone volume reduction [186, 187]. Thus, a team prepared a self-assembled bone-like substitute with osteogenesis-induced ADSCs and BMP-9. The composite materials favorably preserved alveolar bone volume, which was superior to that achieved with clinical biomaterials (Fig. 3A) [188]. Another research illustrated the delivery of ADSCs.

Following the delivery of ADSCs in a rat model of periodontitis, researchers observed that the mitigation of alveolar bone loss resulted from the activation of the aryl hydrocarbon receptor by kynurenine, mediated by indoleamine 2,3-dioxygenase. This activation facilitated enhanced binding to the nuclear factor (erythroid-derived 2)-like 2 promotes in macrophages, ultimately promoting their polarization towards an anti-inflammatory phenotype. Consequently, this process created a conducive microenvironment that facilitated the repair of adjacent cells [189]. A group fabricated novel cell-free scaffold that was composed of PLGA and ADSC-EVs. The ADSC-EVs were enriched with calcitonin gene-related peptide (CGRP), and this scaffold was designed to gradually release EVs, facilitating the delivery of CGRP to PDLSCs and then effectively promoting repair of alveolar bone defects [190]. Another viable method involved the use of a 3D-printed PCL-TCP scaffold seeded with ADSCs [93].

Platelet-enriched plasma (PRP) was utilized as a reservoir of growth factors in alveolar bone regeneration [191]. Tobita et al. have previously linked PRP with ADSCs as a scaffold material in animal experiments to explore the fundamental research of ADSCs transplantation for periodontal defects and validate the outcomes of

periodontal tissue regeneration [192, 193]. Building upon this foundation, the research team is presently engaging in a clinical trial to examine the potential of combined ADSCs and PRP transplantation in enhancing alveolar bone height in 10 individuals with moderate or severe periodontal disease after 36 weeks [194]. If proven effective, this cell therapy using autologous ADSCs may represent a promising medical technique for the regeneration of periodontal defects.

Gingival regeneration

Diabetes mellitus (DM) easily resulted in periodontal destruction and delayed wound healing [195]. A team developed ADsp-mTG hydrogel in the treatment of DM-related periodontitis. After implantation into diabetic mouse model, an enhanced gingival healing and keratosis was observed, indicating accelerated healing of diabetic periodontal wounds (Fig. 3B) [155]. Bisphosphonate-related osteonecrosis of the jaw (BRONJ), a common complication in usage of bisphosphonates, could impair gingival and bone tissues [196]. In clinic, soft tissue coverage was the key factor in the prevention of BRONJ, in order to reduce the secondary contamination, and establish a vascularized tissue bed that nourished damaged bone tissue [197, 198]. As a consequence, the transplantation of ADSCs within a HA scaffold was found to prevent enhance primary gingival healing by up-regulating the expression of TGF-β1 and fibronectin in rabbit models (Fig. 3C) [199]. Furthermore, BMP-9 was illustrated to expedite gingival healing when combined with osteogenically induced ADSCs [188].

Regrettably, the efficacy of stem cell-based treatments is frequently influenced by various factors [200, 201]. For instance, the DM can impact stem cell functionality and the utilization of ADSCs may elevate the potential for systemic immunosuppression, but the occurrence of BRONJ is common in patients with bone metastatic tumors undergoing immunosuppressive therapy. Consequently, it is imperative to explore alternative approaches to enhance gingival growth. ADSCs-Exo presents a

Table 5 The in vivo trials of ADSCs in facial nerve regeneration

Application	Experimental subjects	Methods	Conclusion	References
Facial nerve regeneration	Rat, underwent CFNG after transection of the right main trunk of the facial nerve	Added 1×10^6 ADSCs along the autologous nerve graft and the lines	Enhanced axonal regeneration	[227]
	Rat, underwent CFNG after transection of the left main trunk of the facial nerve	Wrapped an ADSC sheet around the autologous nerve graft, which was made from 1.5×10^6 cells in a 35 mm dish	Promoted axonal outgrowth, reduced the time to reinnervation, and improved the therapeutic effect of CFNG in patients with facial nerve palsy	[228]
	Rabbit facial nerve defect models	Combined 20 μL CM-Dil-ADSCs and acellular xenogeneic nerves for facial nerve repair, post-operatively, injected 0.5 mL autologous PRP on days 1, 2, 3, 5, and 7. Density of 1×10^6 cells / mL	Obtained preferable early curative effects, and comparable outcome to autologous nerve repair	[229]
	Rat facial nerve defect models	Implanted and sutured a 1 cm long decellularized arterial catheter at the 8 mm nerve defect site, then injected 25 μL autologous ADSC suspension into the lumen of the catheter. Density of 1×10^6 cells / 50 μL	Exerted a facilitative effect on facial nerve injury recovery	[230]
	Rat facial nerve defect models	Implanted a hybrid PGA-Col nerve conduit filled with type I collagen and ADSCs. Density of 1×10^5 cells / 10 μL	Promoted nerve regeneration	[231]
	Dog facial nerve paresis models	Utilized Gore-Tex tube filling with undifferentiated ADSCs encapsulated in Alg hydrogel. Density of 2×10^6 cells / mL	Enhanced neural repair from a functional standpoint	[232]
	Rat facial nerve paresis models	Utilized artificial nerve conduits–PGA filled with type I collagen and ADSCs. Density of 1×10^5 cells / 10 μL	Facilitated nerve recovery	[234]

CFNG: cross-facial nerve grafting; CM-Dil-ADSC: ADSCs labelled with CM-Dil living cell stain; PRP: platelet-rich plasma; PGA: polyglycolic acid; Col: collagen; Alg: alginate

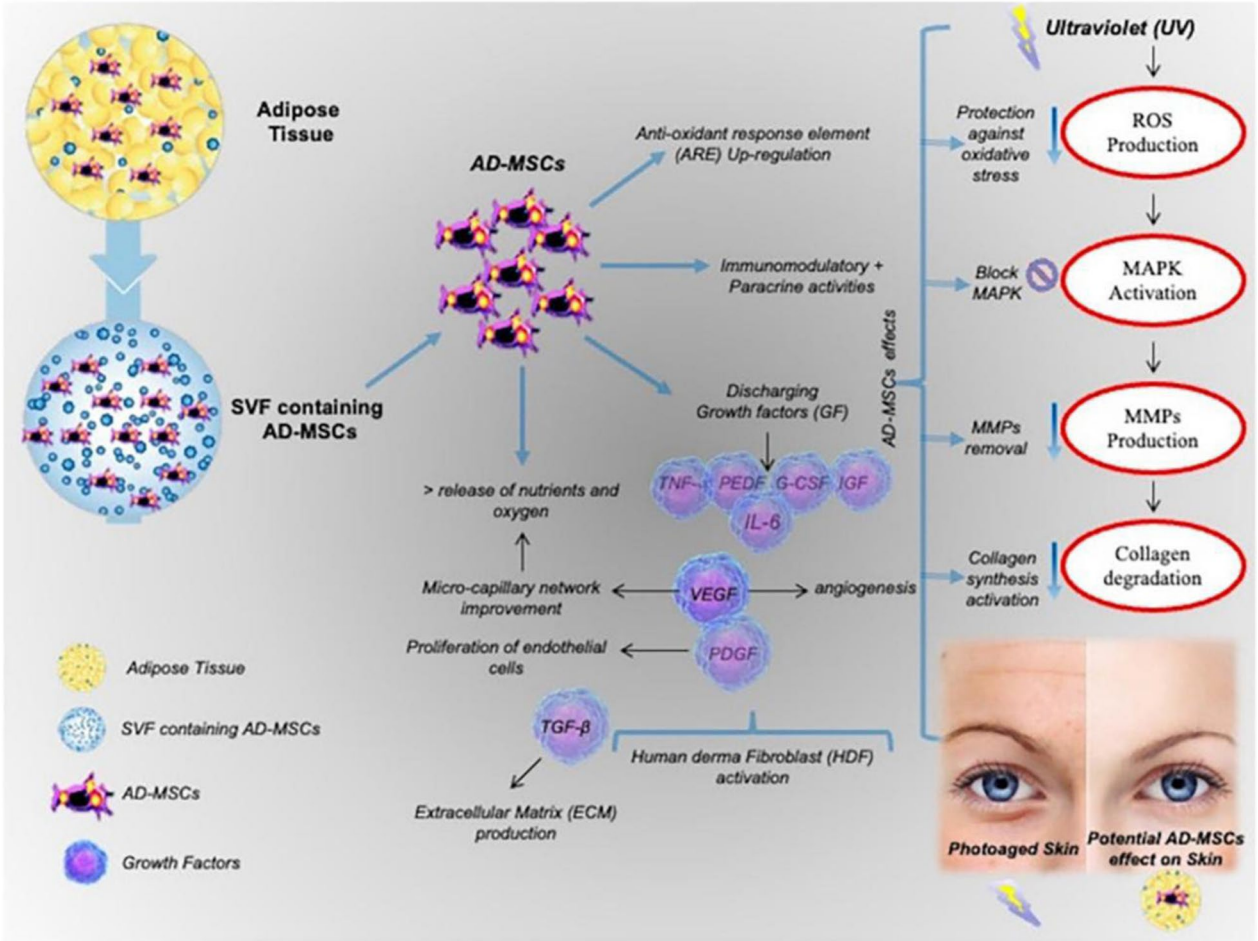


Fig. 5 The protective role of AD-MSCs [236]. The left half of this diagram elucidates that the AD-MSCs existing in the SVF extracted from adipose tissue possess functions such as anti-oxidation, immunomodulation, paracrine activities, growth factors discharge, nutrients and oxygen release. The right half of the figure demonstrates four mechanisms by which UV causes photoaging, including ROS production, MAPK activation, MMPs production and collagen degradation. AD-MSC primarily targets the aforementioned mechanisms to provide protection for photoaged skin. Reproduced with permission from Ref. [236] Copyright 2021 MDPI (Basel, Switzerland)

promising alternative as an acellular entity that mimics the functions of ADSCs. Therefore, future investigations could concentrate on the therapeutic potential of exosomes in promoting gingival regeneration.

Cell sheet technology is another promising approach in the periodontal tissue regeneration. Multiple layers of cells and ECM secreted by target cells mimicked the microenvironment to promote cells activities. ADSCs on the decellularized human amniotic membrane (DAM) were favor for the mineralization of ECM on the Col fibers of the DAM, providing a 3D framework for cell invasion and differentiation [202, 203]. In vivo test indicated ADSCs/DAM effectively repaired periodontal bifurcation defects, leading to successful regeneration of periodontal tissue [204].

Periodontal disease remains a significant issue in clinical practice due to its high prevalence, resulting in tooth loss and associated dysfunctions. The utilization of biomaterials derived from ADSCs for periodontal regeneration holds significant importance and promising potential (Table 4).

Tooth regeneration

Based on the data from the Fourth China Stomatology Health Epidemiological Survey, the prevalence of complete dentition among individuals aged 35–44 is 67.7%, while it is 33.8% among those aged 55–64 and only 18.3% among those aged 65–74 [215]. The current state of dentition defects and loss is concerning, with available treatments such as fixed partial dentures, removable dentures, and implant-supported dentures presenting drawbacks such as reduced mastication efficiency and risk of peri-implantitis. Consequently, stem cell-based tooth

regeneration has emerged as a promising therapeutic approach in addressing these challenges.

Current research in the field of stem cell-based tooth regeneration encompasses various aspects such as whole tooth, tooth root, dentin-pulp, and periodontal tissue regeneration, all of which rely on the unique differentiation capabilities of stem cells. Stem cells utilized for tooth regeneration include dental MSCs, such as DPSCs and PDLSCs, as well as non-dental MSCs like BMSCs and ADSCs, in addition to neural crest stem cells [13]. Wang and his research team have focused on the study of tooth regeneration. In 2006, they utilized human papillary epithelial stem cells and PDLSCs to successfully generate the root/periodontal complex in conjunction with crown technology, ultimately achieved functional regeneration of porcine teeth [216]. This success suggests that ADSCs may serve as appropriate seeding cells for tooth regeneration, a notion supported by a substantial body of literature, as follows [217].

ADSCs, recognized as a prominent category of multipotent stem cells, demonstrate characteristics akin to PDLSCs and possess the potential for odontogenic differentiation. Moreover, due to their minimally invasive harvesting procedures and substantial proliferative capabilities [17, 18], a growing body of research has investigated their application in dental regeneration to overcome the challenge of obtaining adequate quantities of PDLSCs [218]. The successful regeneration of whole tooth relies on the intricate interplay between epithelial and mesenchymal cells. By mimicking the in vivo interactions between these cell types, ADSCs have been demonstrated to transdifferentiate into a specialized 3D structure resembling a dental bud, accompanied by the expression of dental tissue-related markers [219]. This achievement highlights the potential of ADSCs in whole tooth regeneration. Nevertheless, challenges such as uncontrolled morphogenesis and tooth eruption continue to hinder the progress and practical implementation of this regenerative approach. Consequently, partial tooth regeneration may be a more viable option in the foreseeable future, utilizing seed cells, scaffolds, and signaling molecules for the biological regeneration of roots [220]. Specifically, ADSCs/porcine-treated dentin matrix complexes have manifested greater efficacy in regenerating dentin-like, pulp-like, and periodontal fiber-like tissues compared to dental-derived stem cells [221]. Additionally, ADSCs have demonstrated a higher capacity for odontogenic differentiation than BMSCs [222]. In addition to the aforementioned studies, a separate investigation has proposed that the microenvironment created by dental follicle cell conditioned medium has the potential to induce ADSCs to differentiate into cementoblast-like

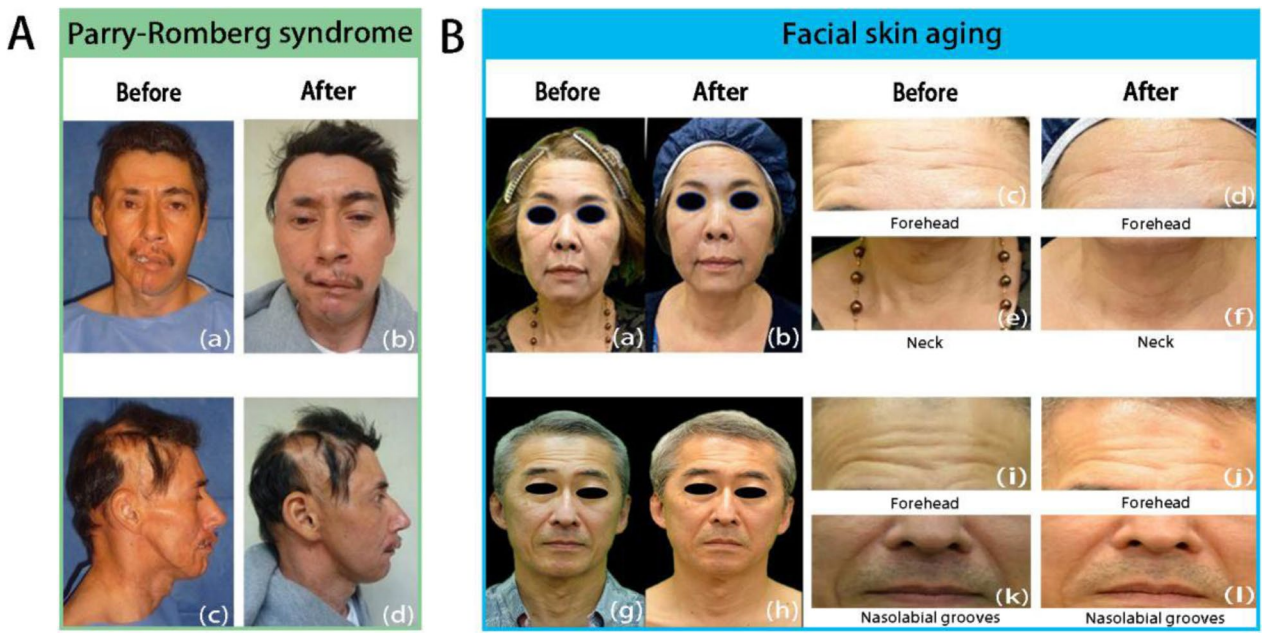


Fig. 6 The applications of ADSCs in plastic and cosmetic surgery [261, 264]. **A**. A 35-year-old male patient diagnosed with Parry-Romberg syndrome. **a**, **c** Preoperative view. **b**, **d** Postoperative view 12 months after lipoinjection enriched with stem cells and elements of the SVF. Reproduced with permission from Ref. [261] Copyright 2012 The Korean Society of Plastic and Reconstructive Surgeons. **B**. Photographs of 58-year-old lady, before (**a**, **c**, **e**) and 8 months after ADSCs treatment (**b**, **d**, **f**). Reduced wrinkle of forehead (**c**, **d**) and neck (**e**, **f**). Photographs of 61-year-old male, before (**g**, **i**, **k**) and 3 months after ADSCs treatment (**h**, **j**, **l**). Reduced wrinkle of forehead (**i**, **j**) and shallowing of nasolabial grooves was confirmed by comparison of (**k**) to (**l**). Reproduced with permission from Ref. [263] Copyright 2023 MDPI (Basel, Switzerland)

Table 6 The in vivo trials of ADSCs in plastic and cosmetic surgery

Application	Source	Experimental subjects	Methods	Conclusion	References
Anti-photoaging	ADSCs' secretome– LncRNA H19	Mouse photoaging models	H19-Exo injection. Dose of 1×10^{10} particles / mL and 0.5 mL per mouse	Prevented epidermal thickening and Col reduction and up-regulated the expression of SIRT1 by binding to miR-138	[238]
	ADSCs	Rat photoaging models	CO_2 laser treatment, then injected ADSCs. Energy: 10 J/CM^2; density: 9.6; degree: 3; spot size: 1.3 mm, pattern: square. Density of 1×10^7 cells / mL	Improved photoaging skins by up-regulating perturbed Wnt/β-catenin signaling imposed by UV irradiation to activate TGF-β2	[251]
	ADSCs' secretome	Mouse photoaging models	Injected 1×10^4 ADSCs with overexpressed VEGF	Inhibited senescence and recover from the injury caused by UV by down-regulating SA-β-Gal, p21 and MMP-1	[253]
	ADSCs	Mouse photoaging models	ADSCs injection. Density of 5×10^6 cells / 0.5 mL	Restored skin barrier by ameliorating the down-regulation of α6 integrin, CD34, and Col I by UVB, reducing the over-expression of COX2 and TNF-α induced by UVB	[254]
	Protein extracts of ADSC-CM	Female volunteers who had not received any anti-aging or whitening treatments within three months prior to the start of the study	Injected protein extracts of ADSC-CM via microneedles	Improved melanin levels, brightness, skin gloss, roughness, elasticity, and wrinkles	[255]
	ADSCs	Mouse photoaging models	ADSCs injection. Density of 1×10^3, 1×10^4, and 1×10^5 / 100 μL	Medium and high doses of ADSCs significantly reduced wrinkles, increased dermal thickness, regulated HDF proliferation and apoptosis, and modulated protein expression. Low doses showed no significant effect	[268]
	ADSCs	Mouse models	ADSCs injection and UVB irradiation. Density of 1×10^6 cells / 30 μL	Inhibited melanin formation	[269]
	ADSCs	Mouse photoaging models	ADSCs injection. Density of 5×10^5 cells / 50 μL	Attenuated tanning through suppression of tyrosinase activity	[252]
Anti-scarring and fibrosis	ADSCs	Pig full-thickness skin defect models	Injected 1×10^6 ADSCs	Alleviated scar formation with smaller scar sizes, better color quality and scan pliability	[256]
	ADSCs	Rat scald burn models	ADSCs injection and LLLT. Density of 1×10^6 cells / mL. Energy: 660 nm wavelength, 30 mW power, BIOSET Equipment, each point receives 1 J/cm^2 for approximately 3 s	Reduced inflammation and edema, increased angiogenesis and Col deposition, and better organization of the ECM	[258]
	SVF	Patients with soft tissue defect and scar on the face	SVF-enhanced autologous fat grafts	Enhanced the effect of scar correction	[260]

Table 6 (continued)

Application	Source	Experimental subjects	Methods	Conclusion	References
Improving facial defects	SVF	Patient with a 5-year history of progressive right facial hemiatrophy	SVF and fat injection	Reduced the severe depression of the frontotemporal region and provided better volume and symmetry	[261]
	ADSCs	Patients with Parry-Romberg disease	Implanted 1×10^7 ADSCs and microfat grafts	Better survival of grafted fat	[262]
	SVF	Patients with stable hemifacial atrophy for at least 2 years	SVF-supplemented autologous fat grafting	Better fat survival and clinical improvement	[263]
Beauty and anti-aging	ADSCs	Eight patients (six females and two males) aged 32 to 62	Injected 1×10^8 ADSCs	Wrinkles were improved, double eyelids became prominent and facial pores became smaller. All effects persisted for more than 1 year	[264]
	ADSC-CM	Twenty-two patients (twelve females, ten males) aged 24 to 50	Applied 3 mL ADSC-CM to the skin that had undergone FxCR treatment	Increased subject satisfaction, elasticity, skin hydration, and skin elasticity and decreased TEWL, roughness, and the melanin index	[265]
	ADSCs' secretome	Thirty women, aged 35 to 59, with signs of facial cutaneous senescence	ADSCs' secretome assisted MN or FL treatments. MN: 36 fine needles (vertical, horizontal, diagonal) at 150 μm depth. FL: 15 mJ energy, 900 μs pulse, density 15, depth 2. Total secretome volume: 3 mL	Both MN and FL groups achieved significant improvements in total DPAS and wrinkles, but no statistical significance between them	[267]
	ADSCs	Mouse models	ADSCs injection. Density of 5×10^5 cells / 30 μL	Increased dermal thickness and Col density	[270]

UVB: ultraviolet B; ADSC-CM: conditioned medium of adipose-derived stem cells; LLLT: low-level laser therapy; SVF: stromal vascular fraction; FxCR: fractional carbon dioxide laser resurfacing; TEWL: transepidermal water loss; MN: microneedle; FL: fractional CO_2 laser; DPAS: dermoscopy photoaging scale

cells, thereby presenting a novel approach to stem cell-mediated cementum regeneration [223].

Collectively, these findings lay the foundation for advancements in tooth regenerative medicine. However, the field of dental regenerative medicine remains largely confined to preclinical research, primarily due to safety concerns. The work of Wang and his team has been restricted to a porcine model [216], highlighting the imperative for future researchers to rigorously validate the safety and efficacy of tooth regeneration techniques prior to advancing to human clinical trials.

Facial nerve regeneration

The facial nerves play a crucial role in innervating the musculature of the face and regulating facial expressions. Damage to these nerves can result in paralysis on the affected side of the face, impacting functions such as chewing, speaking, and closing the eyes, as well as restricting social interactions and leading to psychological issues. The causes of facial nerve damage are varied, encompassing pathologic factors such as trauma, infections, and tumors, iatrogenic factors like surgical procedures on the parotid gland or TMJ, and idiopathic origins [224].

Currently, nerve autografting is the predominant treatment for facial nerve gaps, despite challenges such as limited nerve sources, donor site complications, and suboptimal outcomes [225]. With the advancement of tissue engineering, autologous cell therapy is increasingly utilized to assist nerve regeneration or even substitute the traditional autologous nerve transplantation. Various stem cells, including ADSCs, BMSCs, DPSCs, induced pluripotent stem cells, etc., have demonstrated the ability to differentiate into Schwann cell-like cells and neural stem cells, with ADSCs garnering particular interest [226].

There are primarily two strategies for utilizing ADSCs in nerve regeneration. (i) ADSCs assist autologous or allogeneic nerve transplantation (Fig. 4A). Traditional autologous cross-facial nerve grafting typically requires more than 6 months to achieve facial nerve reinnervation on the affected side. This long recovery period can lead to muscle atrophy due to prolonged innervation loss, ultimately resulting in suboptimal recovery outcomes. To address these challenges, ADSCs have been incorporated into the graft and surrounding tissues, leading to enhanced axonal regeneration and improved facial nerve recovery [227]. Furthermore, the morphology of ADSCs was found to have an impact on the outcomes. Specifically, ADSCs sheets described greater efficacy in promoting axonal growth and reducing recovery time compared to ADSCs in suspension [228]. In the context of allogeneic nerve transplantation, studies have described acellular xenografts incorporating ADSCs and PRP yielded comparable results to autologous nerve transplantation in the early stages [229]. (ii) ADSCs combined with nerve guidance conduits (NGCs) to regenerate nerves, with NGCs categorized into biological and artificial conduits (Fig. 4B). The most prevalent treatment of the former is decellularized arterial catheter, and the ADSCs-catheter arteriosus composite has illustrated promise as a viable therapeutic approach [230]. As for the latter, the combination of polyglycolic acid-Col nerve conduits or Gore-Tex tubes with ADSCs has demonstrated favorable outcomes in promoting facial nerve regeneration [231, 232]. However, certain studies suggest that this method may be less effective than nerve autografting. Nevertheless, advancements in material science and cell biology are expected to enhance the efficacy of nerve guidance conduits in nerve repair in the foreseeable future.

Furthermore, the versatile differentiation capabilities of ADSCs present both advantages and disadvantages. Specifically, when ADSCs differentiate into nerve cells, their potential to differentiate into fibroblasts becomes a drawback. To address this issue, genetic modification was utilized to inhibit procollagen-lysine 1, 2-oxoglutarate 5-dioxygenase 1 in ADSCs [233]. The findings indicated that the gene-modified groups displayed improved facial nerve function and reduced fibrosis in the affected area, offering novel insights into the potential of combining autologous cell therapy with genetic modification. In the future, enhanced comprehension of ADSCs may lead to further enhancement of the therapeutic efficacy of facial nerve regeneration through the modification of additional genes. Moreover, the potential for gene modification of ADSCs to be applied across various disciplines is apparent.

Ultimately, ADSCs represent a promising source of seed cells for tissue regeneration engineering, and ADSCs-based therapy holds significant promise for the regeneration of facial nerves (Table 5).

Plastic and cosmetic surgery

Facial aesthetics are of primary concern in human beauty. Natural or pathological aging can accelerate skin aging, impair the skin's inherent protective function, and lead to scarring, all of which have an impact on beauty. In this section, we gave a comprehensive introduction on ADSCs-treated facial aesthetic.

Photoaging problems in ADSCs applications

Exposure to ultraviolet (UV) radiation is identified to result in facial skin photoaging, with various detrimental effects such as wrinkles, dryness, laxity, rough texture, loss of elasticity, impaired wound healing, and the

proneness to benign and malignant tumor. The reviews elucidate the potential mechanisms on ADSCs-treated photoaging (Fig. 5) [235, 236]. (i) Anti-oxidative [237, 238]. ADSCs had the ability to release antioxidants, and inhibit the generation of reactive oxygen species (ROS) by up-regulating the levels of antioxidant enzymes including glutathione peroxidase, superoxide dismutase, and catalase [239–241]. The down-regulation of myeloperoxidase and NADPH oxidase by ADSCs also reduce ROS generation [242]. (ii) Anti-apoptosis and anti-senescence. ADSCs could inhibit apoptosis by repairing DNA damage and regulating the expressions of anti-apoptotic and/or pro-apoptotic genes [238, 243, 244]. Specifically, ADSCs mediated the phosphorylated histone family 2A variant protein, which was a crucial player in the DNA double strand break process [245]. Furthermore, it was proved that ADSC-Exos inhibited cell apoptosis through the Wnt/β-catenin signaling pathway [246]. (iii) Anti-degradation of the ECM. Zhang et al. demonstrated ADSCs-Exos improved the proliferation and migration of fibroblasts, as well as enhancing the deposition of Col type I and III via the PI3K/Akt signaling pathway [247]. Moreover, ADSCs-Exos decreased the expression of MMP and Col through regulating Nrf2 and MAPK/AP-1, and activated TGF-β/-Smad pathways [248, 249]. (iv) Anti-inflammatory. The secretome of ADSCs contained various types of pro-inflammatory and anti-inflammatory factors. For examples, ADSCs induced a shift in macrophage polarization towards anti-inflammatory M2 phenotypes, and inhibited the production of pro-inflammatory cytokines including TNF-α and IL-12 [237]. Additionally, they inhibited the proliferation and differentiation of Th2-type mCD4$^+$ T cells while promoting those of regulatory T cells, suggesting that the phenotypic conversion of T cells may be one of the mechanisms for the anti-inflammatory effect of ADSCs [250]. Also, a variety of preclinical studies have been investigated on the treatment of photoaging in the use of ADSCs and their secretions [251–255].

Anti-scarring and fibrosis in ADSCs applications

In the fields of anti-scarring and fibrosis, two primary approaches have been introduced. The first involves the direct application of ADSCs in wound healing. Yun et al. demonstrated, using a Yorkshire porcine skin model, that subcutaneous injection of ADSCs in early scars can effectively reduce scar size, improve coloration, and enhance scar flexibility [256]. A separate clinical study further indicated that local ADSC injections significantly improved the texture and vascularity of keloids. During a 3-month follow-up period, patients reported no adverse effects other than transient pain during injection and mild abdominal discomfort for a few days following liposuction [257]. Additionally, the combination of ADSCs with other therapies has shown considerable efficacy. For instance, low-level laser therapy (LLLT) combined with ADSC injection accelerated skin regeneration in a rat scald model [258]. Furthermore, ADSC-assisted autologous fat transplantation markedly improved the survival rate of soft tissue augmentation [259]. Recently, the integration of adipose-derived SVF and PRP in treating facial scars resulted in improved contour recovery after 1 year, compared to simple fat graft implantation, with no additional complications reported [260].

Improving facial defects in ADSCs applications

Progressive facial hemiatrophy, known as Parry-Romberg syndrome, can be effectively treated using ADSCs-based cell-assisted lipotransfer (CAL). Castro-Govea et al. indicated the use of CAL with SVF and lipoinjection could improve facial depression. Patients exhibited satisfactory postoperative outcomes with reduced depression, enhanced volume, and improved symmetry after 12-month follow-up (Fig. 6A) [261]. CAL was proved to be more effective when compared with only fat grafting in the treatment of Parry-Romberg syndrome [262, 263].

Beauty and anti-aging in ADSCs applications

A clinical investigation demonstrated intradermal administration of ADSCs, improved the wrinkles in various facial areas including the glabella, lower eyelids, crow's feet, forehead, and nasolabial grooves with more than 1 year (Fig. 6B) [264]. Furthermore, enhanced treatment outcomes were obtained by the integration of conventional techniques with ADSCs. For instance, ADSCs and FxCR could enhance skin hydration and elasticity, as well as, reducing skin transepidermal water loss, roughness, and the melanin index [265].

In the future, the utilization of ADSCs in plastic surgery was anticipated to evolve towards a less invasive and more effective approach. Conventional macrofat is characterized by large particle diameters, necessitating larger diameters for transplantation to prevent complications such as fat embolism. This presents challenges in grafting macrofats into the deep dermis and subdermis. Therefore, it is suggested that future research efforts focus on the utilization of microfat and nanofat. A comprehensive review of current research progress on nanofat has been conducted [266]. Additionally, there is a need for the development of minimally invasive and efficient methods of administration to improve patient satisfaction and comfort. A comparison of the effects of microneedles and fractional CO_2 laser on ADSC secretome delivery for facial skin rejuvenation revealed that both methods yielded favorable results [267].

Empirical evidence from both animal studies and clinical trials has substantiated the efficacy of ADSCs in these domains (Table 6). Most clinical trials reported follow-up periods ranging from 3 months to 1 year, during which no adverse reactions were observed, thereby suggesting the current safety of ADSC injections. Nonetheless, the long-term efficacy and safety of ADSCs necessitate further investigation through extended follow-up studies. Moreover, the existing clinical trials typically involve small sample sizes, underscoring the need for larger-scale randomized controlled trials to robustly validate the therapeutic effects of ADSCs.

Conclusion and future perspectives

Undoubtedly, ADSCs have a great potential for use in tissue repair and regeneration in the field of reconstructive surgery in maxillofacial region, which were confirmed by numerous in vitro, in vivo and preclinical and clinical studies. Although the current strategies we introduced in this review had updated rapidly in the past decade, the comprehensive understanding of the interaction between ADSCs, scaffolds and growth factors, and their underlying mechanisms are crucial for the development of ADSCs-based biomaterials. Another important issue for the utilization of ADSCs is the clinical translation. Still numerous obstacles need to be carefully addressed: the collection site of donor cells, the optimal concentration of ADSCs and relative growth factors, and the selection of carriers (scaffolds). Overall, the design of ADSCs-based biomaterials with appropriate growth factor is worthy to be explored in the future.

Abbreviations

ADSCs	Adipose-derived stem cells
TMJ	Temporomandibular joint
DPSCs	Dental pulp stem cells
PDLSCs	Periodontal ligamental stem cells
BMSCs	Bone marrow-derived stem cells
EVs	Extracellular vesicles
SVF	Stromal vascular fraction
HA	Hyaluronic acid
CS	Chitosan
PLGA	Poly(lactic-co-glycolic acid)
BMP-2	Bone morphogenetic protein 2
Alg	Alginate
Gel	Gelatin
PCL	Polycaprolactone
PLA	Polylactic acid
HAp	Hydroxyapatite
Col	Collagen
VEGF	Vascular endothelial growth factor
TCP	Tricalcium phosphate
BPs	Black phosphorus
SF	Silk fibroin
BCP	Biphasic calcium phosphate
ECM	Extracellular matrix
Ti	Titanium
Mg	Magnesium
Zn	Zinc
TMD	Temporomandibular disorder
CSF-1	Colony-stimulating factor-1
FGF	Fibroblast growth factor
OA	Osteoarthritis
TGase	Transglutaminase
mTG	Microbial transglutaminase
ADsp	ADSC spheroids
MAP	Mussel adhesive protein
aECM	Artificial ECM
RGD	Alg-Gly-Asp
HC-DCB	Heparin-conjugated decellularized bone matrix
PDGF	Platelet-derived growth factor
PDGFRβ	PDGF β receptor
bdECM	Decellularized ECM
β-TCP	Beta-TCP
μRB	The gelatin-based microribbon
EPCs	Endothelial progenitor cells
Avi-β-TCP	Avidin-coated β-tricalcium phosphate
PRP	Platelet-rich plasma
vhEGCG-GS	Vacuum-heated gelatin sponges modified with epigallocatechin gallate
CGRP	Calcitonin gene-related peptide
DM	Diabetes mellitus
BRONJ	Bisphosphonate-related osteonecrosis of the jaw
DAM	Decellularized human amniotic membrane
AM	Amniotic membrane
ZA	Zoledronic acid
PCL NFs	Polycaprolactone nanofibers
Fn	Fibronectin
Alg	Alginate
SRP	Scaling and root planning
NGCs	Nerve guidance conduits
CM-DiI-ADSC	ADSCs labelled with CM-DiI living cell stain
PGA	Polyglycolic acid
IPJG	Interpositional jump-graft
UV	Ultraviolet
ROS	Reactive oxygen species
CAL	Cell-assisted lipotransfer
UVB	Ultraviolet B
ADSC-CM	Conditioned medium of adipose-derived stem cells
LLLT	Low-level laser therapy
FxCR	Fractional carbon dioxide laser resurfacing
TEWL	Transepidermal water loss
MN	Microneedle
FL	Fractional CO_2 laser

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Author contributions

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Author details
[1]Department of Orthodontics, School and Hospital of Stomatology, China Medical University, Nanjing North Street 117, Shenyang 110002, China.

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