Review Paper: Adipose Tissue, Adipocyte Differentiation, and Variety of Stem Cells in Tissue Engineering and Regeneration

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ABSTRACT

Human adipose tissue represents an abundant, practical and appealing source of donor tissue for autologous cell replacement. Recent findings have shown that stem cells within the stromal-vascular fraction of adipose tissue display a multilineage developmental potential. Adipose tissue-derived stem cells can be differentiated towards adipogenic, osteogenic, chondrogenic, myogenic and neurogenic lineages. However, the success of using autologous fat tissue grafts to repair soft tissue defects is limited. Researchers are now investigating strategies to engineer volumes of adipose tissue that may be used in these cases. A necessary component for engineering a viable tissue construct is an appropriate cell source. Attempts to engineer adipose tissue have involved using preadipocytes and adipocytes as the base cell source. This research reviews the current state of adipose tissue-engineering methods and describes the shift toward tissue-engineering strategies using stem cells.

1. Introduction

Stem cell transplantation has become a promising therapy for many disorders. However, the ethical debate, teratoma formation, and the technical inconsistency regarding embryonic stem cells (ESCs) favored the use of adult stem cells. Moreover, immunorejection seems to be another obstacle in stem cells trials. Clearly, to overcome this problem, autologous stem cells are practically of value [1]. The therapeutic potential of multilineage stem cells for applications such as tissue engineering and gene therapy is enormous.

Conceptually, there are 2 general types of stem cells potentially useful for these applications: embryonic stem

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cells (ESCs) and autologous stem cells. Although theoretically appealing because of their pluripotentiality, the practical use of ESCs is limited due to potential problems of cell regulation and ethical considerations. In contrast, autologous stem cells, by their nature, are immunocompatible and have no ethical issues regarding their use. For the engineering of mesodermally derived tissues, autologous stem cells obtained from bone marrow have proved an experimentally promising source. Human bone marrow is derived from the embryonic mesoderm and comprised a population of hematopoietic stem cells (HSCs), supported by a mesenchymal stroma [2-6].

Adipose tissue may represent such a source. Although it is known that many tissues contain lineage-committed progenitor cells for tissue maintenance and repair, several studies have demonstrated the presence of uncommitted MSCs within the connective tissue matrices of several organs in birds, mice, rats, and rabbits [7-11]. Furthermore, adipose tissue, like bone marrow, is derived from the embryonic mesoderm and contains a heterogeneous stromal cell population [12-16].

Adipose tissue derived stem cells were termed as: adipose derived stem/stromal cells (ASCs), adipose-derived adult stem (ADAS) cells, adipose-derived adult stromal cells, adipose-derived stromal cells (ADSCs), adipose stromal cells (ASCs), adipose mesenchymal stem cells (AdMSCs), lipoblast, pericyte, preadipocyte, and processed lipoaspirate (PLA) cells. To prevent the confusion in the literature, the International Fat Applied Technology Society reached a consensus to adopt the term "adipose-derived stem cells" (ASCs) to identify the isolated, plastic-adherent, multipotent cell population [17]. Adipose tissue derives from the mesodermal layer of the embryo and develops both prenatally and postnatally [18]. Researchers studying the development of adipose tissue have long worked with a fibroblastic cell line, known as preadipocytes, isolated from adipose tissue [19-23]. The reason why adipose tissue would contain a stem cell population is still unclear. There is some discussion whether these cells are subpopulation of fibroblasts residing within the fat tissue or are perhaps mesenchymal or peripheral blood stem cells passing through the fat tissue [24, 25].

The ASCs represent a readily available source for isolation of potentially useful stem cells [26]. In culture, they have shown to have an impressive developmental plasticity, including the ability to undergo multilineage differentiation and self-renewal [27]. When ASCs are compared with BM-MSCs, further similarities have been demonstrated regarding to their growth kinetics, cell senescence, gene transduction efficiency [28], as well as CD surface marker expression [29-31] and gene transcription [30]. Compared to bone marrow MSCs, ASCs have potential advantages for tissue engineering application; because of their tissue accessibility, multipotency, and ease of isolation without painful procedures or donor site injury.

2. Adipose Tissue Structure and Function

Adipose tissue is the most prevalent tissue in the human body. It is commonly found in subcutaneous loose connective tissue, and it also surrounds internal organs. Mature adipocytes constitute the majority of cells in adipose tissue. Beside mature adipocytes, fat tissue contains several other cell types, including stromal-vascular cells (SVC) such as fibroblasts, smooth muscle cells, pericyte, endothelial cells, and adipogenitor cells or preadipocytes [20]. Recent research shows that adipose tissue plays a more dynamic role than previously recognized in physiological processes of the whole body.

Adipose tissue is divided into 2 subtypes: white and brown fat. White fat is widely distributed and represents the primary site of fat metabolism and storage, whereas brown fat is relatively scarce and its main role is to provide body heat, which is essential for newborn babies. White adipose tissue is the major energy reserve and its primary function is to store triacylglycerol (TG) in periods of energy excess and to release energy in the form of free fatty acids during energy deprivation [33-36]. Fat tissue also plays an important role in numerous processes through its secretory products and endocrine functions.

Adipocytes secrete various factors known to play a role in immunological responses, vascular diseases, and appetite regulation. Leptine is a peptide hormone primarily made and secreted by mature adipocytes, and it has various biological activities, including effects on appetite, food intake, body weight regulation, fertility, reproduction and hematopoiesis [36, 37]. Adipose tissue is an important site for estrogen biosynthesis and steroid hormone storage [38, 39]. In addition, adipose tissue secretes a variety of peptides, cytokines, and complement factors, which act in an autocrine and paracrine manner to regulate adipocyte metabolism and growth, as well as endocrine signals to regulate energy homeostasis [20].

Although adipose tissue is vitally important for various normal processes of the human body, it has also many implications for human disease states. Obesity is a common health problem in industrialized countries and is considered a major risk factor for non-insulin-dependent diabetes mellitus [40]. Cardiovascular diseases and hypertension [41]. Obesity is also associated with other

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pathological disorders, including some types of cancer such as breast, ovarian, renal, and colon cancer [42-45].

3. Stem cells as a source of tissue engineering

Different cell types that could be used for repair and regeneration include mature cells obtained from the patient or stem cells (either adult or embryonic) [46, 47]. Using mature cells obtained from the patient minimizes the need for immuo suppressive therapy after implantation, but these cells may not be the best source for tissue regeneration primarily because these adult cells have already differentiated and committed to a specific cell type. This option provides little potential for further growth and limits the source of harvested tissue for repair to the site initial damage [46].

Stem cells, on the other hand, are by definition a population of cells able to provide replacement cells for a specific differentiated cell type [48]. These unique cells are different from other cell types in 3 defined respects. First, stem cells are able to divide and renew themselves over long periods of time [49] can replicate or proliferate several times. By virtue of their ability to self-replicate, stem cells are said to be self-renewing [50]. Second, stem cells are not specialized and they are immature, i.e. that they do not have any tissue specificity and are not required to perform specialized, tissue-specific functions. Third, stem cells differentiate into specialized cells [51]. Stem cells are capable of differentiating into at least one type of specific cell. How potent a stem cell is, or how many different cell phenotypes it can differentiate into (also known as stem cell plasticity) [52] can be described using several terms for classifying them. Stem cells may be defined as either totipotent, pluripotent, or multipotent whereby the stem cell is able to form all, most, or a small number of cells and/or tissues of an organism, respectively. Additionally, stem cells capable of forming the blood cells of the body are defined as hematopoietic stem cells [47].

Stem cell sources and their applications

There are several potential sources for obtaining stem cells to use them in tissue regeneration or repair. Table

1 present these sources. The most commonly used cell types adult and embryonic one, are outlined in the following sections.

Various sources for stem cells include embryonic tissue, bone marrow, adipose tissue, and the brain. Each stem cell type has been shown to have the capacity for differentiating to cell types of multiple lineages (Table 1) [46, 47].

Embryonic stem cells

Embryonic stem cells (ESCs) are pluripotent stem cells that are harvested from the inner cell mass of the pre-implantation blastocyst (3 to 5-day-old embryo), and have been obtained from mice, non-human primates, and humans [53]. Those ESCs obtained from mice can remain unspecialized when they are cultured along with leukemia inhibitory factor (LIF) [53]. The in vitro isolation of human ESCs involves transferring the inner cell mass of the blastocyst to a culture medium that is supplemented with a feeder layer [54] of mice embryonic fibroblast cells that prevents cellular differentiation in human embryonic stem cells. After a period of about 6 months, the embryonic stem cells, which have not differentiated even after all of this time, may be referred to as a complete embryonic stem cell line [46, 47, 53-55].

During aggregation, cells form embryoid bodies are no longer undifferentiated or unspecialized cells. They may differentiate spontaneously, but manipulating them is preferred so that specific cell types are formed. The potency of these cells indicates that they are capable of producing a large range of specific phenotypes, including blood cells, neural cells, adipocytes, muscle cells, and chondrocytes, among others [46, 47, 53]. The ability of researchers to efficiently manipulate ESCs to differentiate them into specifically directed cells will provide means of an unlimited supply of cells that may be used, not only for the growth of implantable tissues, but also for testing new drugs to cure diseases or identification of potentially problematic genes [47, 50, 53, 56, 57].

The use of embryonic stem cells in all areas of biomedical research has been met with opposition due to large

Table 1. Types of human stem cells.

Stem Cell Type	Source	Cell Lineages Produced
Embryonic	Embryonic tissue	All types
Mesenchymal	Bone marrow, adipose tissue	Osteogenic, adipogenic, chondrogenic, myogenic, neurogenic, and marrow stromal
Hematopoietic	Bone marrow	Blood cells (red, white, platelets), endothelial, muscle, immune system lineages
Neural	Brain	Neurons, astrocytes, oligodendrocytes, blood cells

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controversy over the sources from which these cells are obtained. The debate surrounding the use of stem cells involves government officials, religious affiliates, members of the scientific community and or and the general public, all of whom have very decisive views on the use of these cells [58, 59]. Opponents of ESC use most often question the morality of using cells obtained from destroyed embryos, an act they consider equivalent to destroying human life [60, 61]. Current research has been directed towards developing methods that will permit using ESCs while eliminating the ethical concerns surrounding their use. Methods to produce human embryonic stem cells without destroying embryos were proposed in the President's Council on Bioethics report in 2004 [62]. Two of these methods were further investigated in individual proof of concept studies [63-65]. which gleaned promising results. Questions, however, still point to the ethical use of these methods [64]. The use of stem cells derived from adult tissues, and not those derived from embryonic tissues, avoids many of the ethical concerns that may arise from the use of stem cells in research applications.

Adult stem cells

Adult stem cells, also referred to somatic stem cells or mesenchymal stem cells, are those mature, adult cells that are undifferentiated and found in a specific tissue or organ. These cells are self-renewing and able to differentiate into major specialized cell types that serve to maintain the integrity and repair of the tissues in which they are located [46, 47, 66]. Mesenchymal stem cells can undergo self-renewal for several generations while continuing to maintain their specific cell characteristics. They are multipotent cells that can be easily isolated, cultured, and readily expanded in the laboratory setting. All of these attributes make mesenchymal stem cells an attractive cell source for use in several clinical applications [56], including cell based therapies for treatment of diseases such as Parkinson and Alzheimer diseases, spinal cord injuries, burns, heart disease, and osteoarthritis, among other conditions [47]. These adult stem cells typically include hematopoietic stem cells, neural stem cells, bone marrow stromal cells, dermal stem cells, and fetal cord blood stem cells.

Bone marrow contains hematopoietic stem cells and it is also the most recognized source of mesenchymal stem cells. Stem cells obtained from bone marrow are found in the stroma of the marrow. These cells are multipotent, and are therefore able to differentiate into lineages of cells such as adipocytes, osteocytes, myocytes, tenocytes, and neural cells [48, 50, 56, 67]. These cells are typically obtained by bone marrow aspirates from marrow transplant donors. When cultured in vitro, bone marrow stem cells exhibit a fibroblast-like morphology. Marrow stromal cells have been studied and, to date, certain cell surface markers have been identified that are useful in cell selection and determination of preparation of marrow stem cell populations [67]. In addition to their ability to differentiate into multiple cell lineages, the use of marrow stem cells is preferable because they offer a source of cells that is isolated and expanded in vitro with relative ease. The number of cells may significantly increase by subculturing a small sample of donor tissue [56, 67].

In addition to bone marrow, adipose tissue has been identified as a source of multipotent cells that have the capacity to differentiate into cells of adipogenic [31, 68], chondrogenic [69, 70], myogenic [31, 68], and osteogenic [31, 68] lineages when cultured with the appropriate lineage specific stimuli [70, 71]. Adipose-derived stem cells (ADSCs) may be obtained from tissue harvested through liposuction (termed processed lipoaspirate cells [PLAs]), or through abdominoplasty procedures. These cells have also been identified as mesenchymal cells because they are derived from adipose tissue which is, in turn, derived from mesenchyme, much like bone marrow [70]. ADSCs have been shown to be very similar to marrow-derived stem cells in morphology and phenotype [72].

In addition to their common multipotency, several CD marker antigens on the surface of marrow stem cells have been found on the surface of ADSCs [31, 70]. ADSCs are preferable for tissue-engineering applications because they are largely available. Adipose tissue is often available in an abundant, expendable quantity. It is also easy to harvest, in contrast to marrow stromal cell extraction which results in significant pain [73]. ADSCs are limited, however, by several factors. First, ADSCs have not been classified as immortal. ADSCs display obvious signs of "old age", thus limiting their capacity for subculturing. Additionally, adipose tissue is known to vary in metabolic activity and in its capacity for proliferation and differentiation, depending on the location of the tissue depot and the age and gender of the patient [73, 74].

4. Isolation and Expansion of Adipose-Derived Stem Cells

The initial methods to isolate cells from adipose tissue were pioneered by Rodbell and colleagues in the 1960s [75] using rat fat tissue. These methods were further adapted for human tissues by several other groups [76, 77]. The current methods for isolating ASCs rely on a collagenase digestion followed by centrifugal separation to isolate the stromal/vascular cells from primary adipocytes. The pellet is resuspended with a basal medium con-

taining 10% fetal bovine serum [78]. The cell suspension is filtered through 100 μm cell strainer and the cells are plated and incubated at 37°C in the presence of 5% CO_2. The medium is changed once a day until the cells reach 80% to 90% confluence. A large number of ASCs can be harvested in this manner, with yields of approximately 250000 cells per gram of tissue [79, 80].

In order to remove the use of animal products in human ASC cultures, a very low human serum expansion medium and a completely serum-free medium have been recently reported [81]. Furthermore, it was reported that use of platelet- rich plasma can enhance the proliferation of human ASCs. These results can support the clinical application of platelet rich plasma for cell based, soft-tissue engineering and wound healing [82]. ASCs should be harvested at 80% confluence for freezing. Cryopreservation medium consists of 80% fetal bovine serum, 10% dimethyl sulfoxide (DMSO) and 10% DMEM/Ham's F-12. The cells should be stored in a final concentration of 1–2 million viable cells per milliliter of cryopreservation medium. Aliqouted vials are first frozen in an alcohol freezing container and stored at -80°C overnight. On the next day, the frozen vials can be transferred to a liquid nitrogen container for long-term storage. Successful storage of ASCs has been shown for more than 6 months. This ensures the availability of autologous banked ASCs for clinical applications in the future [18, 83].

5. Fat Tissue Engineering

A large proportion of the plastic and reconstructive surgical procedures are performed to repair soft tissue defects resulting from traumatic injuries, tumor resection, congenital defects, or ageing process. Transplantation of autologous fat tissue grafts has been the classical method for soft tissue reconstruction and plastic surgery. Despite the efforts toward improving this procedure, problems such as progressive absorption of fat grafts with time have been observed [84]. The reduction in adipose volume is thought to be partly related to insufficient vascularization of grafted fat tissue [85]. Fat tissue is highly vascularized with extensive capillary networks surrounding each adipocyte, and fat tissue itself has angiogenic properties [86, 87].

Innervation is also an important feature of adipose tissue. There is strong evidence for the role of the autonomic nervous system in modulating the fundamental properties of adipose tissue function and biology at the cellular and molecular level. This is reflected in the modulation of lipolysis/lipogenesis, local insulin sensitivity of glucose and fatty acid uptake, and the modulation of fat cell number [88, 89]. The potential development of tissue-engineered soft tissue represents a promising and innovative solution for many clinical challenges, especially in plastic and reconstructive surgery.

Potential applications of tissue-engineered fat include reconstructive, cosmetic, and corrective indications. Congenital deformities, complex traumatic wounds involving soft tissue defects and post-cancer surgery are reconstructive challenges potentially benefiting from soft tissue engineering strategies. Cosmetic applications include augmentation procedures for lips and chin, and rejuvenation procedures to fill out wrinkles of the aging skin. Correction uses of engineered fat might include the treatment of urinary incontinence or vocal cord insufficiency, in which a stable, long-lasting "bulking agent" is needed [84, 90].

There are 20 possible research strategies of tissue engineering to induce de novo adipogenesis. One method is to use cells that proliferate and differentiate to form adipose tissue. Cells isolated from a patient's own tissue are cultured and seeded onto a biocompatible scaffold withor without bioactive molecules such as growth factors [91, 92]. Engineered implant is then brought into the body site where the formation of adipose tissue is expected [84]. For example, adipose tissue has been formed in the subcutis of rats by seeding autologous preadipocytes on poly(lactic-co-glycolic acid)-collagen scaffolds [93]. Alternatively, adipose tissue formation could be induced in vivo from precursor or stem cells originally existing in the body. Site-specific delivery of potent bioactive factors that influence the growth and development of in vivo progenitor or stem cells in a specific manner could provide a suitable method for de novo formation of adipose tissue [84]. It has been reported that de novo adipogenesis in the subcutis of mice could be achieved by injection of a mixture of basement membrane extract "Matrigel" and bFGF incorporated into biodegradable microspheres [94]. Biomaterials used for adipose tissue engineering may either be fibrous scaffolds or injectable materials, such as hydrogels [95], containing cells and adipogenic or angiogenic factors.

6. Applications of Fat Tissue-Derived Cells for Cell-Based Therapy

Adipose tissue provides a uniquely abundant and accessible source of autologous cells for applications in tissue engineering and regenerative medicine. Adipose tissue can be harvested in large amounts with minimal morbidity. It contains several cell types, including mature adipocytes and stromal-vascular cells (SVC) such as fibroblasts, smooth muscle cells, pericytes, endothelial cells, and preadipocytes that may be advantageous to soft tissue regeneration [32]. Preadipocytes are fibroblast-like cells

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that can be isolated from adult white adipose tissue of various species, including humans, and are able to proliferate and differentiate into mature, lipid-synthesizing, and lipid-storing cells both in vitro and in vivo [95, 97].

There are documented differences in the growth and differentiation of adipogenic progenitor cells derived from different adipose tissue sites [98, 99]. Studies on the responsiveness of stromal-vascular (SV) cultures derived from pig adipose tissue to adipogenic agents have demonstrated several genotype- and age-dependent characteristics [100]. The differentiation capacity of primary preadipocyte cultures has been shown to be donor-dependent and decrease with age [101, 102]. Human adipose tissue-derived stromal cells isolated from multiple donors have been shown to display varying degrees of differentiation in response to an optimal adipogenic stimulus in vitro [103]. It has been proposed that cells from different donors may be arrested at distinct stages of adipocyte development and therefore require a different subset of signals to undergo adipocyte differentiation [20]. Rat primary subcutaneous preadipocytes in culture display a higher capacity to differentiate than epididymal preadipocytes [95].

Human preadipocytes from different sites of the same subject respond differently to a specific adipogenic stimulus at molecular level. Based on lipid accumulation, lipogenic enzyme activity and mRNA levels, preadipocytes from subcutaneous sites were much more responsive to specific adipogenic compounds compared to preadipocytes derived from omental fat of the same individuals [99]. Differences in the expression of mRNAs encoding a number of proteins involved in the control of adipocyte metabolism, including leptin and glycogen synthase, have been demonstrated between human subcutaneous and omental adipose tissue [99]. Further studies could possibly reveal optimal harvest sites for tissue engineering applications of adipose-derived precursor cells.

7. Adipose-Derived Stem/Stromal Cells Differentiation

Adipogenesis

Adipose-derived stem/stromal cells (ASCs) in response to inductive compounds, including glucocorticoid receptor ligands (dexamethasone), insulin, cyclic AMP agonist (forskolin), and peroxisome proliferator activated receptor gamma (PPARγ) undergo adipogenic differentiation [103]. During the differentiation process, ASCs lose their proliferation rate and undergo morphological changes. ASCs are induced in the adipocyte differentiation medium containing biotin, D-pantothenate, dexamethasone, methy-

lisobutylxanthine, insulin and equivalent PPARγ agonist. After induction for 2 weeks in adipogenic medium, the human ASCs accommodate vacuoles filled with neutral lipid cells, which can be further stained for intracellular lipid droplets accumulation using an Oil Red O stain [104]. In addition, these cells secrete increased amounts of the adipocyte protein leptin, and transcribe adipogenic mRNAs such as the fatty acid binding protein, aP2, and lipoprotein lipase [105]. Some of these parameters such as leptin, and aP2 mRNA levels have been quantified and found to be increased by several hundred-fold during the differentiation process [105]. It is reported that ASCs harvested from female mice differentiate more efficiently into adipocytes than those from male mice [106]. One of the most important uses of ASCs is for the replacement of adipose tissue itself. Large soft tissue defects are a common problem following trauma, burns, and oncological resections.

Several studies demonstrated the in vitro differentiation of ASCs along adipogenic lineages, including the accumulation of intracellular lipid droplets, as well as the expression of characteristic proteins and enzymes [106]. ASCs were used to seed artificial scaffolds and were further implanted subcutaneously in mice and rats [107]. The cell-seeded grafts showed significant neovascularization of the implant, as well as penetration of the preadipocytes or ASCs into the scaffolding, and their differentiation into mature lipid-laden adipocytes.

Smooth muscle

ASCs can be differentiated to smooth muscle cells (SMCs) and might offer a cell source for hollow organ engineering. For myogenic differentiation, ASCs at passages 3 through 5 are cultured in smooth muscle inductive medium consisting of MCDB 131 supplemented with 1% fetal bovine serum and 100u/mL of heparin for up to 6 weeks at 37°C with 5% CO_2. Because the medium is changed every 3 days, cell splitting is not required [108]. The cellular changes after differentiation can be investigated by real-time PCR at mRNA level.

As reported, the expression of muscle actin (SMA), calponin and myosin heavy chain showed an increase after growth in differentiation medium [108]. The same was observed at protein levels, induction media induced differentiation of the ASCs into a smooth muscle phenotype in which the expression of smooth muscle specific proteins SMA, caldesmon, and myosin heavy chain (MHC) increased [108]. Differentiation is a complex process and has a dramatic effect on cell size, shape, membrane potential, metabolic activity and responsiveness to external signals. One of the main characteristic of SMCs is their

contractility, which plays an important role in angiogenesis, blood vessel maintenance, and mechanical regulation of hollow organs such as bladder.

Differentiated SMCs can show 2 specific phenotypes, which vary from synthetic and proliferative to contractile and quiescent [109]. SMCs exhibit a contractile phenotype characterized by high expression of specific contractile proteins including SMA, calponin, SM22, smoothelin, h-caldesmon and smooth muscle myosin heavy chain [110]. Because differentiated human ASCs express smooth muscle specific proteins, they may prove to be of value in repairing smooth muscle defects in the gastrointestinal and urinary tracts. Juan et al. reported that the ASCs from different sites showed different myogenic differentiation abilities in vitro. ASCs from the adipose tissues of the neck nape and vicinity of epididymis can be used as ideal seed cells for tissue engineering of lower urinary tract [111]. Similar study was performed by other groups using human subcutaneous and omental adipose tissues. They could show that subcutaneous adipose tissue has higher differentiation capacity than omental adipose tissue. Thus, they can be a suitable cell source for use in regenerative medicine [112].

Osteogenesis: Bone defect repair

In the past decade, several research groups isolated cells from the adipose tissue of humans and other species capable of differentiating into osteoblasts in vitro [113]. ASCs differentiate into osteoblast-like cells in the presence of ascorbate, b-glycerophosphate, dexamethasone and vitamin D3. For osteogenic differentiation confluent ASCs are incubated for 3 weeks in DMEM containing 10% FBS (fetal bovin serum), 100 nM dexamethasone, 10 mM β-glycerophosphate and 50 μM L-ascorbic acid-2-phosphate. After fixation cells are incubated at 37°C for 1 hour with 0.16% naphthol AS-TR phosphate and 0.8% Fast Blue BB dissolved in 0.1 M tris buffer (pH 9.0). For osteogenic differentiation cells were also incubated in 1% Alizarin Red S for 3 minutes to detect calcium deposition [115]. Over a 2 to 4 week period in vitro, both human and rat ASC cells deposit calcium phosphate mineral within their extracellular matrix, and express osteogenic genes. Under osteogenic conditions, ASCs are observed to express genes and proteins associated with osteoblasts phenotypes such as osteopontin, osteonectin, osteocalcin, collagen type I, BMP-2, and BMP-4 [105].

In addition, ASCs are able to form mineralized matrix in vitro in both long term 2-D or 3-D osteogenic cultures. In vivo, ASCs embedded in porous cubes of hydroxyapatite/tricalcium phosphate form bone were used as implants in immunodeficient mice [115]. New osteoid, derived from

the human ASCs is present within a 6-week incubation period [115]. This finding indicates that ASCs will have therapeutic applications in bone repair. The first case of autologous ASC use for osseous repair has been reported in the treatment of a calvarial defect in a 7-year-old girl. Using different type of scaffolds, human ASCs can form bone in immunodeficient mice [115].

Myogenesis: skeletal muscle repair

Based on evidence, ASCs can differentiate along each of the myocyte lineage pathways when cultured in myogenic induction medium containing 0.1 mM dexamethasone, 50 mM hydrocortisone, 10% FBS, and 5% horse serum. ASCs express MyoD and myogenin, transcription factors regulating skeletal muscle differentiation [115]. Skeletal myogenesis is characterized by a period of myoblast proliferation, followed by the expression of muscle-specific proteins and fusion to form multinucleated myotubes. Early myogenic differentiation is characterized by the expression of several myogenic regulatory factors, including myogenic determination factor MyoD1. Terminally differentiated myoblasts can be characterized by the expression of myosin and the presence of multiple nuclei [117]. In the first in vivo report, Bacou et al. injected ASCs into the anterior tibialis muscle of rabbits following cardiotoxin-induced injury. Consistent with prior work using satellite cells, treated muscles were found to be heavier, have an increased fiber area cross-section and exert greater maximal force [118].

Chondrogenesis

ASCs display chondrogenic characteristics following induction with ascorbate, dexamethasone, and TGF-β [119]. Under inductive conditions, ASCs express aggrecan, chondroitin sulfate, collagen type II and IV and proteoglycans associated with chondrogenic phenotype [119]. For chondrogenic differentiation, ASCs are grown to confluent in 30-mm dishes and incubated for 3 weeks in DMEM containing 1% FBS, 50 mM L-ascorbic acid-2-phosphate, 40 mg/mL proline, 100 mg/mL pyruvate, 10 ng/mL TGF-b3, and 1x ITS. Induction medium is replaced every 3 days. At the indicated time points, differentiated cells are fixed for 1hour with 4% paraformaldehyde and rinsed with PBS. Accumulation of chondrocyte matrix is detected with alcian blue staining (pH 2.5, Wako) [120].

Neuronal differentiation

Preliminary evidence suggests that human ASCs can display neuronal and / or oligodendrocytic markers. ASCs at passages 2–5 are seeded in 6-well plates at 40%–60% confluence. After 3 washes with PBS, the cells are in-

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duced with NIM (DMEM supplemented with 500 mM IBMX, 200 mM INDO, and 5 mg/mL insulin) for 1 hour. The cells are then examined for the expression of neuronal markers S100, NF70, and nestin by hematoxylin and eosin (H&E) staining [121]. The in vivo test for the therapeutic potential of ASCs looked at their effects when injected intraventricularly in rats. ASCs survived with increased engraftment at the site of injury compared with controls. Neural lineage markers microtubule-associated protein-2 and glial fibrillary acidic protein were expressed in some engrafted cells. Behavioral tests of the motor and sensory systems showed clear improvements in those treated with ASCs after infarction [122]. It is unclear whether transplanted cells replaced the lost neurons or provided a support role for existing stem cells and injured neurons. Furthermore, in a co culture model, Kang et al. studied the interactions between neural stem cells (NSCs) and ASCs. In comparison to laminin-coated dishes, ASC feeder layers showed ability to support the differentiation and survival of NSCs over 14 days in culture.

Concerns and implications

As with all areas of research, there are specific scientific concern to consider for advancing methodologies. Regarding the use of stem cells for tissue-engineering, there will be numerous concerns to address, including standardization of methods for tissue procurement, cell isolation, and cell culture. Currently, adipose tissue derived stem cells are obtained from liposuction aspirates or abdominoplasty procedures. The methods for harvesting the tissue may have affect the ability of the cells to proliferate and differentiate during in vitro culture, thereby introducing variability into the process of cell retrieval and culture for each tissue sample. Additionally, variability exists with the use of stem cells for tissue-engineering applications because, to date, no definitive adult stem cell markers have been discovered to ensure the purity of all stem cell populations [122].

The absence of such markers could potentially minimize the ability to reproduce populations of viable cells that are in fact multipotent stem cells. Successful engineering of any tissue construct requires careful consideration of all aspects of the device. The material chosen for a particular scaffold is often selected according to the mechanical properties that are best suited to a specific application. Therefore, characteristics of stem cell biomaterial carriers will vary according to the particular application. Because the use of stem cells in tissue engineering is a new research area, there is no clear method to determine determining how the cells, once cultured on biomaterials will behave. Cell surface interactions will have to be further investigated to fully understand the behavior of the stem cells in tissue-engineering applications.

8. Conclusion

The field of tissue engineering has significant potential for developing viable and natural tissue constructs. The basis for any tissue-engineered construct is the cellular source that is used to initiate new tissue growth. ASCs provide an abundant and readily accessible source of multipotent stem cells.

The use of autologous stem cells expanded in vitro combined with novel selected biomaterials for organ reconstruction offers a potential solution for replacement of tissue or whole organs. ASCs do have one important advantage over the other sources of stem cells namely easy availability.

Recent advances in bioengineering and cell biology of fat tissue have led to innovative and new therapeutic potentials for regenerative medicine. Autologous human adipose tissue derived stem cells could have clinical applicability for cell-based therapies and tissue engineering purposes. Promising results suggest that adipose tissue will be a useful tool in biotechnology.

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Conflicts of Interests

The authors declared no conflict of interest.

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