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Evolution of cell therapies derived from adipose tissue: historical perspectives, current development trends and future directions

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Abstract
Over the last few decades, adipose tissue has attracted increasing attention in the field of regenerative medicine, thanks to discoveries related to its regenerative, anti-inflammatory, and pro-angiogenic properties. Over the years, with the advancement of sophisticated research around adipose tissue, there has been a shift from tissue transfer to cell transfer, and then to the application of cell-free derivatives and bioengineering. Understanding the evolution of this scientific revolution around adipose tissue not only helps clarify potential therapeutic products and indications but also allows us to discuss its limitations and future directions.

Keywords Adipose tissue, Cell therapy, Regenerative medicine

Introduction

White adipose tissue is a heterogeneous mix of mature adipocytes, progenitor cells, vascular and immune cells [1]. For a long time, subcutaneous white adipose tissue was considered a filler tissue used in plastic surgery and was mainly studied in science for its involvement in energy metabolism and metabolic disorders.

In the last three decades, research into adipose tissue cell therapy has been enriched by the discovery of its regenerative, anti-inflammatory [2, 3], and pro-angiogenic properties, which have made subcutaneous adipose tissue a valuable source of therapeutics in regenerative medicine. Simultaneously, new advances in tissue bio-engineering are making it possible to use this therapeutic resource through different forms (fat grafting, stromal vascular fraction, direct administration of adipose-derived stromal cells, exosomes, or with biomaterials).

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Understanding the evolution of this scientific revolution surrounding adipose tissue helps us better comprehend future therapeutic products and their indications.

The subcutaneous adipose tissue transfer

At the end of the 19th century, Dr Gustav Adolf Neuber, a German surgeon, carried out one of the first transfers of autologous adipose tissue [4]. He harvested adipose tissue from a patient's arm and reinjected it around the orbital frame to treat invaginated scars caused by a bone infection.

As early as 1984, Dr. Illouz standardized the methods of harvesting subcutaneous adipose tissue by liposuction and reinjecting it into another part of the body to compensate for the deficits caused by surgery [5].

However, this technique of autologous fat transfer proved to be unsatisfactory for a long time: the reinjected fat tended to resorb significantly, with unpredictable results.

It was not until the end of the 20th century that this practice spread to the field of cosmetic surgery, yielding more stable and reproducible results, thanks to the introduction in 1995 by Dr. Sydney Coleman of a rigorous procedure for purifying the lipoaspirate before reinjection [6]. He standardised the methods used to harvest the fat and enabled it to be handled atraumatically in a closed circuit [7].

With sufficient quantities in the body, adipose subcutaneous tissue can be harvested several times to provide a significant amount of material.

With this technique, the reinjected fat is revascularised in the recipient tissue. The surviving adipocytes continue their development cycle in the recipient site, and the graft of surviving adipose tissue generates additional tissue through induction (cell replacement theory) [8]. The ultimate aim of the fat grafting technique is therefore to create adipose tissue from adipose tissue. It is a technique used extensively in reconstruction, especially to fill soft tissue defects, and also in cosmetic surgery, where the aim is to create a volumizing filling effect.

Over the years, the democratisation of this technique has led surgeons who use it to conclude that, in addition to the volumising effect of injecting adipose tissue, there is also a trophic effect, significantly improving the quality and speed of healing of the surgical site.

This regenerative effect was later attributed to the presence of mesenchymal stromal cells (MSCs), which are naturally present in adipose tissue, thanks to the work of Zuk and colleagues in 2001 [8].

Figure 1 shows the timeline of discoveries from the first adipose tissue transfer to the discovery of ADSCs.

The stromal vascular fraction: from the volumising effect to the trophic effect

The study by Zuk and colleagues [8] was a pioneering study that demonstrated the existence, within adipose tissue, of a heterogeneous group of cells attached to the vascular network and participating in the architecture and homeostasis of this tissue: the Vascular Stromal Vascular Fraction (SVF) [8]. Zuk hypothesised that adipose mesenchymal stromal cells may be a variant of the MSC population located in the adipose compartment. They could therefore be used as alternative therapeutic cells to MSCs, which, at the time, had been isolated almost exclusively from bone marrow [9]. This is how adipose tissue gained popularity with researchers, surgeons, and physicians [10]. Adipose tissue-derived stromal cells (ADSCs) share the same characteristics as MSCs previously isolated from bone marrow, exhibiting self-renewal, multipotential differentiation, plastic adhesion, and fibroblast-like morphology [10].

According to the study by Bourin et al. [11], the SVF is composed as follows:

– 15–25% mesenchymal stromal cells (ADSC).
– 25–25% perycites.
– 10–20% endothelial progenitor cells.
– 3–5% perycites.

Adipose tissue-derived stromal vascular fraction (ADSVF) is obtained in a reproducible manner [12, 13], allowing the separation of a lower density layer containing the adipocytes rich in triglycerides, the extracellular fluid, and a cell pellet, corresponding to the stromal vascular fraction. Extraction of SVF involves several steps: washing with phosphate-buffered saline to remove cellular debris, digestion with collagenases at 37 °C to release the cell mixture from the extracellular matrix between the adipocytes, and centrifugation to separate the SVF from the digestion buffer and adipocytes (1500 rpm for 5 min). European legislation requires that SVF extraction, even when automated, has to be performed in an accredited cell therapy laboratory. A mechanical SVF extraction technique is also possible, and it can be realised in the operating room following liposuction. This technique is known as nanofat grafting, in which fat tissue is rapidly transferred from one syringe to another to break down the extracellular matrix and extract the SVF [14]. Despite its practical advantage, this extraction contains less MSC compared with enzymatic extraction [15].

The regenerative effects of adipose tissue mesenchymal stromal cells (ADSCs) are based on their ability to differentiate in situ according to the cellular environment. Indeed, ADSCs display similar properties to bone marrow mesenchymal stromal cells (BM-MSCs) [16]. Still, despite conventional stem cell transplantation therapies, the use of ADSCs within SVF offers multiple advantages: low immunogenicity, the absence of a conditioning

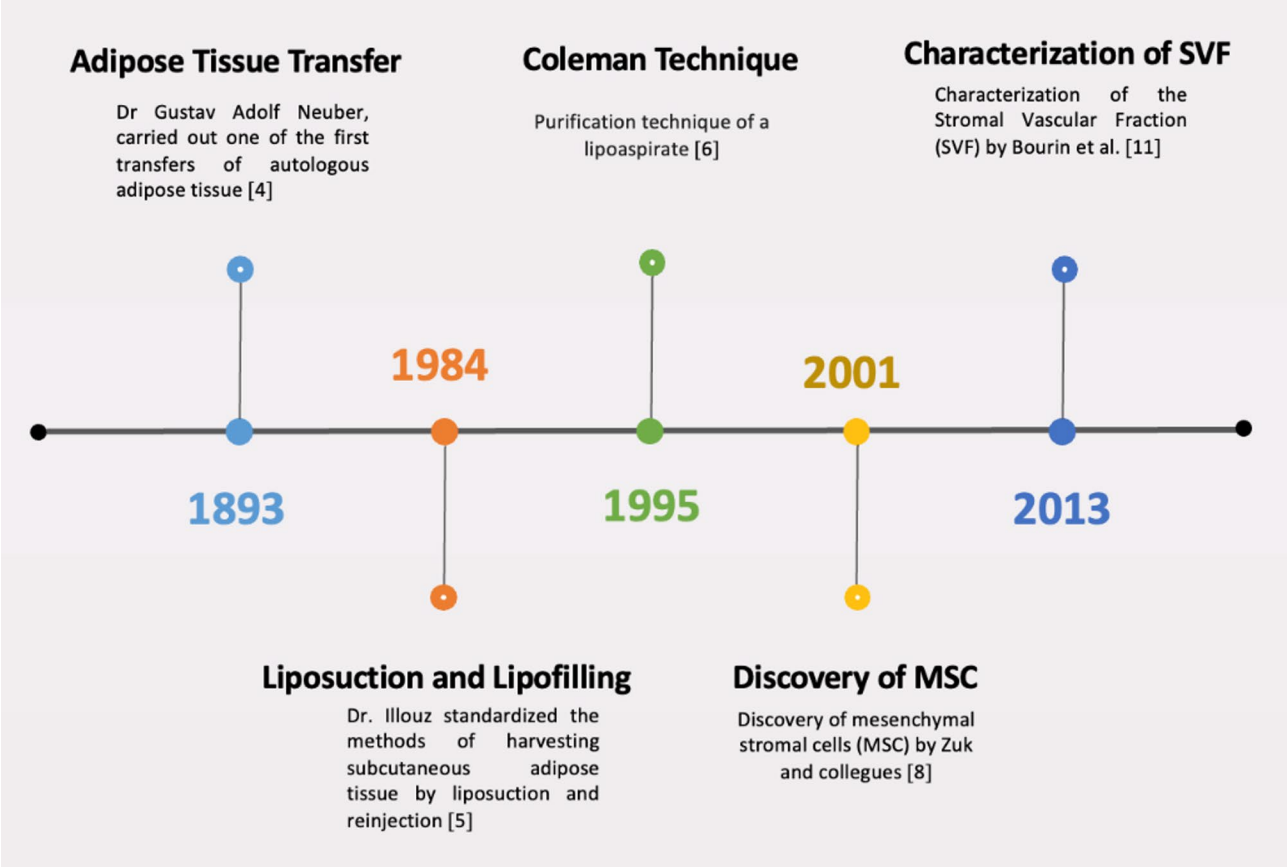

Fig. 1 Timeline of discoveries from the first adipose tissue transfer to the discovery of ADSCs

regimen for the transplantation procedure, and the lack of immunosuppressive treatment after administration [17].

Traktuev et al. [18] demonstrated that vascular endothelial growth factor (VEGF) helps in the migration of ADSCs and promotes secretion of platelet-derived growth factors (PDGF) by endothelial precursor cells within the SVF, which enables ADSCs to proliferate and to migrate [19, 20]. These growth factors help to maintain a vascular-like micro-environment that supports ADSCs either in vitro or in vivo [21, 22].

SVF hematopoietic subpopulation presents distinctive anti-inflammatory properties as macrophages exhibit the expression of the chitinase family member Ym1, the anti-inflammatory cytokine IL-10, arginase, and surface lectins Mgl1 and Mgl2 [23, 24]. Pro-resolutive macrophages M2 generate high levels of anti-inflammatory cytokines, such as IL-10 and IL-1 decoy receptors [25], that attenuate TNF-α inflammatory signals via activation of STAT3 [26] and modulation of inflammatory gene transcription rates [27]. Next to these considerations, immunomodulatory effects of ADSCs are also based on ADSCs intrinsic immunosuppressive properties as the absence of expression of the human leukocyte antigen class II molecules [25], the capacity to inhibit lymphocyte proliferation in response to mitogens and mixed lymphocyte reaction in vitro [26], and the property of secretion of TGF-β [27] and IL-10 promoting the enhancement of T-regs' activity [27].

Preclinical and clinical studies, through clinical and histological parameters, suggest that SVF exerts anti-fibrotic effects regulating the TGFβ1 pathway [28–35]. However, isolated ADSCs seemed to reduce fibrosis more efficiently than SVF [32–36].

The use of SVF has been reported in a variety of indications of chronic diseases for which current and conventional therapies are inadequate. Table 1 summarizes clinical reports utilizing SVF [38–70]. In the majority of clinical trials performed, patients have undergone liposuction and subsequent treatment with their own SVF. Apart from post-operative pain, which is easily controlled in a few days and with conventional analgesics, very few treatment-related adverse events have been noted, demonstrating the safety of this procedure. In all of these clinical studies, good results were primarily mediated through the reduction of inflammation and promotion of tissue repair.

Table 1 Clinical applications of the SVF

	Clinical applications of SVF	Patients (*N*)	References
Neurodegenerative disorders	Amyotrophic lateral sclerosis	6	[38]
	Parkinson disease	8	[37, 38]
	Multiple sclerosis	35	[37, 39, 40]
	Alzheimer disease	10	[37]
	Stroke	1	[37]
	Brain injury	1	[37]
	Spinal cord injury	1	[37]
Autoimmunes diseases	Rheumatic disease	13	[42]
	Crohn's peri-anal fistula	46	[43–46]
Systemic disease	Insuffisance cardiaque congestive	28	[47]
	Maladie pulmonaire obstructive chronique	12	[48]
Affections cutanée	Scleroderma	84	[49–51]
	Radiodermite	1	[53]
	Psoriasis	1	[54]
	Diabetic foot ulcers	74	[55, 56]
	Alopecia	50	[57, 58]
Ischemic diseases	Critical limb ischemia	1	[59]
Orthopedic diseases	Osteoarthritis	104	[60–64]
	Degenerative disc disease	15	[65]
	Tendinopathy	22	[66, 67]
Esthetic indications	Breast augmentation	40	[68]
	Facial rejuvenation	67	[69, 70]

Adipose tissue in regenerative therapy: from tissue grafting to cell-free derivatives administration

Adipose-derived stromal cells properties

ADSCs constitute 1% of SVF cells compared with the 0.001–0.002% of BM-MSCs in bone marrow [71]. Erythrocytes are typically removed using a lysis buffer, and ADSCs in the SVF can be selectively enriched through plastic adherence incubation, immunomagnetic separation, or flow cytometry, followed by in vitro cell culture expansion [72].

ADSCs express CD105, CD90 and CD73. CD34 marker is expressed in SVF but decreases after several passages in culture. Like BM-MSCs, ADSCs can differentiate into cells derived from the mesodermal (osteoblasts, adipocytes, and chondrocytes) lineage after in vitro induction. Differentiation of ADSCs into the specialized cells of interest enables the replacement of damaged and defective tissues. In addition, ADSCs exhibit better pro-angiogenic and anti-inflammatory properties compared to BM-MSCs, which facilitate tissue repair and regeneration through autocrine and paracrine actions [1].

ADSCs secrete pro-angiogenic growth factors and cytokines, such as vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and basic fibroblast growth factor (bFGF). ADSCs also have the property of differentiating into endothelial cells, and thus participating in angiogenesis and vascular repair [73].

Anti-fibrotic effects are associated with the secretion of HGF by ADSCs, whose gene is activated during inflammatory responses. Through the paracrine effect of HGF, ADSCs reduced the expression of TGF-β1 and its target genes, including collagen types I and III, and α-Sma. They induced a significant increase in TGFβ3 expression, resulting in a consequent change in the TGFβ1/TGFβ3 ratio that favors an anti-fibrotic effect [31, 32].

ADSCs also tended to increase MMP-1 and MMP-3, and significantly up-regulated the MMP-2 and MMP-2/TIMP-2 ratio. These results reflect that ADSCs perform a crucial role in the remodelling activity responsible for fibrosis resorption [31, 32].

Additionally, their immunoregulatory function has gained recognition in recent years. In fact, mesenchymal stromal cells (MSCs) stimulated by IFN-γ, TNF-α or IL-1β in the inflammatory environment, acquire immunosuppressive functions [3, 74]. ADSCs have an effect on the activation, proliferation and transition of Th1/17 cells towards Th2 cells, due to the bias of soluble substances such as PGE2. Furthermore, ADSCs are characterized by the absence of expression of class II of the human leucocyte antigen [1], they have the capacity to inhibit lymphocyte proliferation in response to mitogens [75, 76], and they the secrete TGF-β and IL-10 [75] favor the strengthening of the activity of lymphocytes T-regs [1] and the switch of macrophage M1 towards an anti-inflammatory phenotype M2 [73].

These functions could have beneficial effects on autoimmune disorders but also on oncological disorders as tumors are often regarded as "wounds that never heal" [76]. MSCs tend to migrate toward sites of inflammation and tumor microenvironments, therefore, many studies have recommended the use of MSCs as therapeutic vectors to target tumors.

In the study of Ly at al [77], authors characterized the relationship between adipocyte differentiation and immunomodulation in ADSCs. They confirmed that pro-inflammatory cytokines, while eliciting a potent immunosuppressive capacity in ADSCs, inhibit adipocyte differentiation. In fact, the upregulation of the superoxide dismutase 2 (SOD2) induced by IFN-γ and TNF-α, decreased the accumulation of mitochondrial ROS, which are required for adipocyte differentiation of ADSCs. Therefore, blocking of adipogenic differentiation by mitochondrial antioxidant may represent a novel strategy to enhance the immunosuppressive activity of ADSCs in the inflammatory microenvironment [77].

Their immunomodulatory, pro-angiogenic, and anti-fibrotic properties make ADSCs highly attractive cells for

treating inflammatory pathologies and chronic wounds. Figure 2 resumes ADSCs properties.

Administration of adipose-derived stromal cells

Adipose-derived stromal cells can be delivered through a technique called Cell-assisted lipotransfer (CAL) or directly administered.

In 2006, Matsumoto et al. [78] first described the process of CAL using a mouse model injected with human aspirated adipose tissue both with and without supplemental ADSCs. He demonstrated increased survival in the CAL group, with an average 35% greater survival, as measured by explanted graft weight [78]. Cell-assisted lipotransfer has been shown to enhance fat grafting by increasing graft retention and reproducibility.

In 2008, Yoshimura was the first to describe the use of the CAL technique in humans clearly [79]. Since then, numerous researchers have investigated the efficacy of the CAL technique compared to standard lipofilling, yielding promising results [79–106]. Similarly, several systematic reviews or meta-analyses have demonstrated encouraging results, which can reinforce the CAL technique as the gold standard for fat grafts [106, 107]. However, the use of CAL as a surgical technique is not very widespread, being essentially linked to the method of isolating SVF or ADSCs [108]. In fact, the isolation of ADSCs presents a legal problem in many countries, as stromal cell manipulation is strictly controlled by numerous health authorities to avoid potential drift [107].

ADSCs can also be delivered directly to the lesion, as in many models of chronic wounds and inflammatory diseases [109–115]. In a phase III clinical trial, injection of ADSCs from a healthy donor was shown to be effective and safe for the treatment of complex perianal fistulas in patients with Crohn's disease who did not respond to conventional therapies [109]. Promising results have also been obtained using ADSC injections for the treatment of osteoarthritis, with a reduction in pain and an improvement in the function and mobility of the affected joints, without any significant adverse effects [116]. Another phase I clinical trial demonstrated an improvement in ulcer healing in patients with critical ischemia of the lower limb, thanks to the intramuscular injection of autologous ADSCs [117]. However, the delivery of exogenous cells directly into the lesion can be defective [118], which raises concerns about cell engraftment and the preservation of the pro-resolutive phenotype and viability of the cells [119]. In addition, stem cell therapy presents both storage and transportation challenges and risks of induced tumorigenesis or abnormalities [120]. Complementary approaches have therefore been explored, such as the use of cell-free derivatives or biomaterials enriched with therapeutic cells, to improve cell survival and function.

Cell-free derivatives administration

Exosomes or extracellular vesicles (EXOs) have been defined as "particles naturally released from the cell that are delineated by a lipid bilayer that cannot replicate or do not contain a functional nucleus" [121]. Exosomes, as a subtype of extracellular vesicles (EVs), are derived from endosomes and plasma membranes through endocytosis,

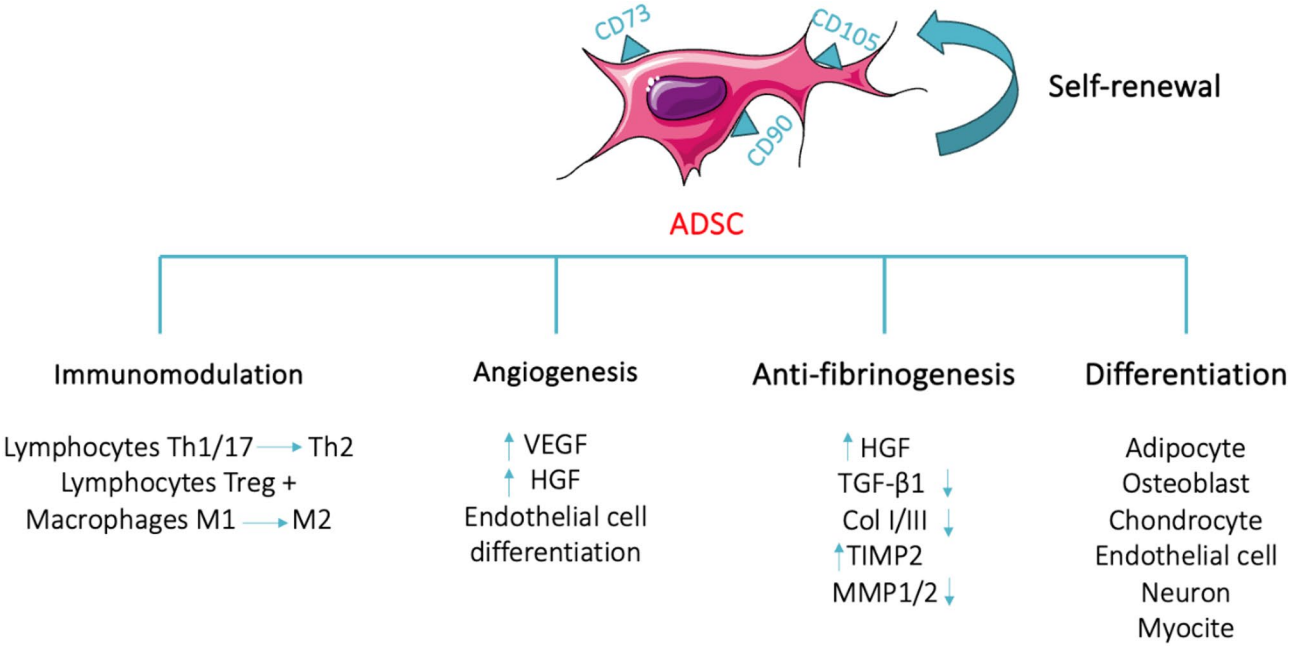

Fig. 2 schematic representation of ADSCs properties

Table 2 Type of bioscaffolds used in regenerative medicine

Type of Scaffold	Mechanism	Potential application
Cell sheets scaffolds	Cells are seeded on sheets and allowed to secrete ECM	Implantation at wound site
Porous scaffolds	Natural, synthetic or composite materials are used for generation of porous scaffolds providing an appropriate environment for cell proliferation	Wound transplants
Hydrogel scaffolds	Monomer or polymeric solution are mixed with cells	Implantation at wound site
Acellular scaffolds	A complete de-cellularization of the organ is performed to create ECM-based matrix	Artificial organs

fusion, and budding processes [122]. They are secretory organelles that act as intercellular communications, delivering bioactive cargos, such as proteins, lipids, nucleic acids, miRNAs, and growth factors. They provide signals regulating cell-to-cell communication, metabolism, and homeostasis. Increasing evidence suggests that exosomes derived from ADSCs exhibit anti-inflammatory properties by inducing the polarization of macrophages to the M2 type through the STAT-3 pathway, thereby reducing inflammation. Most of all, ADSCs-EXOs have become a hot topic in the field of skin wound repairing; in fact, they contain microRNAs [123], which reinforce the acceleration of wound healing [124]. These exosomes can be delivered to the tissue through injections, by being loaded into an alginate hydrogel, or by being incorporated into wound dressings [125]. In a porcine model of full-thickness wound healing, topical application of ASC-derived exosomes combined with hyaluronic acid resulted in accelerated wound closure [126]. The same study showed that these exosomes improved the proliferation and migration of healthy human fibroblasts [127].

Compared to ADSC therapeutics, ADSC-EXOs exhibit high stability and can be easily stored. Additionally, they are not rejected by the immune system and have a homing effect, and their dosage can be easily controlled [128]. However, although their efficacy has been proven, the pro- or anti-cancer status of ADSCS-EXOs remains a burning question. Thus, the safety of ADSCs-EXOs cannot be guaranteed at the date [122].

In vitro, numerous studies have also demonstrated the therapeutic efficacy of ADSCs' conditioned medium on skin repair [126, 128–130]. Adipose-derived mesenchymal stem cells-conditioned medium (ADSC-CM) contains indeed cytokines and growth factors that can facilitate the regeneration and repair of various tissues and organs. ADSCs can secrete a variety of biologically active molecules that affect the surrounding microenvironment via a paracrine mechanism [131]. These cellular factors render ADSC-derived conditioned medium a valuable source for therapeutic application.

In an ex vivo human skin wound model, the conditioned medium from ADSCs improved re-epithelialization and restored tissue integrity [129]. It was equally hypothesized that the ADSC-CM promotes fibrosis resolution in vitro and that this effect is enhanced following ADSC cytokine priming [132]. Using stem cell–conditioned medium (CM) might be a viable alternative to stem cell transplantation, which is often hampered by low grafting efficiency and potential tumorigenesis, however currently available culture media for stem cells contain components that are not intended for human use, such as bovine serum, necessitating the development of an alternative medium that is safe for human clinical use [131].

Adipose-derived stromal cells and bioscaffold

In the era of tissue engineering, functional biomaterials that can maintain cell delivery and cellular viability have had a profound impact in the field of regenerative medicine [73]. In this concept, scaffolds are defined as the ideal materials to restore, maintain, and improve tissue function [133], providing a suitable structure that permits cells to survive, proliferate, and differentiate [134].

Natural, synthetic, or composite biomaterials have been used in bioengineering. Several factors are typically considered in the design of an ideal biomaterial, including hemostatic and antimicrobial properties, ease of sterilization and application, biodegradability, non-toxicity, and non-immunogenicity [135].

Several techniques are described to permit scaffold construction, including the use of extracellular matrix (ECM)- secreting cell sheets [136], the construction of porous scaffolds from biomaterials [137], the use of decellularized ECM scaffolds [138], and the fabrication of cells entrapped in hydrogels [139] (Table 2). Thus, researchers have focused on biomaterials to create a favorable microenvironment for ADSCs, aiming to maximize their therapeutic potential. Several studies have investigated the efficacy of ADSCs in cutaneous wound healing, confirming cell viability and promoting accelerated cutaneous healing while reducing scarring and fibrosis [73].

Given the potential of this field, further investigations will undoubtedly be conducted to estimate the best material to apply to humans.

Conclusion

In the last decades, research into adipose tissue cell therapy has been enriched by the discovery of its regenerative, anti-inflammatory, and pro-angiogenic properties, which have made subcutaneous adipose tissue a valuable source of therapeutics in regenerative medicine. From tissue transfer to the discovery of SVF and ADSCs, and

from the identification of cell-free derivatives to advancements in bioengineering, this field of research is undergoing an increasingly dynamic expansion.

ADSCs Exosomes, the delivery of ADSC-conditioned medium, or the use of ADSCs combined with a bioscaffold have been demonstrated to be effective for their regenerative properties and to avoid ADSC-graft problems related to cell viability, functionality, and storage. However, there is yet a lack of standard procedures for applying ADSCs related to varied cell quality, which makes it difficult to compare results obtained from different studies and standardized methods for applying ADSCs under various conditions and at different checkpoints, including donor site selection, isolation procedure, storage, and characterization, are essential for its use and application.

Nevertheless, based on the discoveries about adipose tissue over the last few decades, we can predict that tissue grafting will progressively give way to cell-free grafting, enabling finer reconstruction with a more precise objective.

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SG and BC: conception and design of the manuscritSG, AV, AC, BS: idea and conception of the manuscritSG, EL and CB wrote the main manuscrit textYB: prepared tableAll authors reviewed the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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