Adipose Stem Cells

Biology, Safety, Regulation, and Regenerative Potential

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KEYWORDS

• Adipose • Adipose-derived stem cells • Tissue engineering • Regenerative medicine • Clinical translation • Mesenchymal stem cells • Stromal vascular fraction • Stem cell safety

KEY POINTS

- Human adipose tissue is now a widely accepted source for stem cells in regenerative medicine, and has been the subject of preclinical studies and clinical studies directed toward numerous applications.
- The nonlipid cell population isolated from adipose tissue is heterogeneous and contains adipose-derived stem cells (ASCs), which can be isolated and cultured.
- ASCs are of mesenchymal lineage and manifest features that are attractive for regenerative therapy approaches, including multipotency and release of growth factors that can induce tissue healing.
- These beneficial characteristics have the potential to affect cancer growth and this issue is still being investigated in preclinical and clinical studies.
- From a regulatory perspective, adipose therapies may be regulated under the category of human cells, tissues, and cellular and tissue-based products by the US Food and Drug Administration in Title 21 Code of Federal Regulations, part 1271, or as a biologic drug under section 351 of the Public Health Services Act, depending on the specific use and the degree of processing.
- To date, 129 active clinical trials are listed in the US National Institutes of Health Web site (www.clinicaltrials.gov), spanning a broad range of applications including arthritis, intervertebral disc degeneration, autism therapy, cell-enriched fat grafting, pulmonary disease, and numerous clinical targets.

ISOLATION AND CHARACTERIZATION

Adipose-derived stem cells (ASCs) are prevalent surrounding the blood vessels and within the connective tissue of human adipose tissue. These non–lipid-laden stromal cells can be isolated from either suction-aspirated adipose tissue or excised human fat by enzymatic collagenase digestion. Passenger erythrocytes can be lysed selectively, and numerous descriptions for cell isolation methods appear in the literature.[1–3] The freshly isolated cell pellet is highly heterogeneous and is named the stromal vascular fraction (SVF). Further discussion of the SVF components is featured later. If the SVF cells are placed in culture, the ASCs adhere to the surface of an untreated tissue culture flask after 6 to 8 hours' incubation at 37°C and 5% CO_2. Once ASCs have adhered to the culture flask surface, nonadherent

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populations, representing 7% to 15% of the SVF and representing mainly hematopoietic origin cells, are washed away with sterile phosphate buffered solution and/or fresh culture media. **Fig. 1** shows a widely accepted protocol for SVF and ASC isolation.[4] A commonly used ASC expansion medium consists of a Dulbecco's Modified Eagle Medium (DMEM) and DMEM/F12 media combination, with 10% serum, antibiotic (eg, penicillin, streptomycin), and a small amount of dexamethasone to prevent differentiation to another mesenchymal lineage. Once in culture, specific growth factors or other additives can be applied to direct the differentiation to a specific phenotype, such as adipose, bone, cartilage, or muscle.

SVF is attractive therapeutically because it may be obtained from tissue within 60 to 90 minutes, and the isolation can be performed in a clean room near an operating room, or even in an operating room using an automated device. Collagenase digestion results in approximately 2×10^5 to 5×10^5 nucleated SVF cells per gram of adipose tissue. However, the complete ASC isolation process takes 20 to 24 hours and requires cell culture facilities. Reasons to culture the cells include the ability to expand the cell number, select for specific subpopulation, or control the microenvironment for directed differentiation or induction of adherence to a scaffold material. Flow cytometry characterization of the surface markers on freshly isolated and cultured adipose-derived cells can be performed, and shows the presence of early progenitor markers such as cluster of differentiation 34 (CD34) and CD90.[4,5]

Nonenzymatic cell isolation has been a topic of interest, driven by a potentially less restrictive regulatory pathway. This strategy has focused on mechanical forces such as ultrasound. However, there is no strong evidence to suggest that this is equivalent to enzymatic digestion. There has also been interest in whether there are viable ASCs in the aqueous portion of the liposuction aspirate without exposure of the tissue to enzymes. Although some cells may be present, the quantity is so low as to preclude clinical utility. Because the ASCs are firmly embedded within the connective tissue, enzymatic digestion is necessary to release them in significant quantity.

Preadipocytes were first described in 1976 by Dardick and colleagues,[6] beginning with rat models then isolated from human tissues.[7–9] Isolated preadipocytes were used to study adipocyte biology in vitro, leading to recognition of different anatomic locations and adipose depots to express different biological characteristics, such as adipocyte size and lipolytic potential. In 2001, Zuk and colleagues[10] first discussed the differentiation

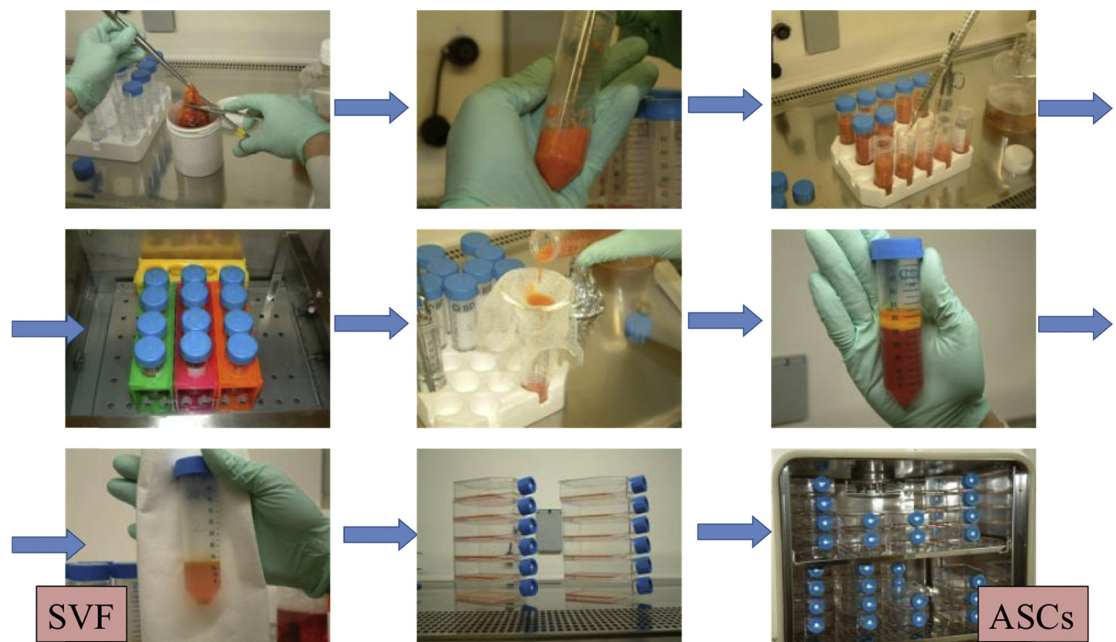

Fig. 1. The SVF and ASC isolation process as described by Rubin and Marra.[4] First, whole adipose tissue or lipoaspirate is finely minced and enzyme digested in at 37°C. Red blood cells are lysed and the suspension is filtered. Following centrifugation, the pellet is considered the SVF. Once plated and cultured on a tissue culture flask at 37°C and 5% CO_2 for 6 to 8 hours, the mesenchymal ASCs are obtained. (*Adapted from* Rubin JP, Marra KG. Soft tissue reconstruction. Methods Mol Biol 2011;702:397; with permission.)

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