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Adipose-derived stem cells: Sources, potency, and implications for regenerative therapies

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ABSTRACT

Adipose-derived stem cells (ASCs) are a subset of mesenchymal stem cells (MSCs) that can be obtained easily from adipose tissues and possess many of the same regenerative properties as other MSCs. ASCs easily adhere to plastic culture flasks, expand in vitro, and have the capacity to differentiate into multiple cell lineages, offering the potential to repair, maintain, or enhance various tissues. Since human adipose tissue is ubiquitous and easily obtained in large quantities using a minimally invasive procedure, the use of autologous ASCs is promising for both regenerative medicine and organs damaged by injury and disease, leading to a rapidly increasing field of research. ASCs are effective for the treatment of severe symptoms such as atrophy, fibrosis, retraction, and ulcers induced by radiation therapy. Moreover, ASCs have been shown to be effective for pathological wound healing such as aberrant scar formation. Additionally, ASCs have been shown to be effective in treating severe refractory acute graft-versus-host disease and hematological and immunological disorders such as idiopathic thrombocytopenic purpura and refractory pure red cell aplasia, indicating that ASCs may have immunomodulatory function. Although many experimental procedures have been proposed, standardized harvesting protocols and processing techniques do not yet exist. Therefore, in this review we focus on the current landscape of ASC isolation, identification, location, and differentiation ability, and summarize the recent progress in ASC applications, the latest preclinical and clinical research, and future approaches for the use of ASCs.

1. Introduction

Stem cells have unlimited potential in advanced tissue engineering and cell therapies because they can renew themselves and differentiate into multiple cell lineages that may provide therapeutic solutions for numerous diseases [1,2]. For cell therapy, stem cells can be directly applied to damaged sites; for tissue engineering [3,4], appropriate scaffolds can be used as carriers for stem cells [5,6]. Compared with differentiated cells, the application of stem cells has proved to be advantageous because of the following unique stem cell characteristics: (1) ease of harvesting in larger numbers, (2) much higher proliferation capacity, (3) ability to undergo a larger number of passages, (4) ability to undergo senescence and subsequent differentiation into a wide range of desired cell phenotypes, and (5) ability to support the vascularization of scaffolds. Although current clinical stem cell strategies can treat a number of disorders, such as organ failure, congenital structural anomalies, and tissue loss, and can be used for organ transplantation or autologous tissue transfer, these strategies have potential limitations, including immune rejection, organ shortages, allergic reactions, and damage to healthy tissues during treatment [7–9]. Advanced regenerative therapies have therefore concentrated on the use of stem cells to repair tissue damage and, eventually, to replace organs.

Stem cell candidates include embryonic stem cells obtained from embryonic tissue, induced pluripotent stem cells, genetically reprogrammed differentiated somatic cells, and postnatal adult stem cells obtained from specific locations in the adult organism, such as fat, skin, bone marrow, blood, or skeletal muscle. Mesenchymal stem cells (MSCs), originally identified in bone marrow, are adult stem cells [10,11]. It has been demonstrated that MSCs can be isolated from almost every tissue of the body [12–14], including adipose tissue, trabecular bone, skin, skeletal muscle, pericytes, umbilical cord blood, periosteum, peripheral blood, synovial membrane, dermis, dental pulp, periodontal ligament, and even tumors [15,16]. However, although there are many sources of MSCs, the amount of tissue that can be

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retrieved is limited and few cells can be harvested. In 2018, Mushahary et al highlighted variations in the differentiation potential of MSCs from different tissue sources [17]. Adipose-derived stem cells (ASCs) have become one of the most promising stem cell populations identified so far because they are ubiquitous and can be relatively easily harvested in larger quantities with less donor-site morbidity. Subcutaneous adipose tissue is the most clinically relevant source of ASCs among the several adipose tissue types, and can be isolated from subcutaneous adipose tissue of the abdomen, thigh, and arm. As adipose tissue is relatively abundant in the human body, ASCs can be obtained in higher numbers. The multi-lineage capacity of ASCs offers the potential of cell therapy and tissue engineering [18,19].

The aim of this review is first to highlight recent progress in the isolation, identification, and location of ASCs, and second to focus on the differentiation ability of ASCs in vivo and in vitro. Finally, we discuss the current and possible future clinical applications of ASCs.

1.1. Isolation, identification, and location of ASCs

ASCs harvested from different anatomical areas exhibit different characteristics. For example, ASCs harvested from superficial abdominal regions undergo significantly less apoptosis than do ASCs harvested from the upper arm, medial thigh, trochanteric, or superficial deep abdominal depots. ASCs isolated from different locations, cell types, and species have different density [20,21], and different procedures may affect ASC quality, functionality, and plasticity [22,23]. White adipose tissue and brown adipose tissue are the two main types of adipose tissue. White adipose tissue is found in subcutaneous and visceral adipose tissue whose function is mainly to store excess energy in the form of triglycerides [24,25]. Compared with visceral fat, ASC yields are greater in subcutaneous depots. The highest concentrations of ASCs are found in arm adipose tissue depots and the greatest plasticity in inguinal adipose tissue depots in white adipose tissue. Brown adipose tissue is much less abundant than white adipose tissue, and can be found in the mediastinum, neck, and interscapular areas in neonates; its main function is thermogenesis. There are also ASCs within brown adipose tissue depots, but these ASCs have different characteristics from those isolated from white adipose tissue and more easily undergo skeletal myogenic differentiation [26,27]. Since Zuk et al described a harvesting procedure for ASCs from adipose tissue in 2001 [21], many modified experimental procedures have been proposed [28–30]. However, there have been few studies comparing the efficacy of various methods, and therefore no standardized method has been defined. The protocol reported by Zuk et al is still the most widely used method for ASC isolation. According to this method, ASCs are isolated from white adipose tissue. Adipose tissue is washed several times with equal volumes of phosphate-buffered saline and minced to small pieces, before undergoing enzymatic digestion at 37 °C for 30 min with 0.075% collagenase type II. After digestion, the resulting pellet yields a heterogeneous population of many cell types and is termed the stromal vascular fraction (SVF). The SVF contains ASCs, pre-adipocytes, endothelial cells, fibroblasts, endothelial progenitor cells, resident monocytes/macrophages, pericytes, vascular smooth muscle cells, leukocytes, lymphocytes, and erythrocytes. Approximately 2 to 6 million cells in the SVF can be obtained in 1 ml lipoaspirate. Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal bovine serum (FBS) is added to neutralize enzyme activity. The cell suspension is centrifuged at 1200 × g for 10 min to obtain a high-density SVF. The supernatant is discarded and the SVF pellet is resuspended in NH_4Cl and incubated at room temperature for 10 min to remove erythrocytes. The SVF is collected by centrifugation and then filtered through a 100-μm mesh to remove undigested tissue fragments and incubated at 37 °C overnight in control medium (DMEM, 10% FBS, 500 IU penicillin, and 500 μg streptomycin) with 5% CO_2. ASCs are obtained as a plastic-adherent population after overnight culturing.

In 2017, Li et al compared two methods for erythrocyte removal with NH_4Cl or NaCl hypotonic solution [31], and evaluated their effects on the function of lipoaspirate-derived ASCs. Their results indicated that hypotonic NaCl solution is more effective than NH_4Cl solution with regard to ASC purification and meets the standards of good manufacturing practice/good clinical practice guidelines. Palumbo et al [30] recently analyzed the influence of two common fat processing techniques on SVF cell and adipocyte yield and viability, namely, lipoaspirate spontaneous stratification at different times (10, 20, or 30 min) and centrifugation at different centrifugal forces (90, 400, or 1500 × g). They mainly analyzed the yield of SVF and number of ASCs, plastic adhesion ability, and differentiation potential of ASCs. Their results indicated that: (1) ASCs stratified spontaneously at 20 or 30 min were comparable with those obtained after centrifugation at 90 or 400 × g for 3 min, because the ASCs successfully differentiate into adipogenic, osteogenic, and chondrogenic lineages, suggesting that the differentiation ability of ASCs is not influenced by any of the handling methods; and (2) after either spontaneous stratification at 20 min or centrifugation at 400 × g, the middle layer obtained from lipoaspirate samples can provide sufficient ASCs and maintain adipocyte integrity, demonstrating that the two approaches are effective.

Notably, ASCs are not a homogenous population. Many authors have attempted but failed to use a unique single surface marker to characterize ASCs via flow cytometry analysis [32,33]. In 2006, the International Society for Cellular Therapy (ISCT) proposed a minimum set of criteria for identifying cells as ASCs: (1) adherence to plastic; (2) expression of CD73, CD90, and CD105 but lack of expression of CD45, CD34, CD14 or CD11b, CD79a or CD19, and HLA-DR surface molecules; and (3) potential to differentiate into pre-adipocytes, chondrocytes, and osteoblasts [34]. In 2013, the ISCT denoted additional surface markers including CD13, CD29, and CD44 as being constitutively expressed at > 80% on the surface of ASCs, while CD31, CD45, and CD235a are the primary negative markers that should be expressed on less than 2% of cells [35]. Li et al categorized subpopulations of ASCs: (1) the highest subpopulation was pre-adipocytes (CD31-/CD34+; 67.6%), (2) the second highest subpopulation was premature endothelial cells (CD31 + CD34+; 5.2%), and (3) the remaining two subpopulations were pericytes (CD146+/ CD31-/CD34-) and mature endothelial cells (CD31+/CD34-; less than 1% each) [36]. Among all cells types, pre-adipocytes showed the greatest proliferation and the highest adipogenic differentiation. Many studies have been conducted in an attempt to determine the localization of ASCs within adipose tissue, but the precise localization remains unclear [37,38]. Zimmerlin et al believed that ASCs are located in the vasculature of adipose tissue. Other findings suggest that ASCs reside within adipose tissue in a perivascular location [39].

1.2. Differentiation ability of ASCs

There have been numerous reports that ASCs can be differentiated into multiple lineages both in vitro and in vivo (Fig. 1), and some of the findings have been translated for multiple clinical applications. Although ASCs are of mesodermal origin, it has been shown that they can differentiate into cells of ectodermal, endodermal, and mesodermal origin [40,41]. It is widely accepted that ASCs can differentiate into adipogenic, osteogenic, chondrogenic, myogenic, angiogenic, cardiomyogenic, tenogenic, and periodontogenic lineages because of the mesodermal origin of ASCs. ASC differentiation in vitro is induced by selective medium containing lineage-specific induction factors [40,42].

1.3. Adipogenic differentiation

Adipogenic differentiation can be induced in medium that typically contains DMEM (with 10% FBS), 0.5 mM 3-isobutyl-1-methylxanthine, 50 mM indomethacin, 0.5 mM dexamethasone, and 10 mg/ml insulin [18,43]. The medium should be changed every 3 days, and multiple lipid droplets will develop after about 1 week with the number of

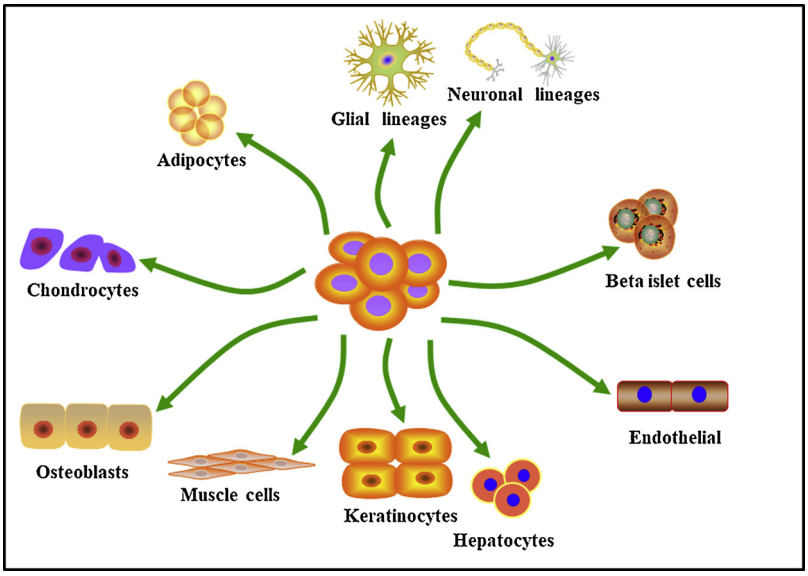

Fig. 1. The differentiation capability of ASCs.

droplets increasing over time. After 12–14 days of differentiation, mature adipocytes are obtained. During this period, extracellular matrix (ECM) proteins, including fibronectin, laminin, and various types of collagen, are expressed by mature and immature cells. At the same time, a type-I collagen network is gradually formed to help ASCs differentiate into mature adipocytes. Adipogenic cell differentiation was evaluated by staining the cells with a solution of 0.3% Oil Red-O in 60% isopropanol for 15 min at room temperature [44]. The gene expression of mature adipocytes is specific, including leptin, aP2, peroxisome proliferator activated receptor-γ2, and glucose transporter type 4 [45]. Of interest, it has been reported that adipogenic differentiation of ASCs is closely related to sex [46].

1.4. Osteogenic differentiation

For differentiation of ASCs into osteoblasts, the culture medium should contain DMEM (with 10% FBS), 10 mM β-glycerol phosphate, 40 μg/ml gentamicin, 8 M dexamethasone, 2 mM L-glutamine, 8 M dihydroxyvitamin D3, and ascorbic acid [47,48]. The osteogenic medium is replaced every 3 days. For approximately 14 days, the cells are induced into osteoblast-like cells. After fixation in 10% formalin, calcium phosphate within the ECM produced by the osteoblast-like cells can be assessed using 40 mM Alizarin Red or von Kossa (pH 4.1). During this period, the expression of genes including Runx-1, bone morphogenetic protein (BMP)-2, BMP-4, type I collagen, osteoponin, alkaline phosphatase, osteocalcin, bone sialoprotein, and parathyroid hormone receptor will be up-regulated [45].

1.5. Chondrogenic differentiation

For chondrogenic differentiation, a micromass pellet culture system should be used because cells require a three-dimensional environment to increase cell-to-cell interaction and produce a cartilage-like matrix. The cell pellets are cultured in chondrogenic differentiation medium supplemented with basic fibroblast growth factor (bFGF), dexamethasone, transforming growth factor-β1, insulin, ascorbate-2-phosphate, and BMP-6. The medium is replaced every 3 days for a period of 21 days. During this period, differentiated chondrocytes express aggrecan, prolyl endopeptidase-like, type II collagen, type IV collagen, and sulfate-proteoglycan. After fixing in formalin, embedding in paraffin, and sectioning, the pellet can be stained with alcian blue and collagen type II to indicate the presence of chondrocytes [49,50].

1.6. Differentiation into other cells types

Under certain conditions, ASCs can also differentiate into other cells types including vascular smooth muscle cells, keratinocytes, hepatocytes, and beta islet cells [51–53]. Although controversial, many studies have demonstrated that ASCs may have the capacity to differentiate toward cells of ectodermal origin, such as neuronal and glial lineages [54–56]. It is relatively difficult for ASCs to differentiate toward vascular endothelial cells, however when ASCs were co-cultured with human umbilical vein endothelial cells in EGM-2 medium supplemented with epidermal growth factor, vascular endothelial growth factor, insulin-like growth factor 1, bFGF, FBS (final concentration of 2%), and antibiotics, the cells successfully differentiate into vascular endothelial cells and interconnect with the vascular network [18].

Despite the fact that ASCs can be easily harvested from abundant adipose tissue and are easy to culture, differentiation of ASCs is more complex in vivo than in vitro. After injection or implantation of ASCs in vivo, most of the cells die. This is partly because of the hypoxic environment [19,57]. Therefore, most clinical applications use suitable biomaterial scaffolds that can support attachment, proliferation, and differentiation of ASCs to provide an ideal environment for cell survival. The scaffold should be porous, bio-active, and biodegradable; it should also have low immunogenicity and good mechanical integration [58].

1.7. Clinical applications of ASCs

ASCs have practical advantages in clinical medicine, and research has made their application more feasible [59–62]. ASCs can secrete numerous growth factors and cytokines that are critical for wound healing. In addition, enhanced tissue granulation, increased macrophage recruitment, and improved vascularization by ASCs make them effective wound therapies [4,63]. Rigotti et al [63] recruited 20 patients to receive lipoaspirate containing ASCs repeatedly over a period of 31 months. Improvements in ultrastructual tissue characteristics with neovessel formation were observed in patients, indicating significant clinical improvement [64–66]. ASCs also proved to be useful to treat wounds complicated by ischemia, for example in patients with diabetes or thromboangiitis obliterans. These findings suggest that ASCs may be effective for the treatment of severe symptoms such as atrophy, fibrosis, retraction, and ulcers induced by radiation therapy. Moreover, ASCs have been shown to be useful for the treatment of pathologic wound

healing such as aberrant scar formation. In animal models, scars injected with ASCs showed a reduction in surface area and improvements in color and pliability compared with the control group [4,67,68]. Some authors [69,70] concluded that treatment with ASCs may target the inflammatory processes associated with scar formation because ASCs have been proven to have immunosuppressive and anti-inflammatory effects. In two studies, the intravenous infusion of allogenic ASCs has been shown to be effective in treating severe refractory acute graft-versus-host disease and hematological and immunological disorders such as idiopathic thrombocytopenic purpura and refractory pure red cell aplasia, indicating that ASCs may have immunomodulatory effects [3,71]. The tropism of ASCs to damaged tissues and tumor sites makes them a promising vector for therapeutic delivery to tumors and metastatic niches [72].

Plastic surgery is a growing field uniquely positioned for the application of ASCs. Fat grafting demonstrates the clinical regenerative potential of ASCs [73–75]. Several standard protocols are available for fat grafting based on simple procedures such as lipoaspirate, gravity separation, and filtration or centrifugation to remove impurities and obtain relatively pure samples with a high-quality SVF as the source of ASCs. Cell-assisted lipotransfer (CAL) was proposed by Matsumoto et al in 2006 to enrich aspirated fat with SVF obtained after enzymatic isolation, and improve the long-term volume retention, which significantly improves the survival rate of transplanted fat with less fat resorption and a marked decrease in the adverse effects of lipoinjection, such as cyst formation and fibrosis [76–79]. It has been reported that fat grafting may complicate breast imaging and breast cancer surveillance because of fat necrosis and calcification in breast tissue. However, in 2008 Yoshimura et al applied CAL for cosmetic breast augmentation in 40 patients. No major complications were observed and the aesthetic outcome was favorable [80–84]. Subsequently, CAL has been widely used in breast augmentation and for facial lipoatrophy and augmentation during face-lift and facial contouring surgeries, among other applications [85–87]. Whether the use of ASCs in the form of CAL for breast augmentation can be used after breast cancer therapy remains unclear Several studies have demonstrated that MSCs can enhance the metastatic potential of breast cancer cells when mixed with them and reimplanted. However, the interaction between ASCs and cancer cells are not fully understood [88,89].

It is well known that ASCs are able to differentiate into osteoblasts and chondroblasts, and current clinical stem cell therapies for bone regeneration have demonstrated exciting and promising results [90–92]. In 2004, Lendeckel et al described the first clinical use of ASCs in a case report. A7-year-old girl with widespread calvarial defects after severe head injury with multifragment calvarial fractures [93]. SVF was placed at suitable locations, and computed tomography scans showed the formation of new bone 3 months after the reconstruction. It was noted that compared with bone marrow-derived MSCs, ASCs have more advantages in terms of cell yield especially for pediatric patients. Studies have shown that ASCs can form new bone and repair large calvarial defects as well as defects involving the maxilla and mandible [94,95]. To date, the clinical reconstruction of cartilage defects remains challenging because the intrinsic capacity of the tissue for self-repair is limited [96,97]. Although animal studies have yielded promising results, there have been no clinical trials of the use of ASCs to treat cartilage defects. In animal studies, ASCs fully repaired hyaline cartilage defects in patellofemoral joints and ear auricle defects; these finding are promising for future clinical applications [98,99]. Most studies of peripheral nerve injuries have focused on replacing host support cells, such as the Schwann cell, because they are crucial for providing trophic, structural, and directional support for regenerating axons [100,101]. It has been reported that ASCs can promote neurogenesis by differentiating into neuron-like lineages [102–104]. Choi et al developed clinically applicable ASCs expressing therapeutic genes and investigated their therapeutic efficacy for brainstem glioma in mice and established a clinically applicable safe and effective stem cell-based gene therapy for brainstem gliomas [105]. Factors derived from conditioned medium of adipose-derived MSCs and frizzled-related protein 4 significantly decreased tumor cell viability and migration rates in MCF-7 cells, accompanied by enhanced apoptotic activity through inhibition of canonical Wnt signaling [106].

2. Conclusion

The abundance of ASCs, the ease with which the cells can be obtained, their ability to differentiate into multiple lineages and secrete various cytokines, and their immunomodulatory effects, mean that ASCs may have a prominent role in tissue regeneration. Numerous studies have been conducted to determine the biology of ASCs, and preclinical studies have been performed to further understand the applicability of ASCs for regenerative medicine. Moreover, many clinical trials have been conducted to determine the efficacy of ASCs; however, very few phase III clinical studies have been reported. Further studies are needed to explore among other topics the long-term safety of ASCs, their precise mechanism(s) of action, and the ability to translate experimental findings to the clinical.

Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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