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The Role of Fat Stem Cells in Regenerative Medicine

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Abstract:
Adipose tissue has become a useful "stem cell depot" for regenerative medicine. ASCs and their derivatives, such as microfat, nanofat, SVF, microvascular fragments, secretomes, and exosomes, are all promising sources of multipotent cells and paracrine factors. Moreover, they are less encumbered by ethical concerns when compared to embryo-derived stem cells. Their pro-angiogenic, anti-inflammatory, anti-apoptotic, and anti-fibrotic activities adjust the hemispheric injured environments and promote repair in dermatologic, orthopedic, cardiovascular, neurologic, hepatic, and reconstructive indications. Clinical ASC preparations can be rapidly processed from lipoaspirate and used autologously, enhancing immunogenicity. The benefits work mechanically through cellular engraftment and paracrine signaling (secretomes/exosomes), which enhance vascularization and limit fibrosis. Likewise, the mechanism that regulates collagen metabolism also comes into play. As isolating, conditioning, and biomaterial scaffolds improve, ASC applications will broaden. Meanwhile, several individuals are comparing ASCs with other mesenchymal sources, such as bone marrow and DFAT cells. In general, cellular and acellular therapies derived from fat represent a flexible, scalable platform for tissue engineering and translational regeneration standardization, which is a priority area for long-term outcome reports.

INTRODUCTION

Regenerative medicine has shown promise for years using a wide range of approaches. This field encompasses biologics, stem cell therapy, tissue engineering, cellular reprogramming, and gene therapy, to name a few, to curb these ever-increasing needs (Hoang *et al.*, 2022; Iqbal and Ashraf, 2025). These approaches have one goal in common: to modulate the local milieu of diseased tissue or organ into a regenerative environment to aid in the healing process (Lufkin *et al.*, 2022). Among the various regenerative approaches, stem cell therapy has gained much significance mainly after the isolation of human embryonic stem cells and induced pluripotent stem cells (Mousaei Ghasroldasht *et al.*, 2022). The intended use of these cells, however, brought ethical controversies and the difficulty of their use in clinical applications (Ali *et al.*, 2016; Irfan *et al.*, 2019; Taei *et al.*, 2021). This paved the way to look for other conceptions to curb those needs (Pulido-Escribano *et al.*, 2022). Exciting efforts are underway to test the feasibility of using pluripotent stem cells derived from adult tissue, which also have regenerative potential (Jeyaraman *et al.*, 2021). However, due to difficulty with the reprogramming process and the formed teratoma, their applicability is rather limited (Yu *et al.*, 2021).

Over the years, the use of adipose tissue and its by-products has sharply increased among almost every medical specialty and researcher (Bunnell, 2021). After bone marrow derived, adipose tissue is the second most common source of mesenchymal stem cells (Costela-Ruiz *et al.*, 2022). Apart from the presence of mesenchymal stromal cells as progenitor cells within the structure of adipose tissue, its abundance and easy accessibility have contributed to the heightened interest (Krawczenko and Klimczak, 2022). The harvesting of adipose tissue has replaced liposuction for cosmetic needs. So, adipose tissue is considered as “stem cell depot” (de Celis-Ruiz *et al.*, 2022). Adipose stem cells (ASCs) (or adipose-derived mesenchymal stem cells) have added advantages such as accessibility, harvesting potential, and fewer ethical controversies (Ritter *et al.*, 2022). In addition to progenitors, several potential paracrine mediators are produced in abundance within the adipose tissue. Products of the adipose tissues include whole adipocytes, microfat, nanofat, microvascular fragments, stromal vascular fraction (SVF), adipose-derived stem cells, secretomes and exosomes, among others (Rashid *et al.*, 2021). The number and activity of paracrine mediators are far more in the extracts than whole adipocyte (González - Cubero *et al.*, 2021). It is a cocktail of growth factors, cytokines, adipokines, transcriptional factors, etc. (Dragoo *et al.*, 2021). With the addition of a few enzymes and swirling, the extraction can be easily processed within a very short time. Coating cell free products of ASCs is an approach to study the paracrine effects of ASCs (Nammian *et al.*, 2021). The nanofat and SVF, among other products, have been most studied and are of utmost utility in clinical practice currently. What's unique with these products is their preparation results in an increased quantity of ASCs (Abu-El-Rub *et al.*, 2025) (Table 1).

Table 1. Adipose Tissue Sources, Harvest Methods, and Typical Cell Yields

Source / Depot	Harvest Method	Processing (Basic)	Product	Typical Yield / mL Lipoaspirate*	Notes (Donor, BMI, Site Effects)
Abdominal subcutaneous fat	Tumescent liposuction	Wash, filtration, centrifugation	SVF, microfat	2–5 x 10^5 nucleated cells	Yield varies with age, BMI; gentle handling preserves viability
Thigh/gluteal fat	Manual aspiration	Mechanical emulsification	Nanofat	Lower nucleated cell counts; high secretome	Useful for dermal indications; small cannula
Perivascular adipose	Surgical excision	Enzymatic digestion (collagenase)**	ASCs (culture-expanded)	~1–3 x 10^4 ASCs after expansion	Higher purity; regulatory oversight for enzyme use

Understanding Fat Stem Cells

There are two main types of stem cells known that are associated with fat: adipose-derived stem cells (ASCs) and dedifferentiated fat cells (DFAT cells) (Saler *et al.*, 2017). ASCs are the most widely investigated mesenchymal stem cells (MSCs) in the field of tissue engineering and regenerative medicine (Gentile *et al.*, 2021). ASCs have low immunogenicity, and they can be harvested with minimal invasion from body regions with high fat deposits. Furthermore, ASCs can be effortlessly isolated, expanded, and cryopreserved (Jeyaraman *et al.*, 2021). Aside from their MSC characteristics, ASCs also exhibit some anti-angiogenic properties (Bunnell, 2021). On the other hand, DFAT cells were first reported as an abundant source of stem cells in adult tissue with the discovery of a simple and reproducible dedifferentiation protocol (Al-Ghadban *et al.*, 2022). These adipocytes, unlike ASCs, cannot be expanded outside of the fat compartments (Bukowska *et al.*, 2021). On the other hand, they have a higher proliferative potential and higher expression of stemness and differentiation markers (Laloze *et al.*, 2021) (Table 2).

Table 2. Processing Pipelines and Quality Attributes.

Pipeline Step	Mechanical vs Enzymatic	Expected Output	Turnaround Time	QC/Characterization	Regulatory Considerations
Harvest → Wash → Centrifuge	Mechanical	Microfat/SVF	30–60 min (point-of-care)	Viability %, cell count	Minimal manipulation in many jurisdictions
Harvest → Emulsify → Filter	Mechanical	Nanofat (acellular-rich)	15–30 min	Particle size, sterility	Often minimal manipulation; device-dependent
Harvest → Collagenase digest → Isolate → Culture-expand	Enzymatic	ASCs (expanded)	Days–weeks	MSC markers (CD73/90/105+; CD45/34-), sterility, karyotype	More-than-minimal manipulation; GMP and IND/CTA may apply

Biological properties of fat stem cells

Since their first description, many aspects of the biological characteristics and therapeutic applications of adipose-derived stem cells (ASCs) have been elucidated; expanded on, and improved (Al-Ghadban *et al.*, 2022). With existing sources of adipose tissue worldwide and the continuous growth of aesthetic surgery and reconstructive surgery, ASCs are not only the most widely used somatic stem cells in regenerative medicine, but are also the most promising adult stem cell source for future applications in pediatric regenerative medicine (Jeyaraman *et al.*, 2021). Before turning to the clinical significance, safety, and future role of ASCs in regenerative medicine, it is important to summarize the many facets of their biological characteristics (Gentile *et al.*, 2021).

At the time of their first description recline as precursor cells by a minimum two-dimensional criterion (plastic-adhering and fibronectin-augmenting cell populations obtained from fatty tissue, buccal mucosa, and bone marrow) were isolated in an unspecified manner and further experimented on (Nahmgoong *et al.*, 2022). Subsequently, several other isolation methods were reported, and there was an explosion of related articles (Mazini *et al.*, 2021). Careful reports described efficiently, reproducibly, and universally applicable three-dimensional isolation protocols (Gentile *et al.*, 2021). Computer simulations of not only ASCs but stem cells in general uncovered that the population sizes of pluripotent stem cells and their niche location, cell aging, and structures are of critical importance (Gentile and Garcovich, 2021). Downstream to these two-dimensional selection methods was the quest of those cells' stem cell niche (Bunnell, 2021).

Knowing these signals presumes that at least some unknown, mature cells should be present in the sample (Olpe and Jessberger, 2023). This had never been the case among ASCs (Russ *et al.*, 2021). As a result, the potential stem cell phenotype of ASCs became unclear (Coorens *et al.*, 2021).

Differentiation potential of fat stem cells

The differentiation potential of stem cells is a key issue in the field of regenerative medicine (Figiel-Dabrowska *et al.*, 2021). The primary finding of the study is that hASC and DFAT cells, despite their distinct origins, both exhibit similar differentiation potential toward different lineages in vitro (Lau *et al.*, 2024). DFAT takes on differentiated features over a period of five weeks following initiation of the differentiation protocol (Feddern *et al.*, 2024). Moreover, human DFAT are an alternative source of multipotent stem cells for regenerative medicine applications (Figiel-Dabrowska *et al.*, 2021). Although hASC and DFAT have been studied independently, the in vitro differentiation potential of these two stem cell populations has yet to be investigated (Deo *et al.*, 2022). Prior to comparison with hASC, all in vitro studies involving DFAT were carried out using murine cells (Dan-Jumbo, 2023). The data show that mouse DFAT cells can be induced to differentiate into chondrocytes and adipocytes in vitro using similar protocols to those established for hASC (Saler *et al.*, 2017).

Mesenchymal stem cells can be differentiated toward endothelial cells in vitro. Considered a rare population in adipose tissue, intestinal or thyroid adenoma specimens, and articular cartilage, facilitators or inhibitors of angiogenesis are under investigation for their utility in tissue repair/regeneration (Rautiainen *et al.*, 2021). For evaluation of the stemness, angiogenic, and immunomodulatory potential of hASC and DFAT, several self-renewal, pluripotency, and pericyte markers were assessed via semiquantitative RT-PCR (Huang *et al.*, 2021). Regardless of significant differences in the intensity of expression, all eleven factors involved in vessel formation, recruitment, and pericyte-like stabilization, were expressed by samples of standard and alternative or hASC as well as DFAT (Li *et al.*, 2021). Two-thirds of the basic and acidic FGF family, each member of which exerts vasculogenic and angiogenic effects on different levels of magnitude and timeframe, were preferentially expressed in hASC, as opposed to DFAT, where inhibition of FGF1, 7, and 18 was observed over a time frame of up to 14 days (Ormazabal *et al.*, 2022).

Fat stem cells in tissue engineering

The potential of stem cells in regenerative medicine lies in their ability to recreate tissues that have been destroyed or damaged (Porro *et al.*, 2021). Adult stem cells offer numerous advantages in regenerative medicine, including ethical advantages, easy availability, and low rates of tumor formation and infection transmission (Audano *et al.*, 2022). As well as murine embryonic stem cells, adult mesenchymal stem cells have been isolated from many tissues (Bunnell, 2021). The main sources of MSC isolation are bone tissue, umbilical cord blood, muscle, and fat (Morena *et al.*, 2016). Fat tissue includes both mature adipocytes as well as preadipocyte stem cells (Stefkovich *et al.*, 2021). This new cellular source has a plethora of advantages in regenerative medicine (Zhong *et al.*, 2021). Access to fat tissue is simple and minimally invasive compared to bone marrow extraction for the use of mesenchymal stem cells (Yang Loureiro *et al.*, 2023). Pre-adipocytes, with similar properties to bone marrow derived cells, can be isolated from liposuction aspirate (Sárvári *et al.*, 2021). Additionally, the cells are procured for use as an autologous transplant, reducing the chance of rejection (Angueira *et al.*, 2021). Absorbable fat grafts in similar fat tissue appear not to cause additional rejection when compared to the scaffolding used in bone regeneration (Robledo *et al.*, 2023). Despite these many advantages, lipofilling has had only limited clinical application so far (Sugii *et al.*, 2022). This may be related to a retractile origin, rapid cell death, clogging of the syringe filter or excessive filtration (Jeyaraman *et al.*, 2021).

Adipocyte stem cell micro-gel allows for targeted reseeding without diffusible factors; however, growth is furrowed, and cells still arrange randomly (i.e., not polarized) (Khlusov *et al.*, 2022). The extraction process, isolation, and test are detailed. Adipocyte stem cells can be distinguished from other cell types using multilayered in vitro encapsulation and confirmation by PNU (Xie *et al.*, 2022). These cells differ morphologically from regular cells arising from other tissues or types (Gibler *et al.*, 2021). The in vivo scaffold 3D aggregate size is larger than scaffoldless; however, growth stops earlier in vitro than scaffoldless (Najafi *et al.*, 2023). Seeding density has a demonstrable effect on growth, where higher density would confer rapid coalescence or aggregate formation (side effect zero growth) (Yuen Jr *et al.*, 2022). These findings provide insight into the possible adjustment of the bioreactor to ensure efficient growth in the desired pattern and configuration (Lin *et al.*, 2025). The results of miRNA target validation suggest that the regulation of SOX6 and PNU by miR-335, whose activity is negatively regulated by let-7, results in an efficient, detailed, and tuned system in the minimum number of steps (Jiang *et al.*, 2022).

CONCLUSION

Regenerative medicine is one of the latest trends in the treatment of various disorders. It encompasses a wide range of therapeutics, including molecular approaches, cellular approaches, reprogramming approaches, and nanoscaled drug delivery. Among the various regenerative approaches, stem cell therapy is considered one of the significant due to its capabilities. Currently, stem cells of different origins are being used to cure ailments such as neurological disorders, joint disorders, immune disorders, skin defects, and cardiovascular defects. Fat stem cells (adipose-derived stem cells) are considered an upcoming therapeutic agent among many other available stem cells. Adipose tissue is one of the richest and easily accessible sources of stem cells. The vast utilization of fat products is seen in several medical specialties such as dermatology, orthopaedics, cardiac surgery, neurosurgery, and urology. Still, research interests are predominantly in aesthetic dermatology for scar treatment, skin rejuvenation, and regenerative skin grafts.

CONFLICT OF INTEREST

The author hereby declares no conflict of interest.

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