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Combination of scaffold with adipose-derived mesenchymal stem cell on knee joint cartilage defects: A literature review

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Abstract: Knee joint cartilage defects are a significant clinical challenge due to the limited regenerative capacity of articular cartilage, often leading to joint degeneration and osteoarthritis (OA). Conventional treatment methods, such as surgical repair and conservative management, frequently fail to restore cartilage function fully. In recent years, scaffold-based tissue engineering using adipose-derived mesenchymal stem cells (ADMSCs) has emerged as a promising strategy for cartilage regeneration. ADMSCs, known for their abundant availability, ease of isolation, and chondrogenic potential, provide a viable cellular source for repairing damaged cartilage. When combined with biocompatible scaffolds, ADMSCs can enhance tissue regeneration by promoting cell proliferation, differentiation, and extracellular matrix (ECM) formation at the injury site. Various scaffold materials, including natural and synthetic polymers, have been explored to provide the structural support necessary for cell attachment and tissue formation. This literature review examines the current advancements in the application of ADMSC-loaded scaffolds for knee joint cartilage defects, focusing on their biological properties, scaffold designs, and the outcomes of preclinical and clinical studies. The review also addresses the challenges, such as scaffold degradation, mechanical properties, and cellular migration, that must be optimized for successful clinical translation. Overall, this review highlights the potential of ADMSC-based scaffold systems to offer a viable solution for knee cartilage repair and provides insights into future directions for improving therapeutic strategies in cartilage tissue engineering.

Keywords: *Adipose-derived mesenchymal stem cells, Knee joint cartilage defects, Literature review, Regenerative medicine, Tissue scaffold.*

1. Introduction

The knee joint, owing to its anatomical position and complex biomechanics, is particularly prone to injury [1,2]. Patients, especially those over 40 years old and athletes recovering from traumatic injuries, frequently report pain in this joint, primarily in the medial compartment and the patellofemoral region. These symptoms are typically attributed to structural alterations in the articular cartilage, potentially leading to osteoarthritis (OA) [2]. Cartilage damage in major joints is a frequent occurrence and may present as an isolated issue or in conjunction with bone defects, ligament injuries, limb misalignment, or associated traumatic injuries [1]. Cartilage, particularly articular cartilage, is a specialized connective tissue of chondrocytes embedded within an extracellular cartilage matrix. This tissue is vital in joint mechanics, ensuring durability and mobility by facilitating nearly frictionless movement and enabling efficient transmission of mechanical loads across joint surfaces [2–4]. Its lack of vascularization and limited cellularity contribute to a poor intrinsic capacity for self-repair. Furthermore, the dense, three-dimensional structure of the ECM impedes stem cell migration, hindering cartilage regeneration [3]. In general, articular cartilage injuries are identified in 34–62% of knees during arthroscopic procedures [2,3].

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Nonoperative management is typically the first-line approach for focal cartilage lesions; however, up to 90% of patients undergoing conservative treatment continue to experience pain and mechanical symptoms, often necessitating surgical intervention [5]. Surgical options are guided by factors such as the size and severity of the defect, adherence to postoperative rehabilitation protocols, weight-bearing limitations, and the patient's goals and expectations [5,6]. Nevertheless, these two therapeutic modalities frequently fail to restore the native structure and function of the damaged cartilage, driving the need for advanced regenerative strategies [7]. Cell-based therapy has garnered significant attention over the past decades, offering promising potential to revolutionize the treatment of various injuries and diseases [8,9].

The differentiation of mesenchymal stromal cells (MSCs) into chondrocytes has been extensively studied, resulting in cartilaginous tissue formation In laboratory experiments, MSCs have demonstrated the ability to generate cartilage-like tissue when cultured with the appropriate growth factors and scaffolds, highlighting their potential in cartilage repair and regeneration [10]. In both in vivo and in vitro studies, adipose-derived mesenchymal stem cells (ADMSCs) have demonstrated the potential to differentiate into a variety of cell types, including mesenchymal cells and non-mesenchymal cells. This remarkable differentiation capacity highlights the versatility of ADMSCs and their potential for a wide range of regenerative applications, particularly in tissue engineering and cellular therapies for repairing damaged tissues, including cartilage [11]. ADMSCs, with their ability to differentiate into chondrocytes and secrete ECM components, present a promising alternative for cartilage regeneration [11,12]. Combined with scaffolds, these stem cells can provide structural support, promote cell proliferation, and enhance tissue formation at the defect site. Furthermore, ADMSCs are relatively easy to isolate from adipose tissue, a readily accessible and abundant source, making them a feasible option for personalized treatments. Incorporating scaffolds in tissue engineering strategies is essential to create a suitable environment for cell attachment, migration, and matrix deposition [11–13]. Therefore, investigating the use of ADMSC-loaded scaffolds for knee joint cartilage defects is crucial to developing more effective, sustainable, and minimally invasive therapies for cartilage repair, with the potential to significantly improve clinical outcomes in patients suffering from cartilage-related disorders [11,12]. This literature review evaluates the current progress and challenges in combining scaffolds with ADMSCs for knee cartilage regeneration.

2. Methodology

This study was conducted following a comprehensive review of relevant literature. Data were gathered through electronic databases such as PubMed, ScienceDirect, and Google Scholar, focusing on articles published within the last ten years. The search utilized key terms including "adipose-derived mesenchymal stem cells", "knee joint cartilage defects", and "tissue scaffold". Only English-language studies focusing on the application of ADMSC-loaded scaffolds for knee joint cartilage defects were included in the analysis.

3. Results

3.1. Scaffold-ADMSC Synergy in Knee Cartilage Repair

The dynamic interaction between ADMSCs and scaffolds is a cornerstone of effective cartilage repair strategies. Upon scaffold seeding, ADMSCs adhere to the scaffold surface via integrin-mediated binding, which triggers intracellular signaling cascades essential for cell survival, proliferation, and differentiation. The success of these interactions is strongly influenced by the scaffold's biophysical and biochemical properties, including porosity, mechanical stiffness, and surface functionalization. Scaffolds designed with optimized properties provide mechanical and biochemical cues that replicate the natural cartilage ECM, thereby promoting the chondrogenic differentiation of ADMSCs. Moreover, scaffolds can be engineered to incorporate bioactive molecules, such as transforming growth factor-β (TGF-β) and bone morphogenetic protein-2 (BMP-2), to further augment cellular activity and steer lineage-specific differentiation pathways [14].

Effective tissue integration is paramount for the long-term success of scaffold-based cartilage repair. Seamless integration between the scaffold and surrounding native tissue is essential to establish a stable

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interface capable of withstanding load-bearing activities. ADMSCs play a pivotal role in this process by secreting matrix metalloproteinases (MMPs) and other remodeling enzymes, which facilitate the degradation of damaged cartilage and the deposition of newly synthesized matrix components. Concurrently, ADMSCs produce pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), that drive neovascularization within the adjacent subchondral bone. This vascularization enhances nutrient and oxygen delivery, supporting cellular activity and tissue maturation. Advanced scaffold designs featuring gradient architectures or hierarchical structures further promote effective integration by replicating the natural transition between cartilage and subchondral bone, thereby optimizing biomechanical and biological compatibility [15].

The primary objective of scaffold-ADMSC synergy is the regeneration of hyaline-like cartilage that closely mirrors native tissue in both structural and functional properties. Under optimal mechanical and biochemical cues, ADMSCs differentiate into chondrocytes, synthesizing critical cartilage-specific matrix components such as type II collagen and proteoglycans. Scaffolds serve not only as a structural framework but also as a template for organized ECM deposition. Biodegradable scaffolds gradually break down in response to enzymatic activity, creating space for new tissue formation while preserving mechanical integrity throughout the repair process. Advanced techniques, such as dynamic mechanical loading in bioreactors, further enhance cartilage regeneration by simulating physiological conditions and promoting the alignment of collagen fibers [16].

The interplay between scaffolds and ADMSCs significantly enhances cartilage repair by synchronizing cellular activity with structural support. Scaffolds provide a protective niche for ADMSCs, ensuring their localization and prolonged functionality, while the bioactive factors secreted by ADMSCs accelerate scaffold remodeling and stimulate endogenous tissue repair. This synergistic interaction establishes a microenvironment optimized for the regeneration of durable, biomechanically robust cartilage with extended functional longevity [14–16].

3.2. Clinical Studies and Current Applications

The systematic review by Perdisa et al. (2015) highlights the considerable potential of adipose-derived mesenchymal stem cells (ADMSCs) for treating articular cartilage defects, supported by both preclinical and clinical evidence. In animal studies, ADMSCs showed effective chondrogenic differentiation, cartilage repair, and integration with surrounding tissues, especially when combined with suitable scaffolds or used in cell-based therapies. Clinical trials reinforced these findings, demonstrating notable improvements in cartilage repair, pain reduction, and functional recovery in patients with knee OA and cartilage defects. Nevertheless, the review underscores the importance of establishing standardized treatment protocols, refining delivery methods, and conducting long-term follow-up studies to realize the benefits of ADMSCs in cartilage regeneration fully [17]. The meta-analysis by Meng et al. (2021) concluded that administering ADMSCs or stromal vascular fraction (SVF) resulted in improvements in clinical, imaging, and histological outcomes, with no severe adverse events reported. Although the studies included in the analysis were heterogeneous, the findings provide evidence supporting the use of ADMSCs or SVFs for the treatment of focal cartilage defects [18].

Song et al. (2016) developed a 3D bilayered osteochondral (OC) construct incorporating ADSMC to treat large OC defects. This composite scaffold consisted of porcine cancellous bone and a chitosan/gelatin hydrogel placed on opposite sides to facilitate bone and cartilage regeneration, respectively. ADMSCs were seeded in the hydrogel to promote chondrocyte-like differentiation and in the cancellous bone to support osteoblast-like differentiation. The study demonstrated that the bilayered scaffold significantly enhanced ADMSC proliferation through intercellular interactions, outperforming single-layer scaffolds [19]. Additionally, a rabbit model of OC defects was used to test a poly(l-glutamic acid)-based bilayer scaffold combined with autologous ADMSCs for simultaneous regeneration of hyaline-like cartilage and subchondral bone. In this design, BMP-2 was used in the lower region to induce osteogenesis, while TGF-β1 and insulin-like growth factor-1 (IGF-1), were applied to the upper region to induce chondrogenesis, promoting the aggregation of ADMSCs into multicellular spheroids. Upon implantation into the knee's patellofemoral groove, scaffolds with BMP-2 and preinduced ADMSC spheroids successfully regenerated both cartilage and subchondral bone after 12 weeks. In

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comparison, scaffolds with only BMP-2 showed limited regeneration, promoting subchondral bone repair, while bare scaffolds resulted in poor tissue regeneration overall [20].

A recent study investigated the use of 3D-printed full-thickness scaffolds for treating OC defects in the trochlear grooves of minipigs. The researchers developed bilayer scaffolds by incorporating tricalcium phosphate (TCP) within a polycaprolactone (PCL) base to promote osteogenic differentiation on the bottom layer, while decellularized bovine cartilage ECM was placed on the superficial side to facilitate chondrogenesis in ADMSCs. Additionally, an electrospun disk was inserted between the two layers to replicate the natural tidemark, preventing blood vessel infiltration and ossification in the cartilage layer. Five experimental conditions were tested: (a) open lesion defects as a negative control, (b) acellular scaffolds without tidemarks, (c) acellular scaffolds with tidemarks, (d) ADMSC-seeded scaffolds, and (e) autologous explants as a positive control. After four months, autologous explants yielded the best results, while ADMSC-seeded scaffolds closely resembled the positive control. In contrast, open lesions showed disorganized repair tissue and acellular scaffolds promoted subchondral bone regeneration. The scaffold without the tidemark more effectively filled the lesion but inhibited native cell migration and cartilage regeneration [21]. Further studies also explored the use of human umbilical cord blood MSCs seeded in bilayer scaffolds consisting of hyaluronic acid (HA) and gelatin-based microcrystals to promote bone and cartilage regeneration, respectively. In a dog model with OC defects in the femoral trochlear groove, these scaffolds successfully filled the defects with newly formed tissue, exhibiting a biphasic structure of bone and cartilage [22].

A systematic review by Issa et al. (2022) demonstrated that ADMSCs are effective in alleviating knee OA symptoms, as evidenced by significant improvements in both function and pain levels. Additionally, ADMSC injections led to enhanced cartilage integrity, suggesting their potential for regenerating knee cartilage and offering a promising therapeutic approach to OA treatment [13]. This is also supported by studies by Kangari et al. (2020) and Zhang et al. (2022) which emphasize that ADMSCs demonstrate significant regenerative capabilities in preclinical models and clinical trials, with improvements observed in tissue healing, functional recovery, and pain reduction [24,25]. The meta-analysis by Ow et al. (2023) concluded that scaffold-implanted MSCs provide moderately effective short-term outcomes in the repair of knee chondral defects. The analysis showed notable improvements in cartilage repair, functional recovery, and pain reduction, suggesting that scaffold-implanted MSCs are a promising therapeutic approach for managing knee chondral defects in the short term. However, the study highlights the need for further investigation into long-term outcomes to assess the sustainability of these benefits fully [23]. Recent advances in biomaterial-based scaffolds have significantly enhanced the promotion of cartilage regeneration. These scaffolds are crucial in providing structural support, facilitating cell migration, and improving tissue integration during cartilage repair. Innovations in natural and synthetic materials have shown great promise in creating scaffolds that closely mimic the native ECM of cartilage. This approach has improved cell differentiation, matrix deposition, and tissue remodeling, thereby advancing the potential for effective cartilage regeneration [14]. Overall, a summary of studies related to the use of scaffolds with ADMSCs in knee cartilage joint defects is shown in Table 1.

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Table 1.
Summary of studies on using scaffolds with ADMSCs in knee cartilage joint defects.

Authors, year	Study design	Models	ADMSCs harvesting and isolating methods	Scaffolds	Key findings
Perdisa et al., 2015 [17]	Systematic review	Humans and animals with knee OA (naturally occurred and induced)	Various (mostly autologous ADMSCs)	Fibrin glue scaffold (1 study)	ADMSCs demonstrated significant chondrogenic differentiation, cartilage regeneration, and seamless integration with adjacent tissues, particularly when employed with appropriate scaffolds or within cell-based therapeutic approaches.
Meng et al., 2021 [18]	Systematic review and meta-analysis	Humans with present complaints and/or a history of cartilage damage	Various (mostly autologous abdominal ADMSCs	Fibrin glue scaffold (1 study)	The studies demonstrated the safety and efficacy of ADMSCs in treating cartilage defects
Song et al., 2016 [19]	Experimental research	A 49-year-old female with an osteochondral defect (not specified otherwise)	Autologous ADMSC	Cancellous and hydrogel scaffolds produced by blending and cross-linking chitosan and gelatin	ADMSCs are an ideal cell source for osteochondral composite reconstruction. Additionally, the bi-layered scaffold significantly boosted cell proliferation when compared to cells seeded on individual scaffolds.
Zhang et al., 2016 [20]	Experimental research	Animal (rabbit) with osteochondral defect	Autologous ADMSC	PLGA/chitosan-based bilayer scaffold	ADMSCs spontaneously aggregated to form spheroids in situ within the chemically cross-linked PLGA/chitosan chondrogenic scaffold. This process enhanced both the in vitro chondrogenic differentiation of ADSMCs and the in vivo regeneration of hyaline-like cartilage.
Nordberg et al., 2021 [21]	Experimental research	Animal (minipig) with osteochondral defect	Autologous ADMSC	3D-bioplotted scaffold	Lesions treated with scaffolds demonstrated enhanced structural organization and more complete tissue filling compared to untreated open lesions, highlighting the benefits of scaffold-based implants in tissue repair.
Zhong et al., 2021 [22]	Experimental research	Animal (dog) with osteochondral defect	Human umbilical cord blood MSC	Bilayer scaffolds consisting of hyaluronic	These scaffolds effectively repaired the defects by promoting the formation of

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				acid and gelatin-based microcrystals	new tissue, resulting in a biphasic structure comprising both bone and cartilage.
Ow et al., 2023 [23]	Meta-analysis	Humans with high-grade chondral lesions on the tibiofemoral or patellofemoral articular surfaces	Autologous ADMSC	Bioscaffold and acellular scaffold with cBMA augmentation	Cartilage repair using ADMSC with cBMA augmentation shows slightly superior short-term outcomes compared to scaffold-implanted MSCs.

Source: ADMSCs, adipose-derived mesenchymal stem cells; MSC, mesenchymal stem cells; OA, osteoarthritis; PLGA, poly(l-glutamic acid); cBMA, concentrated bone marrow aspirate.

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4. Discussion

The results of this literature review emphasize the potential of combining scaffolds with ADMSCs to regenerate knee joint cartilage defects. Both preclinical and clinical studies have shown that scaffolds, when seeded with ADMSCs, play a crucial role in promoting chondrogenesis, supporting tissue integration, and enhancing cartilage repair. This combination offers a promising therapeutic approach for addressing cartilage damage, improving functional recovery, and reducing pain. In this section, a review will be made regarding ADMSCs and scaffolds in general.

4.1. Properties of ADMSC

All mammalian species and certain non-mammalian species contain adipose tissue, a complex organ with endocrine, immunomodulatory, energy-storage, and structural roles [26]. Its diverse cell population includes mature adipocytes (more than 90%) and SVF, which is composed of hematopoietic cells like granulocytes, monocytes, and lymphocytes (25–45%), stromal/stem cells (15–30%), endothelial cells (10–20%), and pericytes (3–5%) [11,26]. Age, anatomical location, and histological type are some variables that affect the percentage of stem cells in adipose tissue. Brown adipose tissue, which is characterized by its high mitochondrial content, is specialized for thermogenesis, while white adipose tissue, which is more prevalent, primarily serves in energy storage and organ protection [11]. Multi-lineage ADMSCs are found predominantly in white adipose tissue and are more concentrated in subcutaneous fat deposits compared to visceral fat deposits [26].

ADMSCs are multipotent stem cells characterized by an undifferentiated immunophenotype, with inherent capacities for self-renewal and multipotency [11]. These cells can differentiate into various cell types, including osteoblasts, chondrocytes, neurons, myocytes, endothelial cells, adipocytes, and cardiomyocytes [11,26]. Furthermore, ADMSCs respond to inflammatory stimuli by secreting anti-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-4 (IL-4), IL-6, IL-10, and IL-1 receptor antagonists. Additionally, they produce numerous growth factors, including TGF-β1, hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), and stromal cell-derived factor-1 (SDF-1), which play pivotal roles in tissue remodeling, angiogenesis, and anti-apoptotic processes [11,26–28]. Notably, ADMSCs also exhibit immunomodulatory properties by inhibiting the proliferation and function of various immune cells, such as T cells, B cells, macrophages, monocytes, and natural killer cells [26–28].

4.2. Harvesting and Isolation Technique

Contemporary approaches to harvesting adipose tissue include using syringes, liposuction techniques, and direct excision. ADMSCs intended for experimental and therapeutic applications can be isolated from subcutaneous fat in the abdomen, thighs, and arms [25]. The reviewed studies isolated ADMSCs from sources such as gluteal or abdominal adipose tissue and the infrapatellar fat pad (IFPF). While the optimal source for ADMSCs remains under investigation, IFPFs present a compelling option compared to other adipose tissues. This is largely because IFPFs are often collected during the surgical excision of inflamed tissue in knee arthroscopy procedures. Furthermore, IFPF-derived MSCs exhibit similar surface marker profiles to cells within the knee joint environment, potentially minimizing the risk of immunological rejection [18].

The isolation and culture of ADMSCs are performed following standardized protocols, which typically involve washing the tissue with phosphate-buffered saline (PBS), enzymatic digestion of fat aspirates using 0.075% collagenase, and subsequent culturing in a medium supplemented with 10% fetal bovine serum (FBS) and 1% antibiotics under conditions of 37 °C and 5% CO_2 for 30-60 minutes [25,26]. A critical aspect of this process is the identification and characterization of ADMSCs via flow cytometry analysis of specific cell surface markers [25,29]. The International Society for Cell Therapy (ISCT) and the International Federation of Fat Therapy and Science (IFATS) have outlined three fundamental criteria for defining ASCs: (1) the cells must adhere to plastic surfaces; (2) they must express markers such as CD73, CD90, and CD105 while lacking expression of CD14, CD11b, CD45, CD19, CD79, and HLA-DR; (3) they must possess the ability to differentiate into adipogenic, chondrogenic, and osteogenic lineages. Based on the distinct properties of the derived cells, various

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targeted detection techniques can be employed, and relevant animal models can be established. For instance, assays like the 3-(4,5)-dimethyl thiazole(-z-y1)-3,5-diphenyl triazolam (MTT) test and wound-healing models are suitable for fibroblast studies, while functional assessments of re-innervation can be used to evaluate peripheral nerve regeneration [25,26]. The following outlines the steps involved and their respective timeframes when utilizing standard protocols (Figure 1) [30].

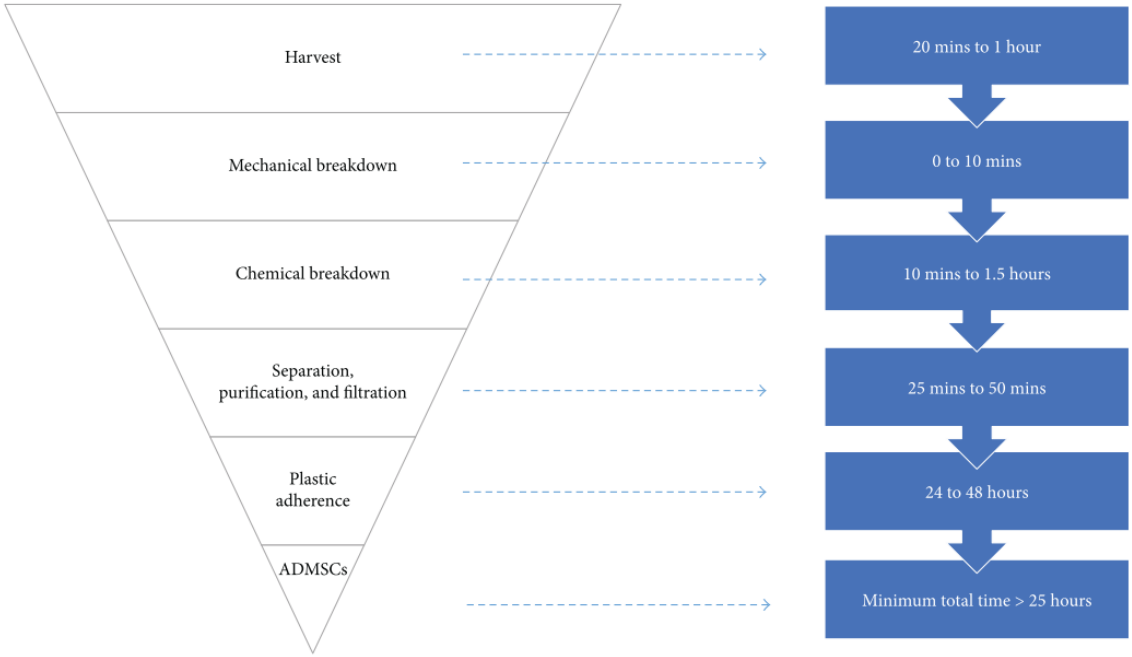

Figure 1.
Protocol for isolating ADMSCs with associated timeframes [30].

Culturing ADMSCs in an osteogenic medium is the method most frequently described for differentiating them into the osteogenic lineage. Usually, a standard base medium, like Dulbecco's Modified Eagle's Medium (DMEM) or Minimum Essential Medium Alpha (α-MEM), is used to prepare this medium. It is then supplemented with phosphates (like β-glycerophosphate), ascorbates (like ascorbic acid or ascorbate-2-phosphate), inductive factors (like dexamethasone), and serum (like fetal bovine serum) [25,26]. Soluble substances such as BMPs, vitamin D3, platelet-rich plasma, human platelet lysate, selenium, or inorganic ionic products like calcium, hydroxyapatite, strontium, or magnesium can all further promote osteogenic differentiation. Additionally, the surface properties of the scaffold or ECM significantly affect osteogenic differentiation. Key factors include fiber alignment, stiffness, porosity, and chemical composition. External stimuli, such as acoustic waves, electromagnetic fields, and shear stress, also influence the differentiation process [26].

4.3. Role of ADMSCs in Cartilage Regeneration

ADMSCs are extensively employed in cartilage regeneration due to their high abundance, ease of accessibility, and robust capacity for in vitro proliferation and differentiation [31]. The therapeutic potential of ADMSCs, including their capacity for tissue repair and differentiation into various cell lineages, has facilitated their expanded application across multiple disciplines, particularly in orthopaedics [13]. ADMSCs can be harvested from various anatomical locations, including the upper arm, medial thigh, buttocks, trochanteric region, superficial and deep abdominal fat depots, and the infrapatellar fat pad (IPFP) of the knee joint. The SVF contains approximately 2 to 6 million cells, which can be extracted from 1 mL of lipoaspirate. The concentration of ADMSCs within adipose tissue can vary, ranging from 5,000 to 200,000 cells per gram [32]. ADMSCs, owing to their mesodermal

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origin, possess the ability to differentiate into adipocytes, osteoblasts, chondrocytes, and endothelial cells. Furthermore, studies have shown that ADMSCs can also differentiate into cells of ectodermal and endodermal origin, including vascular smooth muscle cells, keratinocytes, hepatocytes, beta-islet cells, neuron-like cells, and glial lineages [30,32,33]. The principal benefit of autologous-cultured ADMSCs is their ability to provide rapid pain relief while contributing to substantial improvements in knee function and cartilage regeneration over time [33].

In the process of cartilage regeneration, ADMSCs secrete a diverse array of paracrine factors collectively referred to as the secretome. This secretome includes various proteins that perform critical biological functions such as immune modulation, angiogenesis, anti-apoptosis, antioxidation, cell homing, and the promotion of cell differentiation. ADMSCs release cytokines to initiate cartilage repair, which is subsequently enhanced by chondrogenic proliferation and the secretion of ECM proteases and growth factors, including TGF-β, IGF-1, and fibroblast growth factor (FGF). These components of the secretome play a pivotal role in stimulating and facilitating cartilage repair [33,34]. The paracrine factors secreted by ADMSCs may be encapsulated within extracellular vesicle (EVs), which are complex structures containing a variety of biomolecules, including lipids, proteins, RNA (both mRNA and non-coding RNAs), and specific DNA subtypes. The biological properties of EVs enable them to cross the blood-brain barrier (BBB), achieve targeted delivery to specific cells, and safeguard their molecular cargo from degradation during circulation [34,35].

In addition to their ability to differentiate and exert paracrine effects, ADMSCs possess immunomodulatory functions, which play a crucial role in cartilage repair. Given that damaged cartilage is often subjected to a chronic inflammatory environment, its ability to modulate the immune response contributes significantly to the repair process. ADMSCs are known for their low immunogenicity, resulting in a weak immune response, primarily due to their lack of major histocompatibility complex (MHC) class II expression and the absence of classic costimulatory molecules such as CD80, CD86, and CD40 [31,36]. Furthermore, when exposed to injured tissue or inflammatory cytokines, ADMSCs can exert immunomodulatory effects on various immune cells. It has been shown that specific cell surface molecules, such as programmed death-ligand 1 (PD-L1) and Fas ligand (FasL), mediate the immunomodulatory functions of ADMSCs, inhibiting T cell immune activity upon binding. In addition to direct cell contact, ADMSCs also regulate immune cell function through the secretion of cytokines. For instance, interferon-gamma (IFN-γ) can upregulate indoleamine 2,3-dioxygenase (IDO) expression in ADMSCs via the JAK-STAT1 signaling pathway, leading to inhibition of peripheral blood mononuclear cell (PBMC) proliferation and promoting M2 macrophage polarization [31,35]. In the presence of IL-17A, ADMSCs increase the expression of prostaglandin E2 (PGE2) and significantly enhance the proportion of CD4+Foxp3+ regulatory T cells (Tregs), thereby suppressing T-cell proliferation. Other molecules, including nitric oxide (NO), inducible nitric oxide synthase (iNOS), human leukocyte antigen-G (HLA-G), and IL-10, have also been implicated in mediating the immunosuppressive functions of ADMSCs [31,36]. In summary, the process of cartilage regeneration is influenced by a synergy of paracrine signaling, cellular differentiation, and repopulation, along with immunomodulatory functions [20–23].

4.4. Scaffolds in Cartilage Regeneration

Scaffolds play a pivotal role in tissue engineering strategies for OC repair. To ensure high-quality tissue regeneration, scaffolds must possess several key characteristics: a porous structure to support cell survival and facilitate nutrient and waste transport; a surface conducive to cell adhesion, proliferation, and differentiation; mechanical properties that match those of the surrounding tissue; biocompatibility to minimize immune reactions; and bio-absorbability with a controllable degradation rate to align with the tissue regeneration process [37]. Scaffold-based delivery systems, such as fibrin scaffolds, offer a structured microenvironment for ADMSCs, enhancing cell retention and facilitating more effective cartilage regeneration at the injury site [32,33]. Scaffolds replicate the function of the ECM by directing ADMSCs to effectively integrate into the defect site, supporting progenitor cell differentiation while offering mechanical stability. Scaffolds composed of osteoconductive materials are particularly effective with partially differentiated cells, such as osteoblasts and pre-osteoblasts, but they are

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insufficient to induce osteogenic differentiation in osseous progenitor cells and ADMSCs. Conversely, scaffolds incorporating osteoinductive biomaterials have demonstrated the ability to recruit progenitor cells and enhance osteoblastic commitment and differentiation, thereby promoting bone formation [26].

Several scaffold fabrication techniques have been developed for OC tissue engineering to improve scalability, sustainability, and spatial control. These techniques include particulate leaching, solvent casting, compression molding, sol-gel processing, lyophilization, freeze casting, gas foaming, and phase separation. To modify scaffold characteristics like porosity, mechanical strength, and structural complexity to satisfy the needs of OC tissue repair, each method has special benefits [37]. Materials used in scaffold fabrication range widely and include human-derived allografts such as bovine teeth, alveolar bone, heterogeneous deproteinized bone (HDB), bovine bone, cortical bone, and cancellous bone. Synthetic materials are also extensively employed, including PCL, bioceramics, polylactic acid (PLA), hydroxyapatite, coral-hydroxyapatite (CHA), strontium hydroxyapatite (SrHA), titanium, beta-tricalcium phosphate (β-TCP), poly(lactide-co-glycolide) acid (PLGA), and fibrin gel [26]. We demonstrated that collagen, HA, and PLGA-based scaffolds are among the most commonly used and effective materials for knee joint cartilage defects due to their biocompatibility, ability to support cell differentiation, and ability to mimic the properties of cartilage [20–23].

Recent advances in biomaterials and fabrication techniques have opened new avenues for the development of biomimetic and highly sophisticated scaffolds, which can be categorized into monophasic, biphasic, and multiphasic constructs. Notably, multiphasic scaffolds offer several advantages in terms of bionic performance when compared to monophasic scaffolds. These advantages are particularly evident in applications that require complex tissue structures, such as OC repair, where the scaffold can mimic the distinct properties of bone and cartilage in a single construct [37]. The size, location, and degree of cartilage degeneration of the defect all influence the best scaffold for ADMSCs to use in knee cartilage joint defect repair. Nevertheless, the most promising alternatives are thought to be hydrogel-based scaffolds, collagen-based scaffolds, and biphasic/multiphasic scaffolds (particularly for OC defects). The ability of these scaffolds to promote ADMSC differentiation into cartilage and offer the required mechanical support for tissue regeneration accounts for their effectiveness [23,38].

The role of bioactive molecules in this context is crucial for guiding tissue regeneration. Growth factors such as TGF-β, BMPs, and IGF stimulate the differentiation of stem cells into cartilage-producing chondrocytes, as well as the synthesis of key ECM components like collagen type II and proteoglycans, which are vital for cartilage integrity. Additionally, cytokines such as PDGF (Platelet-Derived Growth Factor) and FGF are involved in the recruitment and proliferation of cells at the injury site, promoting tissue repair. These molecules also regulate the inflammatory response, creating a favorable environment for healing [37,39,40]. Scaffold functionalization refers to the modification of scaffold materials to incorporate bioactive molecules that influence cellular behavior more effectively. Methods such as physical adsorption, covalent binding, and encapsulation can be used to integrate growth factors and cytokines into the scaffold. Encapsulation, in particular, offers the advantage of controlling the sustained release of bioactive molecules over time, which is important for long-term tissue regeneration. Coating the scaffold with ECM proteins like fibronectin or collagen further enhances cell attachment and differentiation, ensuring the scaffold provides a more natural environment for cartilage regeneration [41].

Once ADMSCs are seeded onto the functionalized scaffold, the bioactive molecules guide the cells through the process of chondrogenesis (cartilage formation), stimulating matrix production and facilitating tissue regeneration. The scaffold not only serves as a mechanical support for the cells but also provides the necessary biochemical signals to promote cartilage regeneration [41]. This approach has demonstrated potential in preclinical and clinical studies, offering improvements in cartilage repair and reducing the need for invasive procedures such as knee replacements [20–23]. This method has significant implications for clinical applications, offering the possibility of effective repair of cartilage defects in the knee joint, enhancing joint function, and potentially preventing the progression of degenerative conditions like osteoarthritis. The combination of ADMSCs, bioactive molecules, and scaffold technology presents a promising approach to improving cartilage regeneration and providing an alternative to conventional treatment options for knee joint injuries [14].

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4.5. Challenges and Future Directions

The application of scaffolds with ADMSCs for the repair of knee joint cartilage defects presents several challenges, particularly in achieving optimal cell survival, differentiation, and integration within the scaffold. Despite the potential of ADMSCs to promote chondrogenesis, the efficiency of cartilage formation in vivo remains suboptimal due to factors such as the mechanical properties of the scaffold, insufficient nutrient exchange, and the complex biological environment of the joint. Additionally, the controlled delivery and release of bioactive molecules, including growth factors and cytokines, requires precise engineering to ensure their sustained and localized activity without causing adverse effects like excessive inflammation or fibrosis. The long-term stability of the engineered tissue and the immune response to the scaffold material also represent significant concerns. Future research should focus on developing advanced scaffold materials with improved biocompatibility, vascularization, and mechanical properties that more closely resemble the native cartilage matrix. Furthermore, incorporating techniques such as gene editing or cell preconditioning may enhance the regenerative potential of ADMSCs, leading to more efficient cartilage regeneration. Ultimately, clinical trials and personalized therapeutic approaches will be crucial for translating these technological advances into effective treatments for knee joint cartilage defects.

5. Conclusion

This literature review highlights the importance of scaffold modality with ADMSCs as a regenerative treatment for knee joint cartilage defects. Scaffolds serve as a supportive framework, providing an ideal environment for ADMSCs to proliferate, differentiate, and facilitate tissue regeneration. ADMSCs, through their paracrine effects, promote cartilage repair by secreting factors that regulate inflammation, encourage chondrogenesis, and assist in ECM remodeling. Although clinical results are encouraging, additional research is required to optimize scaffold materials, ADMSC delivery techniques, and treatment protocols. Collectively, scaffolds and ADMSCs offer a valuable approach to restoring knee cartilage function and advancing regenerative treatments in orthopedic medicine.

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