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Cutting-edge biotechnological strategies to enhance autologous fat graft survival

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Summary

Autologous fat grafting (AFG) is a widely used technique in both reconstructive and aesthetic plastic surgery. Despite its clinical popularity, the main limitation remains the unpredictable viability of the transplanted volume, which ranges between 18–80%. This variability reflects a complex interplay of biological processes and technical factors, placing AFG at the interface between a relatively simple surgical procedure and a challenging tissue engineering problem. The primary cause of volume loss is early ischemia. A cascade of inflammatory responses, oxidative stress, cyst formation, and fibrosis results in variable degrees of volume reduction. Current research on improving AFG outcomes focuses on two main areas. One aim is to be technical factors related to harvesting, processing, and application of the fat. The second area, which is the subject of this review, examines the possibilities of increasing the survival of autologous fat grafts by applying biotechnological procedures. In the center of these procedures are neovascularization, mechanical and structural support to the graft, and promoting regeneration of adipose tissue rather than just survival of transplanted cells. Graft enrichment using stromal vascular fraction (SVF) and adipose-derived stem cells (ADSCs), both autologous populations from lipoaspirate, enhances angiogenesis, adipogenesis, and immune modulation. Preclinical data show improved vascularization and graft retention, but clinical outcomes vary. ADSC-derived exosomes offer a cell free alternative with strong proangiogenic and anti-inflammatory effects. Growth factors, including vascular endothelial growth factor (VEGF), fibroblast growth factor-2 (FGF2), or transforming growth factor-β (TGF-β) – can be delivered directly or via platelet-rich plasma (PRP) and platelet-rich fibrin (PRF), though results remain inconsistent. Hydrogels, scaffolds, acellular adipose matrix (AAM), molecular interventions, and preconditioning strategies show big promise but lack standardized clinical evidence so far. Despite promising preclinical results, clinical application faces several challenges and obstacles. Future research should focus on rational combinations of therapies and strategies and further development of biomaterials. Improving the survival of autologous fat grafts requires a multidisciplinary approach combining refined surgical techniques with targeted biotechnological interventions.

Key words

autologous fat graft – lipotransfer – adipose-derived stem cell – growth factor – exosomes – angiogenesis – hydrogel

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Introduction

Autologous fat transplantation is a long-established method in aesthetic and reconstructive surgery due to its availability, biocompatibility, and low risk of complications. However, variability in fat graft survival remains a significant clinical problem. This variability results from a combination of mechanical, biological, and technical factors affecting early adipocyte survival and subsequent angiogenesis.

In the past decade, several biotechnological approaches have been developed aiming to reduce early ischemic loss, promote angiogenesis, and optimize fat graft regeneration. This review synthesizes current understanding and recent advancements in optimizing autologous fat grafting (AFG) outcomes, focusing on the biological background of fat graft survival and exploring novel strategies for enhancing graft retention and viability [1–3].

Evaluation of the topic

Mechanisms of graft survival and integration

Prior research demonstrates that survival and integration of fat grafts depend on a sequence of interconnected biological processes. This involves vascularization, adipogenesis, extracellular matrix maintenance and the mitigation of cellular loss after transplantation. The early phase after transplantation is particularly susceptible to ischemia, which leads to apoptotic loss of adipocytes and restricted nutrient diffusion inside the central part of the graft. Observations shows that fat graft viability is predominantly supported by diffusion from surrounding host tissue during first 48–72 h until neovasculariza-

tion occurs [4]. This leaves central part of graft prone to necrosis. Adipocytes have limited tolerance to hypoxia, so their survival depends on the restoration of sufficient blood supply through angiogenic responses. Angiogenesis in fat grafts is mediated by several molecular factors. Platelet-derived growth factor (PDGF) attracts and activates reparative cells, which are an integral part of regeneration; hepatocyte growth factor (HGF) enhances angiogenesis while promoting proliferation and migration; vascular endothelial growth factor (VEGF) and fibroblast growth factor-2 (FGF2) promote vessel formation by stimulating endothelial proliferation and migration [1]; tissue metalloproteinase inhibitors modulate extracellular matrix remodeling and facilitate vessel incorporation. Adipose-derived stem cells (ADSCs) play an important role in enhancing graft survival due to their ability to proliferate, differentiate into various cell types, and secrete paracrine factors that facilitate neovascularization and tissue repair, even under hypoxic conditions. Key player is hypoxia-inducible factor-1α (HIF-1α). This transcription factor stabilizes and, in turn, drives the expression of VEGF through ADSCs [5–7]. Almost half of the adipose secretome contains angiogenic factors, underscoring the intrinsic ability of adipose tissue to stimulate neovascularization [8]. The mechanisms regulating angiogenesis appear to be closely linked to those controlling neo-adipogenesis. Experimental work has shown that endothelial cell-preadipocyte interactions can have reciprocal effects on both processes, suggesting shared regulatory pathways. VEGF inhibition blocks preadipocyte differentiation in addition to its known antiangiogenic effects [9]. This further highlight the crucial role of revascularization for fat graft survival, as insufficient blood flow leads to adipocyte degeneration and subsequent loss of graft volume.

Biotechnological strategies

Growth factors

Studies focusing on growth factors work with the idea of accelerating neovascularization and reducing early ischemic loss by supplementing the graft microenvironment with proangiogenic signals. This group includes platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) as well as more recently the addition of individual growth factors directly to fat transplant.

Platelet-rich plasma and platelet-rich fibrin

PRP is a rich autologous source of growth factors. However, its effects are relatively short-lived (≈ 8 days) [10], which has led to strategies such as repeated or "two-step" applications. PRP attenuates hypoxia-induced damage and enhance tissue neovascularization and regeneration. But clinical evidence is mixed, mainly due to significant methodological heterogeneity in PRP preparation [11–14]. PRF offers a slower and more sustained release of growth factors, potentially providing long-term regenerative support and improving tissue integration [15]. Unlike PRP, the effect of PRF on long-term fat graft retention has not yet been demonstrated.

Targeted growth factor delivery

In addition to PRP and PRF, research also focuses on other biomaterials containing growth factors and, finally, directly on individual growth factors. Liquid phase concentrated growth factor (LPCGF) is a biomaterial that contains VEGF, transforming growth factor-β (TGF-β), fibroblast growth factor (FGF), and leukocytes. In vivo studies on mice have shown improved fat graft survival after enrichment with LPCGF [16]. An innovative approach is the enrichment of fat grafts with adenosine. As an endogenous stress signal, adenosine increases angiogenesis through the VEGF [3]. Growth factors themselves, such as epidermal growth factor (EGF), VEGF or FGF2 have proven efficacy in supporting fat graft survival by stimulating proliferation, differentiation, neovascularization, and migration of stem cells. However, their common limitation is a short biological half-life associated with their rapid degradation *in vivo*. Current developments focus on growth factor stabilization and controlled release systems.

Stem cell-based therapies

Stem cell-based approaches currently represent the most extensively studied strategy for enhancing fat graft survival, utilizing the regenerative potential of adipose-derived stem cells (ADSCs) and stromal vascular fraction (SVF). These interventions aim to promote angiogenesis, adipogenesis, and provide paracrine signals that protect transplanted adipocytes from ischemic injury.

Adipose-derived stem cells

ADSCs represent a multipotent population of mesenchymal stem cells in adipose tissue. They are characterized by multilineage differentiation and robust paracrine activity. Addition of allogeneic ADSCs to fat grafts increases graft survival through several mechanisms. The most prominent are secretion of proangiogenic grow factors and differentiation into adipocytes to replace lost cells. They also possess immunomodulatory effects that reduce inflammatory damage [17,18]. Cell-assisted lipotransfer (CAL) is a technique that involves enriching fat grafts with cells derived from SVF. SVF contains ADSCs, endothelial progenitor cells, pericytes, and immune cells that together support graft integration [19]. Systematic reviews confirm that fat grafts with increased ADSC support achieve better volume retention compared to conventional techniques [20,21]. Recent research has focused on genetically modifying ADSCs to enhance their therapeutic effects. Human ADSCs enriched with modified VEGF have shown enhanced angiogenic potential and have promoted long-term graft survival in preclinical models

through sustained VEGF expression and accelerated vascularization [22].

ADSCs exosomes

Exosomes are extracellular vesicles of 30–150 nm in size secreted by cells. It is a newly investigated, cell-free alternative to direct stem cell transplantation. ADSC--derived exosomes (ADSC-Exos) are rich in miRNA, proteins, and lipids with significant paracrine effects. The study shows that ADSC-Exos enhance fat graft survival through distinct mechanisms [23]. Preclinical studies show marked improvement in angiogenesis and graft retention, in some cases more effective than SVF. Yang et al. demonstrated that ADSC-Exos promote the proliferation, migration and formation of endothelial cells [24]. Chen et al. reported that ADSC-Exos promote adipogenic differentiation and lipid accumulation by modulating the pathway. Enhancing the prolipogenic capabilities of adipocytes [25]. Clinical studies are still lacking, but exosomes offer advantages like higher stability, minimal immune rejection, easier standardization and lower regulatory barriers compared to cell therapies.

Alternative stem cell sources

Current research is also focusing on non-adipose stem cells, which also offer regenerative potential. Fascia-derived stem cells (FDSCs) have shown increased vascularization and better graft retention when co-transplanted with fat grafts [2]. Other alternative sources are bone marrow derived stem cells (BMSCs) and umbilical cord-derived mesenchymal stem cells (UC-MSCs).

Biomaterial scaffolds

Biomaterial scaffolds provide structural support, modulate the local microenvironment, and allow for the controlled release of growth factors and potential other additives. This group of materials aims to preserve graft volume, increase vascular ingrowth, and reduce complications, particularly cyst formation and calcification.

Hydrogel-based delivery systems

Hydrogels are water-swollen, hydrophilic, three-dimensional networks. Typically, they are injectable, often amorphous fillers or cell carriers. They provide seamless integration with the surrounding adipose tissue. The main functions of hydrogels are to create a protective environment and act as a "carrier" for transferred adipocytes. They increase cell viability by providing mechanical support. Hydrogels can also be modified to release bioactive molecules such as VEGF to promote early angiogenesis [9]. Hydrogels can experience a rapid initial volume decrease due to "fluid mobilization" from the water-rich matrix [26]. Their mechanical strength is lower than that of native adipose tissue, however, unless specifically modified. They are typically composed of materials like alginate, collagen, fibrin or hyaluronic acid.

Scaffolds

These are stiffer structures designed to provide a three-dimensional architecture for tissue growth. They can be made from synthetic polymers like polycaprolactone (PCL) or poly(lactic-co-glycolic) acid (PLGA). They can also be made of natural materials such as acellular adipose matrix (AAM). Scaffolds were primarily developed to maintain the volume and shape of the graft [4]. They provide a stable structure for host cell infiltration into predefined spaces. AAM is a biomaterial derived from human adipose tissue that supports adipogenesis and angiogenesis and is gaining increasing clinical application. However, long--term volume retention remains variable, and current evidence is limited, with a lack of standardized protocols and high-quality clinical studies [27,28].

Hybrid systems

An alternative to both scaffolds and hydrogels is the use of PLGA microspheres (250 µm in diameter). These microspheres can be impregnated into other scaffold materials (like collagen-chitosan) or used with growth factors like VEGF. PLGA can also be formulated into a hydrogel when it is chemically combined with hydrophilic polymers like polyethylene glycol (PEG). Unlike solid PLGA, these systems are water-rich, injectable and designed to mimic the extracellular matrix more closely [29–31].

Biochemical and molecular interventions

These represent a targeted approach to directly influence the pathways regulating adipocyte survival and fat graft revascularization. These strategies include the application of recombinant proteins and molecules that enhance natural survival mechanisms in an ischemic environment. Leucine-rich α-2-glycoprotein 1 (LRG-1) has been identified as one of the factors that increase survival. It suppresses apoptosis of adipose stem cells through a mechanism mediated by RAB31 [32]. In addition to apoptosis, ferroptosis, a form of cell death dependent on iron, also plays a role. Inhibition of ferroptosis by glutathione has been demonstrated in animal models [33]. Among other substances, salvianolic acid B appears to be promising. It supports preadipocyte proliferation, adipogenesis and at the same time has an anti-inflammatory effect, thereby reducing the degree of fibrotization [34]. The iron chelating agent deferoxamine (DFO) inhibits prolyl hydroxylase, the enzyme responsible for the degradation of hypoxia-inducible factor (HIF-1α). Knowing that, DFO can pharmacologically induce hypoxic conditions by stabilizing HIF-1α, which increases VEGF expression. DFO has been successfully applied across various tissues to enhance vascularization and regenerative capacity [35] and seems to be very promising, especially in preconditioning.

Preconditioning strategies

Current research also focuses on the preparation of fat and recipient site prior to AFG. This preconditioning does not

necessarily involve the addition of external components but focuses also on triggering an endogenous response within the tissues themselves. A common goal of preconditioning strategies is the enhancement of stress-response gene expression or the secretion of cytokines and growth factors. Such stimuli include hypoxic conditions, caloric restriction, localized mechanical loading, thermal exposure, and treatment with a fractional carbon dioxide laser. Preclinical evidence indicates that these factors support cellular viability, stimulate adipogenic and angiogenic processes, and concurrently attenuate inflammatory responses, fibrosis, and cyst development, thereby improving both the survival and overall quality of fat grafts [35–37].

Discussion

On the field of biotechnological procedures, the future of AFG lies in combining multiple strategies tailored to individual patient characteristics and clinical indications. Rather than seeking a single "optimal" enhancement method, we should accept the complexity of fat graft biology and develop decision algorithms matching specific interventions to patient needs.

Today, some of the most promising ways seem to be HIF-1α-targeted preconditioning, hydrogels loaded with growth factors, or VEGF-exosome based immunomodulation. In the future, advanced biomaterials, precision cell engineering and molecular therapeutics will work together. Data-driven optimization will further support these approaches. This approach has the potential to transform AFG from a poorly predictable procedure into a reliable and reproducible technique. Its application may completely change modern regenerative medicine and plastic surgery, both reconstructive and aesthetic.

Conclusion

From a simple volume replacement technique, autologous fat transfer has evolved into a sophisticated approach in regenerative medicine. The presented overview of current knowledge identifies four main biotechnological areas: stem cell-based therapies, growth factor modification, biomaterial scaffolds with hydrogels, and biochemical interventions. All of these approaches target the main areas of improving the viability of the transplanted fat graft. These are angiogenesis, adipogenesis, structural stability, and influencing apoptosis. Partial successes are being achieved in each of the above areas. However, it appears that a truly great effect on fat graft survival will be achieved by a combination of individual strategies. Hydrogels with bound growth factors, or exosomes, new sources of stem cells in combination with already known procedures, stabilization of growth factors. The use of multiple mechanisms at once has a synergistic effect on fat graft survival. The HIF-1α/VEGF signaling pathway appears to be key in angiogenesis under hypoxic conditions, opening the door to possible further future developments.

Despite promising preclinical results, clinical application faces several challenges and obstacles. These include difficult standardization of cell products, regulatory complexities, economic demands, and the need for robust data and high-quality clinical trials. Future research should focus on rational combinations of therapies and further development of biomaterials.

Roles of the authors

Tomáš Votruba – conceptualization, methodology, investigation, writing – original draft preparation; Jakub Holoubek – conceptualization, writing – review and editing; Břetislav Lipový – conceptualization, writing – review and editing, supervision.

All authors have read and agreed to the published version of the manuscript.

Disclosure

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