Article type: Review article

Title: Reassembling Adipose Tissue Complexity for Next-Generation Tissue Regeneration

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Highlights

Reassembling Adipose Tissue Complexity for Next-Generation Tissue Regeneration

- The deconstruction–reassembly framework tracks what adipose processing preserves, removes, or rebuilds.
- Reassembly can preserve existing tissue relationships or reconstruct those disrupted during processing.
- Product selection should match the required repair function and the main barrier in the recipient bed.
- Greater tissue complexity alone does not establish therapeutic benefit or clinical readiness.

Keywords: adipose tissue; tissue regeneration; burn wound; soft-tissue reconstruction; biofabrication; organoid technology; extracellular vesicles; extracellular matrix

Manuscript word count: 5907

Abstract word count: 190

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References: 152

Figures: 3

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Abstract

Repair of complex soft-tissue injury often requires more than volume replacement; it depends on coordinated restoration of vascular supply, matrix organization, immune balance, and tissue structure. Adipose tissue contains living cells, extracellular matrix, and local signals that may contribute to these processes. This review uses a deconstruction–reassembly framework that traces the evolution of adipose-based therapy from a vascularization-dependent living graft to fragmented derivatives, cellular products, acellular signals, and biofabrication substrates. Deconstruction separates selected components and can make delivery more flexible, but it also breaks native tissue organization. Reassembly is achieved through the preservation of existing relationships within tissue units or the reconstruction of relationships lost during processing. Neither greater complexity nor a position on this continuum establishes therapeutic superiority, standardization, or clinical maturity. Established grafts, investigational derivatives, and preclinical constructs differ in the strength and clinical relevance of the supporting evidence. We propose that product choice should start with the function that is missing at the recipient site and the main barrier to repair, such as ischemia, fibrosis, or structural loss. This complexity-matched perspective

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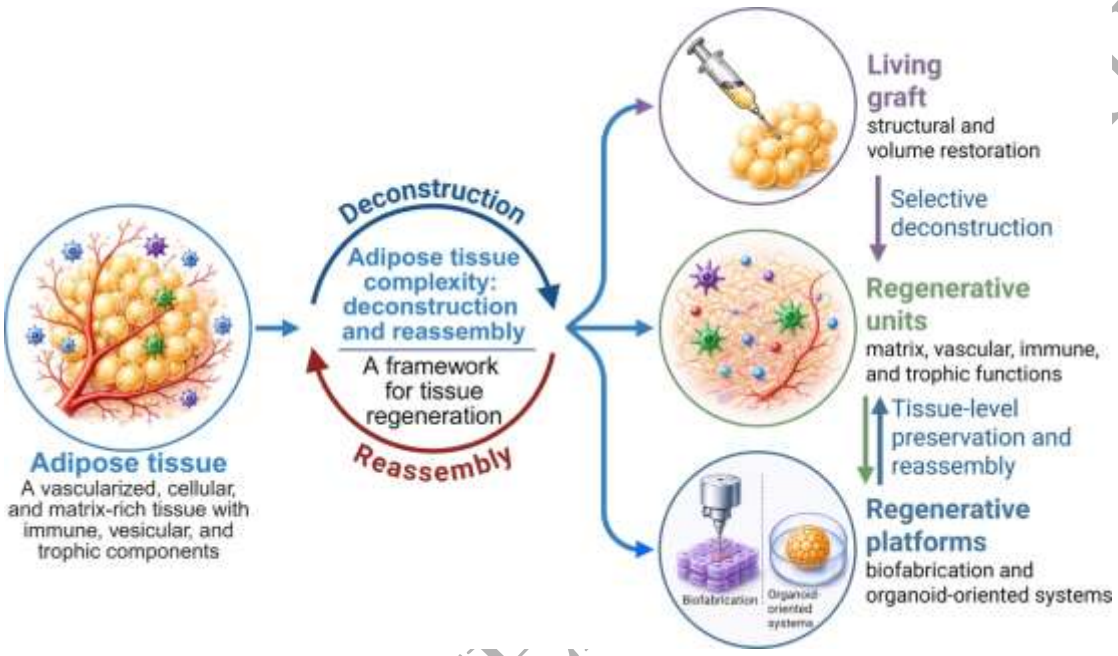
provides a translational framework for product selection and development in burns, trauma, and soft-tissue reconstruction.

Graphical abstract



1. Background

Adipose tissue transplantation has become a widely used strategy in plastic and reconstructive surgery, but its importance now extends beyond volume restoration. Because adipose tissue is abundant, autologous, biocompatible, and naturally suited for soft-tissue replacement, fat grafting has been applied in facial rejuvenation[1] and breast and body contouring[2, 3]. It has also been applied in post-traumatic and post-oncologic reconstruction[4, 5], scar treatment[6], radiation injury[7, 8], chronic wound repair[9], and selected inflammatory skin disorders[10]. These applications have

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prompted investigation of how transplanted fat affects tissue repair beyond volume retention.

In the repair of damaged tissue, restoring tissue volume may address only part of the problem. Successful repair requires restoration of vascular supply, remodeling of fibrotic or damaged matrix, control of inflammation, recruitment of host cells, and integration with the recipient tissue environment. Adipose tissue is relevant to these reconstructive challenges because it contains living cells, extracellular matrix (ECM), and secreted signals that may support different aspects of repair.

This broader clinical role reflects a continuing redefinition of adipose tissue as a therapeutic material. Initially considered a passive autologous filler, transplanted fat was later recognized as a vascularization-dependent living graft whose survival depends on diffusion, revascularization, and host integration[11-13]. With reports of improvements in scar quality, irradiated tissue, and skin texture after fat grafting, adipose tissue has come to be understood as a biologically active material composed of cellular, matrix, immune, and trophic elements[14, 15]. These observations support studying adipose tissue as a source of regenerative materials, although clinical improvement alone does not identify the component responsible. More recent work has explored adipose tissue as a starting material for biofabrication[16] and organoid generation[17, 18]. Such approaches seek to use or rebuild tissue organization, as well as the properties of individual components.

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Here, we propose a deconstruction–reassembly framework to examine how processing changes the organization and potential uses of adipose tissue, connecting intact grafts and their derivatives with biofabrication and organoid-oriented systems. Deconstruction separates or enriches selected components, but processing also disrupts their native relationships. Reassembly encompasses both preservation-based and reconstruction-based strategies. Preservation-based tissue reassembly retains existing relationships within processed tissue units, including those between cells, microvessels, and ECM, while reconstruction-based reassembly rebuilds relationships that are disrupted during processing. Both approaches seek to address tissue-level functions that cannot be adequately reproduced by isolated cells, matrices, vesicles, or soluble factors.

Previous reviews classify adipose-derived therapies by features such as processing method, cellular content, or clinical use[14, 15, 19-22]. These classifications distinguish intact grafts from preparations such as stromal vascular fraction (SVF), adipose-derived stromal/stem cells (ADSCs), extracellular vesicles (EVs), and matrix-based products. Our framework builds on this work by examining how processing changes tissue organization and function. It also asks whether the recipient bed can supply a missing function or whether that function needs to be rebuilt within the product. **Table 1** compares the framework with existing product-based classifications.

Literature search and selection strategy

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This narrative review employed a structured literature search to improve transparency. The PubMed/MEDLINE, Web of Science, and Scopus databases as well as Google Scholar were searched from database inception to July 2026 using combinations of terms related to adipose tissue transplantation, adipose-derived products, burns and soft-tissue injury, regenerative mechanisms, biofabrication, and organoids. Only English-language publications were considered. Clinical studies, preclinical animal studies, in vitro mechanistic studies, technical reports, consensus or guideline documents, and relevant review articles were considered. Priority was given to studies that directly addressed product composition, processing, mechanism of action, clinical application, safety, manufacturing, or translational readiness. Studies were excluded if they were not relevant to adipose-derived therapy, lacked sufficient information to identify the product or processing method, or described evidence already represented by more complete reports. Evidence was interpreted qualitatively according to study type, product category, clinical maturity, methodological relevance, and applicability to burns, trauma, chronic wounds, scars, radiation injury, and soft-tissue reconstruction. The writing of this narrative review was informed by the principles of the Scale for the Assessment of Narrative Review Articles[23].

2. Review

1. Clinical Challenges That Redefined Adipose Tissue as a Living Graft

The early use of adipose tissue transplantation was guided by a straightforward reconstructive idea: autologous fat could be transferred from one site to another to

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restore contour and correct soft-tissue deficiency. Since the first reported clinical attempts at fat transplantation in the late nineteenth century, the procedure has been repeatedly revisited because adipose tissue is abundant, autologous, and naturally suited to soft-tissue replacement[24]. In its earliest applications, adipose tissue was largely regarded as an autologous filler whose therapeutic value was determined primarily by the amount of volume retained after transplantation. However, this apparently simple strategy exposed two persistent clinical problems. The first was biological: transferred fat did not always survive or maintain its volume[25, 26]. The second was anatomical: fat could not be delivered effectively or safely without regard to the structure of the recipient site[27-32]. These problems made graft survival and recipient-site anatomy central to fat grafting practice (**Figure 1**).

1.1 Survival and Integration: The Biological Problem

Graft survival and long-term retention remain central problems in autologous fat grafting, as they directly challenge the assumption that adipose tissue behaves as a passive filler. Clinically, transferred fat may maintain stable correction, but it may also undergo fat necrosis, oil cyst formation, or partial resorption[33-35]. This variability reflects a basic biological constraint: transplanted fat initially behaves as a nonvascularized particulate graft. Once removed from its native blood supply, the graft must undergo an early ischemic phase during which cell viability depends on plasmatic diffusion from the surrounding recipient bed before effective revascularization is established [12, 13]. Because oxygen and nutrient diffusion are limited, centrally

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located adipocytes are more vulnerable to ischemia-induced death, whereas regions close to the graft–host interface tend to survive[11, 36]. These observations indicate that adipose tissue survival depends on the same biological principles that govern the survival of other living grafts, including diffusion, revascularization, and host integration.

These biological characteristics have reshaped the technical logic of fat grafting. Efforts to improve retention have gradually converged on two principles: increasing the graft–host contact area and reducing graft trauma. Coleman's structural fat grafting technique represents an important conceptual transition in the field: rather than focusing solely on volume augmentation, this procedure emphasizes the preservation of graft viability through atraumatic harvesting, careful processing, and strategic microparcel placement within vascularized recipient tissue[37]. The "3L3M" technique later leveraged a refined, principle-driven approach, integrating low-pressure suction and low-speed centrifugation with low-volume, multi-plane, multi-tunnel, multi-point injection to improve graft survival and long-term volume retention[38-40]. Amar's facial autologous muscular injection (FAMI) technique extended this idea through anatomically selected deep tissue placement, particularly within well-vascularized facial muscle planes[41]. Although these techniques differ in terms of their operative design and anatomical priorities, they share a common biological premise: fat survival depends on minimizing tissue injury and placing each graft parcel close to a vascularized recipient bed.

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Parcel size, handling, and placement optimization have improved the predictability of fat grafting but have not fully resolved variable retention, especially in large-volume grafting or damaged recipient beds. This limitation led to a second line of development: biological graft support by improving vascularization, stromal support, and host integration. Cell-assisted lipotransfer thus became the most influential clinical example of this strategy, in which lipoaspirate is supplemented with ADSCs to improve angiogenesis and graft maintenance[42, 43]. Related approaches, including supplementation with SVF[44], platelet-rich plasma[45], platelet-rich fibrin[46], or concentrated growth factor[47], were developed to improve the biological conditions for rapid and effective graft vascularization and integration after transplantation[48, 49].

These developments reframed retention as a biological problem rather than a technical inconvenience: fat grafting depends not only on the transferred volume but also on early diffusion, revascularization, and host integration. This concept is particularly important for the treatment of burn scars, irradiated tissue, chronic wounds, and traumatic defects, where recipient beds are often fibrotic, inflamed, or poorly vascularized.

1.2 Delivery and Safety: The Anatomical Problem

Delivery exposed a second limitation of transplanted fat: the need for adipose-based therapies to interact with anatomically complex recipient sites. In aesthetic surgery, this problem becomes visible through overcorrection[50, 51] and vascular embolic complications[52-54]. In reconstructive settings, the same principle manifests

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differently: scarred, irradiated, burned, or traumatically injured tissues often contain distorted planes, altered vascular pathways, fibrotic walls, and reduced tissue compliance, all of which make the delivery strategy a part of the regenerative mechanism rather than a purely technical step. Although initially defined largely in aesthetic practice, these principles can also be applied to reconstructive recipient beds with distorted anatomy or impaired vascularity.

A major breakthrough was the recognition that facial adipose tissue is not a homogeneous substance but rather a compartmentalized structure shaped by the fascial septa, retaining ligaments, vascular pathways, and region-specific transition zones[28, 30, 31]. These anatomical insights changed the approach to facial rejuvenation. Age-related soft-tissue changes could no longer be considered simply global volume loss; instead, they were understood as region- and compartment-specific changes in volume, position, and support. Effective fat grafting therefore requires not only the addition but also the restoration of volume within anatomically appropriate compartments that can support both aesthetic goals and biological integration.

The concept of compartment-based lipofilling developed from this principle. Li and colleagues proposed compartment-based fat grafting as a strategy for restoring volume according to the anatomy and aging pattern of specific recipient-site compartments[55, 56]. This approach was first translated into a clinical strategy for the midface[57], then extended to the temporal region[58, 59], and later to the dorsum of

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the hand[60]. Across these sites, the central concept was that fat grafting should be planned according to the organization of the recipient site rather than as indiscriminate volumizing. The access port, injection plane, injection sequence, and graft volume should be selected according to the anatomical structure and functional requirements of the target region. Small aliquots distributed through multiple tunnels and the use of appropriate tissue planes increase graft–recipient contact and prevent large bolus deposition[37-40].

These anatomical considerations have also sharpened the safety logic of fat grafting. In the temporal region, fat compartments lie close to important vessels and nerves. Huang and colleagues identified a “zone of caution” in the anterior half of the lower temporal compartment, where the sentinel vein, middle temporal vessel perforators, and temporal branches of the facial nerve are located[59]. Graft placement must therefore account for both contour correction and neurovascular safety. In gluteal fat grafting, vascular mapping and clinical safety analyses have reinforced the need to avoid intramuscular injections and limit fat placement to subcutaneous planes with more amenable safety profiles[61, 62]. More recently, similar principles have been extended to other anatomically complex recipient sites, including the forehead[63], upper lip[64], and posterior calf[65].

After burns, trauma, or radiation injury, normal anatomical landmarks and tissue planes may be altered. Delivery planning needs to account for the remaining vascular supply and tissue compliance. These local conditions affect whether transplanted fat

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survives and integrates. They also provide the context for examining how adipose components may contribute to tissue repair beyond volume replacement.

2. A Turning Point: From Volume Restoration to Functional Repair

A major turning point in adipose tissue transplantation occurred when clinical outcomes could no longer be explained by volume replacement alone. Fat grafting was initially judged by contour correction and long-term volume retention, but clinical observations also described improvements in skin texture, scar pliability, radiation-induced fibrosis, and chronic wound environments[37, 40]. These findings suggested that transplanted fat could influence the surrounding tissue. A report by Rigotti and colleagues on radiotherapy-induced tissue damage demonstrated the reparative effects of lipoaspirate transplantation[66]. Their work drew attention to its possible role in tissue repair. Assessment of fat grafting therefore began to include changes in the recipient microenvironment, alongside the amount of volume retained.

These observations raised questions about which parts of adipose tissue contributed to the reparative effects. Mature adipocytes alone did not adequately explain the reported remodeling and antifibrotic effects, or the support for vascular growth and tissue repair. Attention therefore shifted from adipocyte survival alone toward the broader tissue environment contained within fat tissue, including stromal and progenitor populations, endothelial and perivascular cells, immune cells, ECM, and secreted factors. This shift broadened the meaning of therapeutic success from volume retention to recipient tissue modulation.

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2.1 From Living Graft to Regenerative Material

In addition to mature adipocytes, adipose tissue contains stromal and progenitor cells, endothelial and perivascular cells, immune cell populations, ECM, and trophic mediators[67, 68]. The diverse components of adipose tissue may contribute to the therapeutic effects of fat grafting, which cannot be explained by adipocyte survival or volume retention alone. Within this framework, the non-adipocyte components of adipose tissue became central to the regenerative interpretation of fat grafting. These components offered a biological explanation for clinical effects beyond volume restoration: stromal and perivascular cells may support angiogenesis and tissue remodeling; ECM provides structural and biochemical cues for host-cell recruitment; immune cells influence the balance between regeneration, fibrosis, and chronic inflammation; and secreted factors facilitate paracrine communication at the graft–host interface[21, 69, 70]. Adipose tissue was therefore redefined as a biologically active material rather than a passive volume substitute.

This shift had an important consequence: adipose tissue was no longer treated as a single therapeutic entity. Instead, it became possible to ask which biological components should be preserved, enriched, or removed for different therapeutic purposes. This question initiated a progressive deconstruction of adipose tissue, in which each derivative product preserved some features of the native tissue while sacrificing others. Therefore, in evaluating these products, we must distinguish clinical associations from experimentally uncovered mechanisms. The proposed angiogenic,

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immunomodulatory, antifibrotic, and matrix-remodeling actions of the tissue cannot be assumed to have been causally validated in patients.

2.2 The Deconstruction of Adipose Tissue into Therapeutic Units

The continuum discussed here describes the type and extent of tissue organization retained after processing and should not be considered a ranking of products. Once adipose tissue was recognized as a biologically active material, the field entered a phase of progressive deconstruction. The goal was to adapt adipose tissue to different reconstructive problems by preserving, enriching, or isolating the elements most relevant to each clinical need. This framework builds on existing product-based classifications by emphasizing not only product type, but also the level and organization of adipose complexity retained during processing.

Processing changes both product composition and the organization of the remaining tissue. We distinguish four groups: intact tissue grafts, fragmented derivatives, cellular products, and acellular products. These groups differ in which components remain and how much of their original organization is preserved. Retaining tissue structure may preserve interactions among components, while further processing may improve injectability, concentrate components with a particular function, or allow greater control over preparation, but it can disrupt those interactions. The category alone does not establish therapeutic superiority or clinical maturity. Figure 2 summarizes these differences and trade-offs.

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Processing also changes the immune compartment. Intact or minimally processed adipose tissue may retain resident immune cells within their original stromal, vascular, and matrix environments[67, 68]. Fragmentation, digestion, cell selection, expansion, and acellular processing, however, disrupt these populations and their spatial relationships. That said, an isolated cell or acellular preparation may still exert immunomodulatory effects without preserving the native immune niche.

Because identical product names may refer to different processing protocols, the categories used here should be considered operational rather than universally standardized. Relevant definitions and key characteristics are summarized in **Table 2**.

2.2.1 Intact Fat Tissue Grafts: Macrofat and Microfat

Intact fat grafts retain much of the original tissue structure. Viable adipocytes remain within the ECM alongside stromal-vascular elements, preserving part of their local tissue microenvironment[20]. This preserved tissue complexity gives intact fat grafts their principal clinical advantage: true structural volumization and direct soft-tissue replacement[71, 72]. However, their survival is limited due to the substantial metabolic demands of mature adipocytes. Recipient-site vascularity, parcel size, graft dispersion, and rapid graft-host integration affect the early supply of oxygen and nutrients[11].

Macrofat and microfat are operational variants of intact adipose tissue, differing mainly in cannula aperture, particle size, processing, injectability, and recipient plane. Larger side-port cannulas yield larger fragments, commonly termed "**macrofat**"[20, 73].

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It is most appropriate for deep-volume restoration and larger-volume applications in the breasts[74, 75], buttocks[72, 76], and other body regions[77, 78]. Smaller-port cannulas yield "**microfat**", which retains viable adipocytes and the tissue architecture in smaller parcels[20, 73]. Smaller parcels allow placement in finer tissue planes for superficial contour correction or small defects, including anatomically delicate regions[78-80]. No universally accepted particle size or cannula threshold separates the two preparations. Their interpretation therefore depends on the preparation method and fragment size, together with the intended delivery plane and clinical use.

The main value of macrofat and microfat lies in their preservation of tissue-level organization and filling capacity. Both preparations are mainly used when lasting volume replacement is needed. The amount retained depends on graft survival and local tissue conditions. For burn, trauma, and post-oncologic reconstruction, their filling capacity is useful when the main problem is structural loss, but requires vascularized integration with the recipient bed[11].

2.2.2 Fragmented Fat Derivatives: Nanofat and ECM/SVF-gel

Mechanical processing breaks adipose tissue into smaller fragments and removes part of the mature adipocyte-rich bulk. The resulting preparations have less filling capacity but harbor a greater relative contribution from retained stromal, matrix, vascular-associated, and niche components. These products are primarily used for superficial remodeling and tissue quality improvement[81, 82].

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"Nanofat" is produced by emulsifying and filtering lipoaspirate. Most viable mature adipocytes are lost, leaving little meaningful filling capacity[73, 81]; however, the retained stromal, vascular-associated, matrix, and trophic components may contribute to remodeling, although their individual roles are poorly understood[83]. Nanofat can be delivered through fine needles into superficial tissue planes. Reported uses include skin rejuvenation[84, 85], scar remodeling[86], and infraorbital dark circles[87]. It has also been used for wound-related indications[88] and other applications focused on tissue quality rather than bulk volume replacement[89].

ECM/SVF-gel is a related but distinct fragmented derivative[90, 91] mechanical processing and centrifugation remove much of the free oil and adipocyte debris, leaving a gel-like product enriched in ECM and stromal-vascular niche-associated components[92, 93]. Compared with nanofat, it places greater emphasis on matrix-supported remodeling and may retain a more scaffold-like microenvironment for host–cell interaction. This approach reduces adipocyte-rich bulk while preserving more of the matrix-supported tissue environment.

The biological activity of both preparations depends on which components remain after processing. Neither is uniformly standardized: differences in mechanical processing, filtration, centrifugation, and washing can change residual cells, matrix, and soluble factors and may contribute to variable biological activity across studies[94]. Clinical reports also vary in indication, and many involve small cohorts or combined treatments. These preparations are intended mainly for local remodeling and tissue-

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quality improvement, with limited value as substitutes for volumizing grafts. When used in combination with needling, scar release, or laser procedures, clinical improvement cannot necessarily be attributed to the adipose-derived product alone.

2.2.3 Cellular Products: MVFs, SVF, and ADSCs

Cellular products concentrate vascular or stromal populations and retain different amounts of native tissue architecture. They are studied mainly for vascular support and regulation of the repair response. These products differ substantially in how much native organization they retain.

Microvascular fragments (MVFs) retain intact microvascular segments with associated endothelial, perivascular, and stromal elements. This structure is of interest when rapid vascularization and connection to host vessels are needed for graft integration[95, 96]. However, there is less clinical experience with this preparation than with the SVF or ADSCs; evidence is predominantly obtained from preclinical and early translational work[97, 98]. Broader use will require simpler isolation methods, reproducible product quality, and clearer indications.

SVF contains a heterogeneous mixture of stromal, endothelial, perivascular, immune, and progenitor-associated cells. Dissociated preparations lack the ECM support and tissue architecture of intact fat[99, 100]. The amount of structure retained depends on the isolation method. Mechanical and enzymatic preparations differ in tissue fragments and ECM content, as well as in cell yield and composition[101]. SVF has attracted broad clinical interest because it can be prepared relatively rapidly for

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use during the same procedure[102]. However, the donor characteristics, harvest site, and isolation protocol lead to substantial variability, complicating comparisons across studies.

ADSCs are typically obtained from the SVF via culture expansion or selection. They provide a more defined, expandable stromal population with experimentally reported paracrine and immunomodulatory activities[103, 104]. Expansion separates the cells from their native tissue environment and introduces challenges in product consistency and clinical translation[105].

MVFs, SVF, and ADSCs therefore form an internal gradient within the cellular stage of adipose deconstruction. Studies of these products focus mainly on vascular support, paracrine signaling, and immune regulation as adjuncts to tissue repair.

2.2.4 Acellular Products: EVs, CEFFE, and DAM

Acellular preparations retain selected signals or matrix components after living cells are removed. Their functions differ. EVs carry intercellular signals, cell-free fat extract (CEFFE) contains soluble trophic factors, and decellularized adipose matrix (DAM) provides a matrix scaffold.

EVs retain select intercellular signals but lack living cells or tissue architecture[22, 106]. They can be obtained from adipose-derived cells, especially ADSCs[107], but also directly from adipose tissue[108] or from adipose tissue-derived culture systems[109]. Their encapsulated proteins, lipids, and nucleic acids can mediate communication between cells, while preclinical and early translational studies have

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explored their angiogenic[110, 111], immunomodulatory[112], and wound repair functions[108, 110, 112], and their support of fat grafts[113]. However, EV activity depends on the source, preparation, dose, and recipient context; the cargo responsible for different effects is still incompletely defined[114, 115]. Clinical use in reconstruction remains largely unexplored, with unresolved questions regarding product definition, dosing, storage, and delivery.

CEFFE contains soluble bioactive factors extracted from adipose tissue. Its preparation involves emulsification and freeze-thaw cycling, followed by centrifugation and filtration. These steps remove viable cells and most structural material while retaining soluble molecules[116, 117]. Preclinical and early clinical studies have investigated its utility in hair regeneration[116], wound and soft-tissue repair[118, 119], ischemia-related injury mitigation[120, 121], and inflammation-associated degenerative disorder management[122, 123]. CEFFE remains a complex mixture whose active components are incompletely defined. Further development requires characterization of these components and assessment of batch consistency, potency measures, and indication-specific evidence.

DAM preserves the ECM of adipose tissue while removing living cells. In addition to supplying this scaffold, it provides biochemical cues for host cell infiltration, vascular ingrowth, adipogenic remodeling, and integration[19, 124]. This composition offers a possible source of off-the-shelf matrix support for soft-tissue regeneration and volume restoration. However, its performance depends on adequate decellularization without

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excessive damage to the matrix or unacceptable residual immunogenicity. Mechanical properties and remodeling kinetics also need to be controlled, along with manufacturing consistency.

Acellular products retain select signals or matrix functions but lose their vascular microstructure and coordination among multiple living cell types. This limits their use when repair depends on interactions within organized tissue. Such interactions include those between the vasculature and matrix, together with immune and other resident cells.

3. Beyond Deconstruction: Reassembling Adipose Complexity as a Functional Unit

Processing adipose tissue generates products with selected cellular, matrix, or signaling functions. These products can offer more flexible delivery, but they lose parts of the original tissue organization and remain useful for trophic signaling, immune modulation, or scaffold-guided host repair. However, some functions may depend on relationships among adipocytes, stromal cells, endothelial and perivascular cells, immune cells, and endogenous ECM[125]. Therefore, the engineering problem involves determining which of these relationships needs to be retained or reestablished within a construct.

3.1 Adipose Tissue as a Living Biofabrication Material

Adipose tissue and minimally processed microfragments are being investigated as living materials for biofabrication. Classical fat grafting provides autologous tissue

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with a range of biological components, but remains constrained by unpredictable resorption, diffusion-dependent survival, limited spatial control, and continued dependence on recipient-site vascularity[20, 126]. In contrast, conventional cell-based bioprinting allows greater control over geometry and patterning, but typically relies on dissociated cells embedded in exogenous matrices and therefore does not fully reproduce the matrix-rich, vascular-associated, and multicellular organization of native adipose tissue[16, 127].

Adipose tissue-based biofabrication has emerged as an attempt to bridge these two strategies. It starts with lipoaspirate fragments that already contain endogenous ECM, stromal cells, and vascular-associated elements. In this setting, adipose tissue is explored as a living fabrication substrate that may retain part of its biological context while becoming compatible with engineered design. Studies of live adipose tissue bioinks and printable microfat constructs provide initial evidence that this is technically feasible[16, 128].

A key challenge for this approach is printability, which depends on fragment size uniformity and nozzle compatibility. Once it is fabricated, the construct must then support oxygen and nutrient diffusion until an adequate vascular supply develops[125, 127-129]. Thus, material properties that maintain shape and print fidelity must also allow adipocyte expansion, matrix remodeling, diffusion, and vascular ingrowth[125, 129]. However, vascularization limits construct size. Endothelial or perivascular cells, MVFs, or preformed channels may support vascular organization, but angiogenic

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sprouting or marker expression should not be equated with timely host inosculation, functional perfusion, or durable vascular maintenance[98, 125]. Furthermore, sterility, batch variability, and long-term volume stability also remain concerns[125, 127-129].

The central question is whether adipose tissue-based biofabrication provides a demonstrable functional benefit over simpler constructs made from isolated cells or molecular components. Translation will also require reproducible tissue sourcing, sterile and scalable fabrication, and defined quality-control and release criteria[125, 129]. Adipose tissue-based biofabrication remains an emerging proof-of-concept field rather than an established translational platform[125, 127, 128].

3.2 Adipose Tissue as a Starting Unit for Organoid-Oriented Systems

Adipose tissue is also being studied as a starting material for organoid-oriented culture and lineage redirection studies. Adipose organoids have been described as three-dimensional systems that can reproduce select structural and functional features of native tissue for use in disease modeling, drug screening, and regeneration[18]. Traditional regenerative strategies in stem cell biology and organoid engineering usually follow a cell-centric route, in which tissues are dissociated, progenitor or stem cells are isolated, expanded, and then directed toward specific fates under defined developmental or bioengineering cues[130-132]. This provides control over the cells but removes them from their original tissue and matrix environment.

Adipose tissue-based approaches explore a different experimental logic. They start with adipose microfragments and examine whether tissue organization can be

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maintained during culture to allow remodeling and directed state change under defined culture conditions. In this framework, adipose tissue is treated not only as a reservoir of stromal cells, but also as a multicellular substrate that may preserve biologically relevant interactions among adipocytes, stromal cells, vascular-associated elements, and endogenous matrix[17].

Experiments with reaggregated microfat provide early examples. In suspension culture, mechanically processed adipose microfragments have survived and reaggregated while retaining aspects of tissue integrity and acquiring a more plastic, niche-like state[17]. Earlier developmental engineering studies described the production of hypertrophic, cartilage-like constructs capable of supporting endochondral bone formation from adult human adipose tissue[133, 134]. More recent work has extended these exploratory approaches toward the development of specialized functional microtissue systems, including humanized bone marrow organoids, insulin-secreting islet-like organoids, and neural lineage-like tissues[17]. These experimental systems suggest the presence of tissue-level plasticity but do not establish that the findings are generalizable across sources or culture conditions.

The translational significance of these systems depends on intended use. Non-implantable applications, including disease modeling, drug screening, product comparison, and tissue-level potency testing, depend on biological fidelity, reproducibility, and validated functional outputs[18, 135]. Implantable organoids or engineered tissue units face higher thresholds, including durable vascular integration,

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a stable tissue identity, the absence of substantial necrosis or unintended differentiation, immune compatibility, and benefits over conventional grafting or scaffolds[18, 125, 135]. An autologous origin may reduce immune mismatch, but manipulation, culture, biomaterials, and the diseased recipient bed can still provoke a response[125, 135].

At present, this line of work should be interpreted cautiously. Evidence remains limited to a small number of experimental systems, and generalizability across adipose sources, target lineages, and culture platforms is uncertain. The contributions of resident and induced cells, criteria for organoid identity, and long-term tissue-state stability also need to be clarified. Broader mechanistic and comparative experiments are necessary before the findings can be extended to different adipose sources, target lineages, and culture platforms[17, 18, 130, 135].

4. Perspectives: Complexity-Matched Adipose Strategies for Tissue Regeneration

4.1 Matching Product Form to Therapeutic Purpose

Adipose-derived products retain different tissue features and serve different purposes. The clinical use of these products starts with two questions: what function is missing, and what hinders tissue repair at the recipient site? Product selection should begin with the function needed at the recipient site (**Fig. 3**). Structural volume loss calls for durable tissue replacement, usually with intact fat grafts. Fibrosis or impaired tissue quality may be addressed with fragmented derivatives or signaling-

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based products. Poor perfusion may call for vascular support, while matrix deficiency may justify a matrix-rich preparation. Cellular and cell-free products may also help modify local inflammation. These options differ in their supporting evidence and are not interchangeable. The aim is to choose the least complex product that can provide the required function. Biofabricated and organoid-oriented systems may be considered when simpler preparations are insufficient, but their use for tissue reconstruction remains largely preclinical.

Combining products may be appropriate when several deficits coexist, but synergy should not be assumed. An added component can affect cell viability and the dose delivered. It may also change matrix organization or vascular integration, making the contribution of each component harder to identify. Variable outcomes from cell- or platelet-assisted fat grafting support defining the role of each component and including appropriate single-component controls[136-139].

The recipient bed can alter what a product is able to achieve. Patients with the same diagnosis may differ in perfusion, fibrosis, or inflammation. The extent of tissue loss and the condition of the remaining matrix also matter. Prior irradiation and host-cell availability can further affect graft survival and integration, as well as the response to cellular or cell-free products. Product choice should therefore address the main local barrier to repair as well as the intended therapeutic function.

4.2 Evidence Maturity, Safety, and Translational Challenges

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A product's position within the deconstruction–reassembly framework does not establish its clinical maturity. Established clinical use of intact grafts should be distinguished from the heterogeneous clinical evidence for processed derivatives. Much of the evidence for newer products remains preclinical or exploratory. **Table 2** summarizes their approximate maturity and principal limitations.

Product terminology remains inconsistent because identically named preparations may differ in how they are prepared, what they contain, and the dose delivered[19, 83, 91, 117, 140]. Reports should therefore describe the preparation method and relevant product characteristics, including particle size and cellular or matrix content. The operational definitions in **Table 2** provide a basis for comparison, but do not establish equivalence between preparations.

Product characterization should involve the identification of both what is delivered and whether it can perform the intended function.

Relevant measures include viable tissue fraction and subsequent retention for structural grafts; endothelial viability and sprouting capacity for MVFs; cellular composition, viability, and dose-normalized functional activity for SVF and ADSCs; particle concentration, marker profile, contaminant assessment, and dose-normalized bioactivity for EVs; total protein content and dose-normalized functional activity for CEFFE; and residual DNA, matrix composition and preservation, mechanical properties, sterility, and degradation for DAM[19, 99, 101, 141]. Engineered products need additional assessment of architecture and phenotypic stability, with functional

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testing appropriate to their intended use[18]. These measurements serve different purposes; composition alone does not establish potency.

Donor characteristics and tissue source introduce further variation. Age and health status can affect the starting material, as can the anatomical depot and harvesting method. Local vascularity, fibrosis, and previous treatment may alter the retained cells and ECM, with consequences for secretion and the response to processing[142-144]. These variables should be reported and, where feasible, included in study design and outcome analysis. Evidence remains insufficient to support product-specific recommendations for children versus adults. The effects of acute burns, critical illness, and catabolic states are also poorly characterized.

Safety assessment must account for processing, delivery, and product composition. Intact grafts retain the procedural and survival-related risks, including vascular embolism in high-risk sites. Cellular products require checks for contamination and consistent identity and dose. Culture expansion adds concerns about phenotypic drift, senescence, and genomic stability. For acellular products, impurities and residual processing reagents need control, while sterility and storage stability must be maintained[141, 145]. DAM also requires adequate decellularization without unacceptable residual immunogenicity or damage to the intended matrix properties. For engineered constructs, the vascularization, structural stability, immune compatibility, and long-term safety requirements remain essential[18, 19]. Differences in preparation and limited follow-up make clinical safety findings difficult to generalize.

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Regulatory and manufacturing requirements depend on the extent of manipulation and whether culture expansion or biomaterials are involved[101, 145]. Mechanical and enzymatic SVF cannot be treated as equivalent preparations. Culture-expanded ADSCs generally require more extensive good manufacturing practice (GMP) controls and release testing. For EVs, CEFFE, and DAM, source-material specifications and release criteria should reflect the quality and functional measures described above. Engineered constructs also need criteria for architecture and tissue-level function[101, 141]. Point-of-care preparation may reduce storage and transport needs, but results can depend more heavily on the operator.

Outcome evaluation should distinguish product activity from the repair achieved after delivery. Structural products require retention and integration outcomes; vascular products require functional perfusion; matrix products require remodeling and host integration; and signaling products require potency and pharmacodynamic measures[101, 141]. No single assay can cover all these functions. Translation also requires consistent manufacture and release, followed by delivery and monitoring suited to the intended indication.

4.3 Implications for Burns, Trauma, and Wound Regeneration

Poor perfusion, persistent inflammation, and fibrosis can limit repair after burns, trauma, or radiation injury and in chronic wounds. Abnormal ECM deposition and mechanical tension may further impair graft survival and integration[146-149]. Adipose-derived interventions should therefore be interpreted as context-dependent

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structural or microenvironment-modulating therapies. Reported anti-fibrotic, immunomodulatory, or pro-angiogenic effects may arise from the product itself or from host-cell recruitment. Improved perfusion, resolution of inflammation, and matrix decompression may also contribute, along with concurrent procedures. However, their relative contributions remain incompletely defined.

In burn-associated hypertrophic scarring, human studies have reported a persistent Th2-skewed response, with increased IL-4^{+} T cells and TGF-β-producing CD4^{+} cells[150, 151]. These responses may support fibroblast activation and excessive matrix deposition[150-152]. Tissue stiffness and mechanical tension may sustain this process[146, 148]. Adipose-derived products may influence vascular growth, immune activity, and matrix remodeling, but evidence for their effects on specific pathways remains mainly preclinical. Clinical improvement alone does not establish direct regulation of these pathways.

Adipose-derived products may support repair but cannot replace all missing tissue or correct established anatomical constraints. Mechanical contracture may require scar release or staged reconstruction, with adipose-based treatment serving as an adjunct. Biofabricated and organoid-oriented systems remain exploratory for these indications.

Clinical assessment should capture durable repair and function. For soft-tissue reconstruction, relevant outcomes include tissue volume retention and contour stability, together with complications and repeat procedures. Wound studies should assess

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closure and recurrence. Scar studies should measure scar thickness and pliability, symptoms such as pain or pruritus, and recurrent contracture. Range of motion and patient-reported function help establish whether these changes benefit patients.

5. Conclusions

Adipose-based therapy has evolved from volume replacement toward the selective use and engineering of tissue, cellular, matrix, and signaling functions. The deconstruction-reassembly framework highlights which aspects of native adipose organization are retained, lost, or rebuilt across different products. Reassembled systems remain predominantly preclinical. Their development is justified when simpler grafts or isolated components cannot adequately provide the required function. Future translation will depend on matching product characteristics and supporting evidence to the intended therapeutic goal and the main barrier at the recipient site.

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Abbreviations

ADSC, adipose-derived stromal/stem cell; CD4, cluster of differentiation 4; CEFFE, cell-free fat extract; DAM, decellularized adipose matrix; ECM, extracellular matrix; EV, extracellular vesicle; FAMI, facial autologous muscular injection; GMP, good manufacturing practice; IL-4, interleukin-4; MVF, microvascular fragment; SVF, stromal vascular fraction; TGF-β, transforming growth factor-β; Th2, T helper 2.

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: Not applicable.

Funding: This research was supported by grants from the National Natural Science Foundation of China (82372535, 82361138568, and W2512094) and Shanghai Clinical Research Center of Plastic and Reconstructive Surgery supported by Science and Technology Commission of Shanghai Municipality (22MC1940300).

Conflict of Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors' contributions: R.Z., L.S., and R.-L.H. drafted the manuscript. X.L. and Y.Z. contributed to literature collection and figure preparation. Q.L., L.S., and R.-L.H.

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conceptualized and supervised the review. All authors revised and approved the final manuscript.

Acknowledgements: ChatGPT was used to assist the authors in creating the original figures and language revision.

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Figure Legends

Figure 1

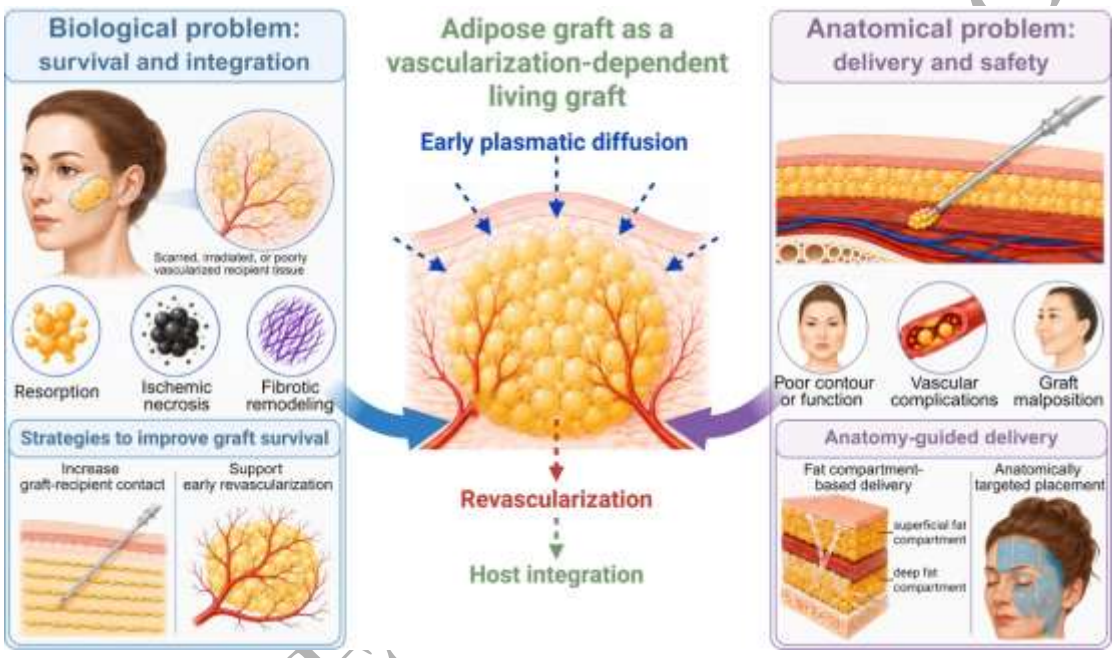

Figure 1. **Adipose Graft as a Vascularization-Dependent Living Graft: Biological and Anatomical Constraints.**

Transplanted adipose tissue does not behave as an inert filler. During the early post-transplantation period, graft survival depends on diffusion from the surrounding recipient tissue, followed by revascularization and host integration. In scarred, irradiated, poorly vascularized, or otherwise compromised recipient beds, biological failure may result in resorption, ischemic necrosis, or fibrotic remodeling. Strategies that increase graft–recipient contact, distribute fat as small parcels through multiple

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tunnels, and support early vascularization may improve graft survival. Anatomical delivery is equally important. Injection plane, regional vascular anatomy, tissue compliance, fibrotic barriers, and graft distribution influence contour, function, malposition, and vascular complications. Anatomy-guided placement should therefore avoid large boluses and deep or intramuscular delivery in high-risk regions.

Figure 2

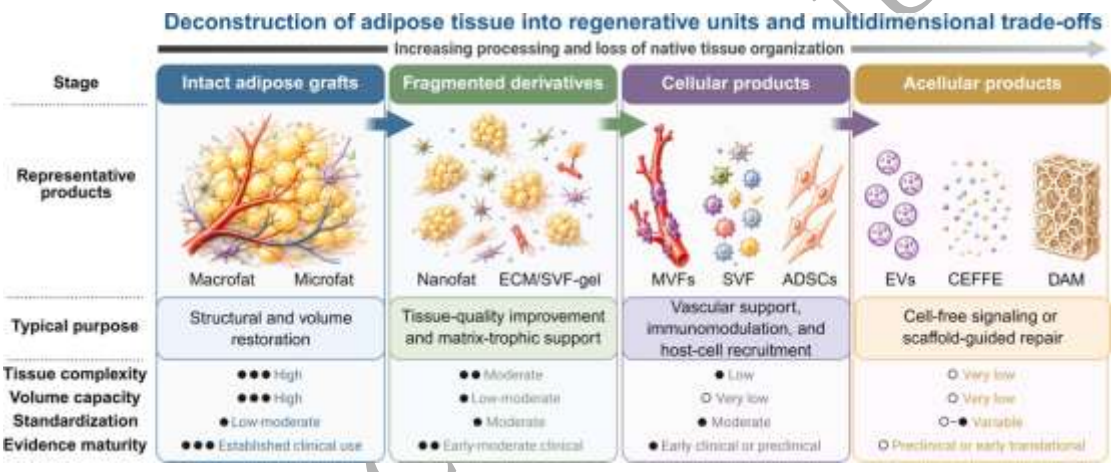

Figure 2. Deconstruction of Adipose Tissue into Regenerative Units and Multidimensional Trade-offs.

Progressive processing of adipose tissue produces product categories that retain different forms and levels of native tissue organization. Intact adipose grafts, including macrofat and microfat, preserve adipocytes, stromal–vascular elements, extracellular matrix, and structural volumizing capacity. Fragmented derivatives, including nanofat and ECM/SVF-gel, reduce adipocyte-rich bulk while retaining variable stromal, matrix, and trophic components that may support tissue-quality improvement. Cellular

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products concentrate vascular or stromal populations but retain different amounts of tissue structure. MVFs preserve microvascular segments, while SVF and ADSC preparations differ in the extent of dissociation and cell selection. Acellular products, including extracellular vesicles, cell-free fat extract, and decellularized adipose matrix, retain selected signaling cargo, soluble factors, or matrix-derived cues but lack living multicellular coordination. Preserved tissue organization and typical volumizing capacity generally decrease with processing; however, product definition, batch variability, injectability, manufacturing burden, regulatory burden, evidence maturity, and recipient-bed dependence vary independently. Lower tissue organization does not necessarily indicate greater standardization, clearer mechanisms, or higher clinical maturity. When isolated components cannot provide the required function, preservation-based or reconstruction-based reassembly may be considered through biofabrication or organoid-oriented systems.

Abbreviations: ADSC, adipose-derived stromal/stem cell; CEFFE, cell-free fat extract; DAM, decellularized adipose matrix; ECM, extracellular matrix; EV, extracellular vesicle; MVF, microvascular fragment; SVF, stromal vascular fraction.

Figure 3

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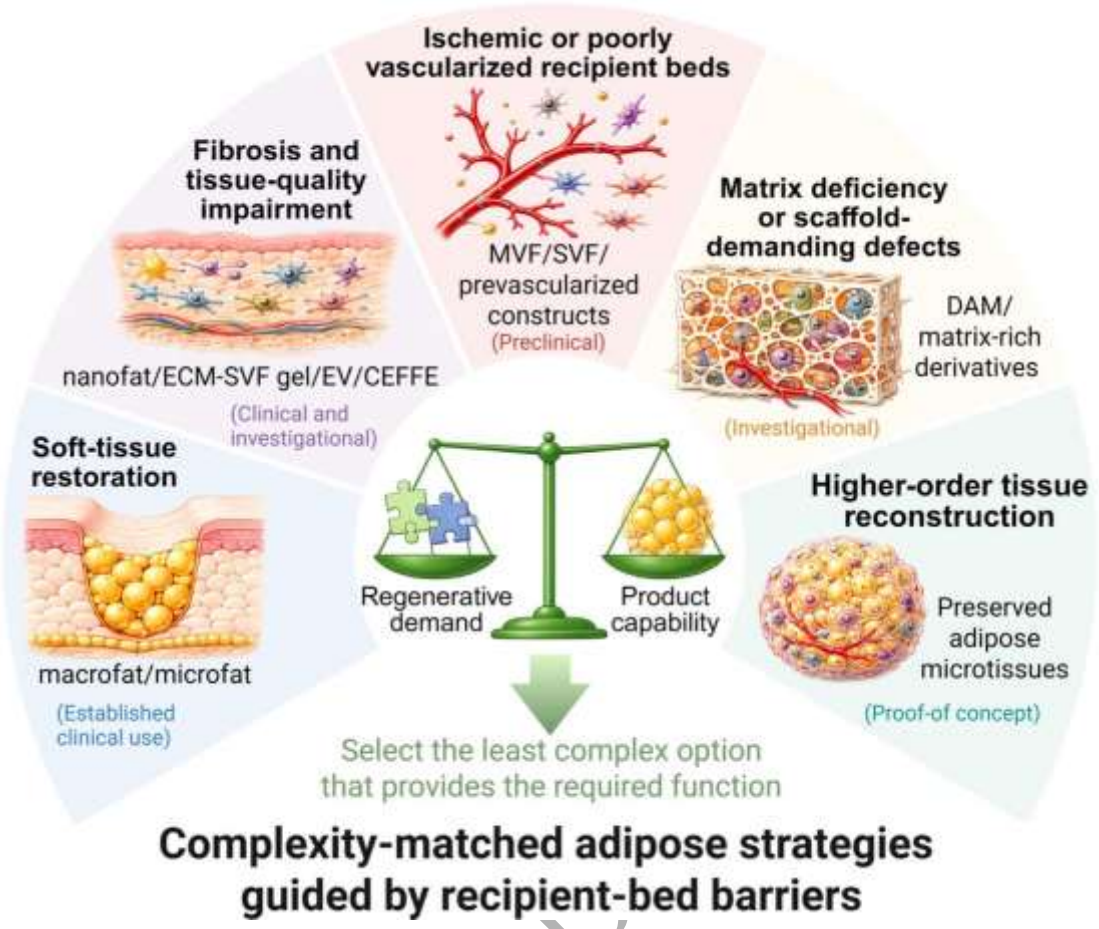

Figure 3. Complexity-Matched Adipose Strategies Guided by Recipient-Bed Barriers.

Adipose-derived products should be selected according to the required therapeutic function and the dominant pathological barrier of the recipient bed rather than by product complexity alone. Structural and volume loss may be addressed with intact adipose grafts such as macrofat or microfat. Fibrosis and tissue-quality impairment may be approached using fragmented or signaling-oriented products, including nanofat, ECM/SVF-gel, extracellular vesicles, or cell-free fat extract, although evidence maturity differs among these products. Ischemic or poorly vascularized recipient beds may require vascular support from microvascular fragments, stromal

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vascular fraction, or prevascularized constructs. Matrix-deficient or scaffold-demanding defects may benefit from decellularized adipose matrix or other matrix-rich derivatives. Higher-order tissue reconstruction may require biofabrication or organoid-oriented systems using preserved adipose microtissues, but these approaches remain predominantly preclinical or proof-of-concept. These are conceptual options, not equivalent or ranked treatments. Selection also depends on the supporting evidence, safety, and feasibility of delivery.

Abbreviations: CEFFE, cell-free fat extract; DAM, decellularized adipose matrix; ECM, extracellular matrix; EV, extracellular vesicle; MVF, microvascular fragment; SVF, stromal vascular fraction.

Table 1

Table 1. Conceptual comparison of conventional adipose-derived product classifications and the deconstruction-reassembly framework

Dimension	Typical emphasis of existing product-based classifications	Deconstruction-reassembly framework proposed in this Review
Primary organizing logic	Classifies therapies according to product type, processing method, cellularity, or clinical format, including fat grafts, SVF, ADSCs, EVs, CEFFE, and DAM.	Organizes strategies according to how adipose tissue organization and function are preserved, reduced, lost, or reconstructed.
View of adipose tissue	Describes adipose tissue as the source of distinct tissue, cellular, matrix, vesicular, or soluble products.	Treats adipose tissue as an organized system integrating structural, vascular, stromal, immune, matrix, and signaling components.

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Dimension	Typical emphasis of existing product-based classifications	Deconstruction-reassembly framework proposed in this Review
Mechanistic emphasis	Associates individual product categories with functions such as volumization, vascular support, paracrine signaling, immunomodulation, or matrix support.	Examines which functions are retained or lost during processing and whether missing functions can be supplied by the recipient bed or require reassembly.
Clinical matching logic	Commonly relates products to broad indications or procedural applications.	Matches product form and preserved complexity to the intended therapeutic function and the dominant barrier of the recipient bed.
Treatment of emerging technologies	Usually discusses biofabrication and organoid systems as distinct tissue-engineering approaches.	Interprets biofabrication and organoid-oriented systems as potential strategies for preserving or reconstructing tissue-level organization and function.
Translational interpretation	Summarizes product characteristics, applications, and evidence within individual categories.	Integrates product definition, evidence maturity, delivery requirements, potency assessment, manufacturing feasibility, and indication-specific outcomes.
Principal limitation	Product names may encompass preparations with different compositions, processing protocols, and evidence levels.	The framework remains conceptual and requires product-specific validation; greater complexity should not be assumed to provide greater therapeutic value.

Abbreviations: ADSC, adipose-derived stromal/stem cell; CEFFE, cell-free fat extract; DAM, decellularized adipose matrix; EV, extracellular vesicle; SVF, stromal vascular fraction.

Note: The comparison describes general differences in emphasis and is not intended to encompass every previous classification system.

Table 2

Table 2. Operational definitions and key characteristics of major adipose-derived therapeutic products

Category / Product	Operational definition	Preserved and lost features	Principal function	Volume	Evidence maturity	Key limitations
Intact tissue grafts						

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Category / Product	Operational definition	Preserved and lost features	Principal function	Volume	Evidence maturity	Key limitations
Macrofat	Large, minimally processed adipose fragments, usually delivered through larger-aperture cannulas.	Preserves adipocytes, stromal-vascular elements, ECM, and partial tissue organization; loses native perfusion.	Structural restoration and volume replacement.	High	Established clinical use	No universal size threshold; ischemia, resorption, necrosis, and recipient-bed dependence.
Microfat	Smaller intact adipose fragments for finer injection and delicate planes.	Preserves adipocytes, stromal-vascular elements, ECM, and partial organization.	Precise structural restoration and contour refinement.	Moderate-high	Established clinical use	Overlaps with macrofat; definitions vary by cannula, processing, plane, and use.
Fragmented derivatives						
Nanofat	Emulsified and usually filtered lipoaspirate with disrupted adipocytes.	Retains variable stromal, vascular-associated, matrix, and soluble components; loses adipocyte-rich architecture.	Superficial remodeling and tissue-quality improvement.	Minimal	Clinical use; heterogeneous evidence	Processing-dependent composition; active components, dose, and treatment attribution remain uncertain.
ECM/SVF-gel	Mechanically processed adipose derivative enriched in ECM and stromal-vascular components.	Retains matrix and variable stromal-vascular elements; loses most adipocytes and intact architecture.	Matrix-supported remodeling.	Low	Limited clinical exploration	Variable processing and non-standardized composition.
Cellular products						

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Category / Product	Operational definition	Preserved and lost features	Principal function	Volume	Evidence maturity	Key limitations
MVF	Isolated adipose microvascular segments with associated cells and matrix.	Preserves vascular microarchitecture; loses broader tissue organization.	Vascular support and prevascularization.	Negligible	Mainly preclinical / early translational	Isolation-, donor-, and storage-dependent quality; potency and scalability unresolved.
SVF	Heterogeneous cells isolated mechanically or enzymatically from adipose tissue.	Retains heterogeneous cell populations; residual ECM and tissue fragments depend on the isolation method.	Investigated for vascular, paracrine, and immunomodulatory support.	Negligible	Clinical investigation; heterogeneous evidence	Mechanical and enzymatic SVF are not equivalent; composition, dose, potency, and regulation vary.
ADSC	Culture-expanded or selected adipose-derived stromal cells.	Retains expandable stromal cells; loses native multicellular and matrix context.	Investigated for paracrine and immunomodulatory support.	Negligible	Early clinical / translational	Passage, senescence, phenotypic stability, potency, GMP, and regulation.
Acellular products						
EV	Vesicles isolated from adipose-derived cells, tissue, or culture systems.	Retains selected molecular cargo; loses cells, ECM, and tissue organization.	Cell-free signaling and paracrine modulation.	Negligible	Mainly preclinical / early translational	Source, isolation, dose, storage, and delivery affect potency.
CEFFE	Cell-free soluble extract generated by tissue disruption, freeze-thaw processing, centrifugation, and filtration.	Retains soluble proteins and trophic factors; loses cells and structure.	Diffusible trophic support.	Negligible	Preclinical / limited early clinical	Incompletely defined mixture; dose, sterility, potency, batch consistency, and storage require validation.

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Category / Product	Operational definition	Preserved and lost features	Principal function	Volume	Evidence maturity	Key limitations
DAM	Decellularized adipose ECM.	Preserves matrix architecture and biochemical cues; loses living cells, vessels, and dynamic tissue function.	Scaffold-guided repair and remodeling.	Low-moderate	Preclinical / early translational	Decellularization, residual DNA, matrix preservation, mechanics, sterilization, and degradation vary.

Abbreviations: ADSC, adipose-derived stromal/stem cell; CEFFE, cell-free fat extract; DAM, decellularized adipose matrix; ECM, extracellular matrix; EV, extracellular vesicle; GMP, good manufacturing practice; MVF, microvascular fragment; SVF, stromal vascular fraction.

Note: Definitions are operational rather than prescriptive. Preparation methods, product composition, dose, and reporting units vary across studies and regulatory settings; products sharing the same name should not be assumed to be technically or biologically equivalent. Evidence maturity is a qualitative summary rather than a formal evidence grade. Processing parameters and dose ranges vary substantially across protocols and should be reported study-specifically rather than interpreted as universally standardized thresholds.

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