Qiu *et al. Stem Cell Research & Therapy* (2025) 16:344
https://doi.org/10.1186/s13287-025-04473-5

Stem Cell Research & Therapy

REVIEW Open Access

Enhancing fat graft retention through adipose tissue browning: a systematic review

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Abstract

Background Recently, existing researches have gradually recognized the critical biological behaviour played by spontaneous or exogenous-induced browning conversion in fat transplantation. However, no comprehensive review explored the fat grafts remodeling process toward browning and such role in fat graft retention.

Aims This study aimed to elucidate the behavioral characteristics of browning changes following fat grafting, as well as its benefits and mechanisms on the survival of transplanted fat.

Methods Databases including Web of science, PubMed, Ovid medline, and Embase were searched from inception through September 2024. Studies related to fat grafts browning in fat transplantation were systematically reviewed, in accordance with the inclusion and exclusion criteria.

Results We evaluated 14 studies including 13 animal works and one clinical report. Five studies directly transplanted fat without any browning induction, while others utilized either beige fat or pre-treated grafts with browning stimuli. Data shown that around the periphery of fat grafts (predominantly in survival zone), early accumulations of graft browning can be observed, dynamically accompanying the stable remodeling of the graft. Post-transplantation spontaneous browning typically begins around day 7, stabilizes after approximately 3 months, and may revert to white adipose tissue. The favorable browning up-regulation behavior of fat graft can enhance graft retention by promoting early angiogenesis, reducing inflammation, and upregulating adipogenesis. The origin of beige adipocytes, whether from the conversion of white adipocytes or the regeneration of progenitor cells, remains underdiscussed.

Conclusions Notwithstanding the relatively limited sample and study levels, this work offers valuable insights into the benefits of browning behavior on enhancing fat graft retention. The in-depth understanding of the underlying mechanism of browning and manipulating its switching in fat grafting will contribute in several ways to achieving desired clinical outcomes.

Keywords Fat transplantation, Beige adipose tissue, Browning, Fat grafts survival

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Introduction

Fat grafting has been clinically employed for three decades, yet remains challenged by unpredictable volume retention and high absorption rate of fat grafts. This retention variability is inherently governed by biological processes, including ischemia-reperfusion dynamics, neovascularization efficiency, adipocyte metabolic adaptation, and immune microenvironment interactions [1]. Critically, the histological evolution of transplanted fat are closely linked to adipose regeneration and graft survival outcomes.

Of particular interest was many researches revealed the developing of brown-like adipocytes in white adipose tissue (WAT) grafts remodeling [2–8]. The involved process in white fat depots referred to as browning ascribed to the plasticity of adipose tissues from one cell type (white adipocyte) conversion into the other (brown adipocyte). Of note, the third type of adipocyte, beige or brite (brown-in-white) adipocyte developping within WAT depots, was also considered as inducible brown adipocyte. Compared to white adipocytes, which contain a large unilocular fat droplet and few mitochondria, brown adipocytes require dense mitochondria, multilocular fat droplets, and rich vascularization to support their high energy demands (Fig. 1) [9]. It is now well established that brown adipocytes exhibit superior vascularization, enhanced innervation, and greater resistance to hypoxia-ischemia compared to white adipocytes. Accumulating evidences have revealed that brown adipose tissue (BAT) mainly participated in regulating metabolism diseases, such as obesity, diabetes mellitus and fatty liver [10–12]. In addition to alter adipose metabolism, the secretory function of BAT also enables it to play a critical role in fat transplantation.

Data from several studies further suggested that the spontaneous browning of WAT can enhance the retention of fat grafts by angiogenesis and induction of early macrophage M2 polarization [6, 13, 14]. Even the effect on the fat retention rate from brown fat transplantation was well comparable to that of adipose-derived stem cells (ADSCs), and superior to that of WAT grafting [7, 15, 16]. By indirect means to activate of BAT or induce browning of WAT, such as drug-stimulation, fat survival rates can also be improved. The presence of uncoupling protein 1(UCP1)-positive beige adipocytes in BAT grafts histologically correlates with up-regulated vascular endothelial growth factor (VEGF), peroxisome proliferator-activated receptor-γ (PPAR-γ), and CCAAT/enhancer-binding protein β (CEBP-β) expression, driving angiogenesis and adipogenesis to markedly enhance graft survival [7]. Taken together, these results suggested that the browning behavior following fat transplantation is a response to fat transfer and a critical event associated with the outcome of the grafts.

Conversely, some researchers found that directly transplanted BAT grafts exhibit an impaired vascularization capacity and survival with a markedly lower functional microvessel density when compared to native BAT [17]. Similarly, a few studies reported no significant difference in fat survival between WAT and BAT grafts. The hypermetabolic properties of BAT may expose it to the risk of necrosis and potential inflammation [18–20]. A research comparing the browning biogenesis of non-necrotic and necrotic fat grafts has found the browning development of the later is more evident [20]. It may be that brown adipocytes are more sensitive to apoptotic stimuli and nutritional shortage. But there has been observed that when the stimuli withrawn or effective intervention, the development of browning may reverse, that is re-whitening, turning to a stable state of graft survival [7].

Despite emerging studies on adipose browning, no systematic review has comprehensively analyzed the pathophysiological significance of adipocyte browning in fat graft retention. Moreover, the spatiotemporal patterns and regulatory mechanisms underlying the whitening-to-browning transition in engrafted adipose tissue also remain poorly understood. Thus, we conducted a systematic review to decipher the browning process in grafted fat and evaluate its relevance to graft differentiation management and its potential benefits. Browning-related therapeutic strategies could be effectively regulated, offering a novel approach to improve fat retention and viability in clinical practice.

Methods

Search strategy

A systematic review of literature reports on browning occurring in fat transplantation was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. The search strategy was a combination of Boolean operators, keywords and corresponding Medical Terms (MeSH) related to "adipose tissue transplantation", "fat transplantation", "fat grafting", "fat transfer", "lipotransfer", "brown adipocyte", "beige adipocyte", "brown adipose tissue", "beige adipose tissue", "beigeing", and "browning". Two independent investigators (H.Q. and H.W.) performed a systematic search of the Web of science, PubMed, Embase, and Ovid medline databases to identify all relevant studies published from 1946 to September 2024. The same 2 authors further conducted a screening of all article titles, abstracts and full texts to determine whether they met the inclusion criteria, and systematically reviewed the included studies.

Eligibility criteria

These studies were included if they provided objective data on the phenomenon of spontaneous or

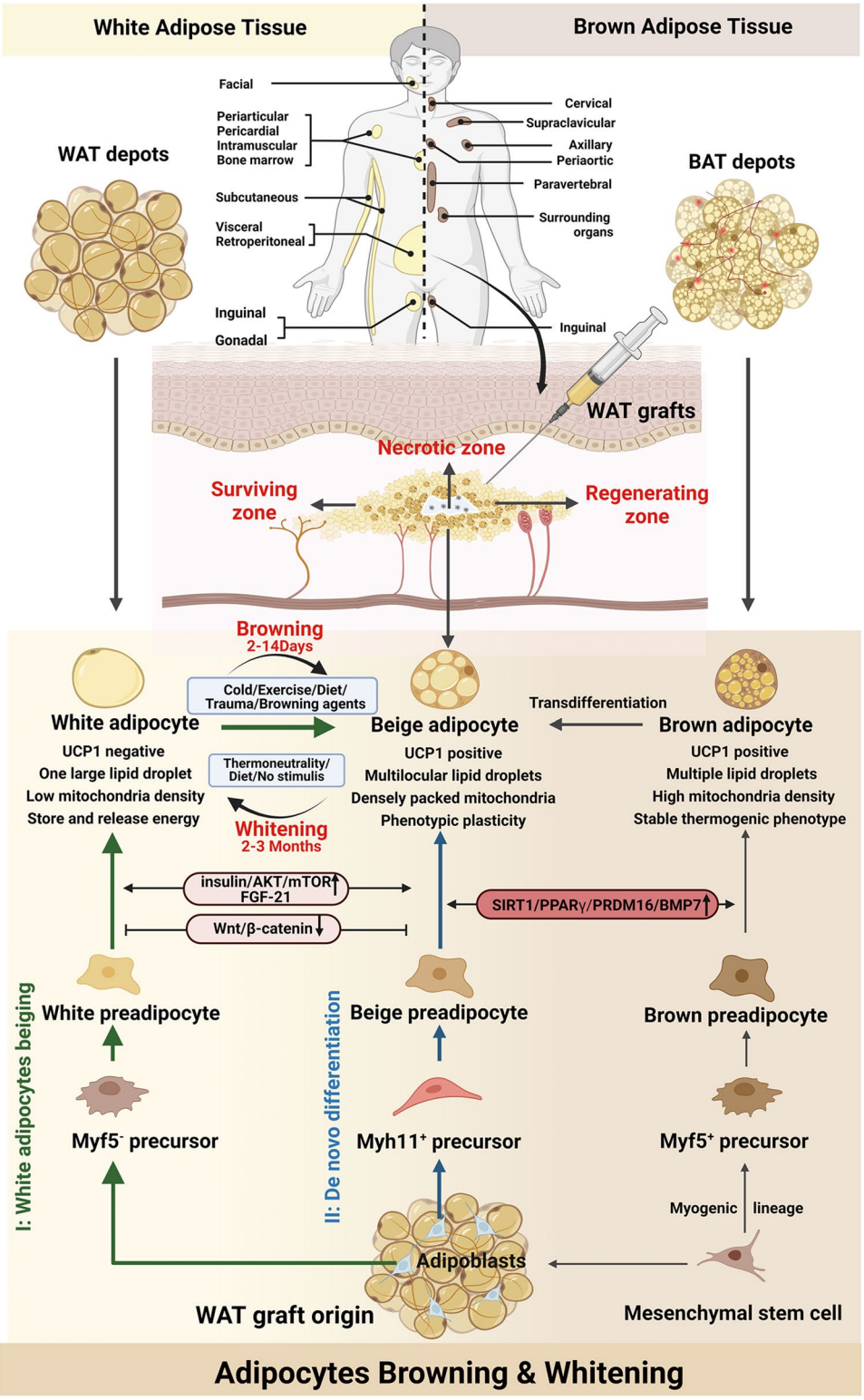

Fig. 1 The process of browning and whitening differentiation of grafted fat in fat grafting

exogenous-induced browning conversion in fat grafting and remodeling procedures. However, studies were excluded if they: (1) did not investigate adipose tissue browning post-transplantation; (2) failed to evaluate the browning phenomena through established methods (e.g., immunohistochemistry for UCP1, qPCR of thermogenic genes, mitochondrial activity assays, adipocyte morphology shifts or adipocyte metabolic assays); (3) lacked the evaluation of fat grafting efficacy after browning; (4) focused solely on browning phenomena without fat transplantation application; or (5) performed in vitro browning models without in vivo grafting validation. Additionally, non-original articles (including reviews, editorials, commentaries, letters), conference abstracts, and non-English publications were also excluded. Figure 2 shows the selection process for the study.

Data extraction and quality assessment

Two independent reviewers (H.Q. and H.W.) independently extracted data from the included studies. Discrepancies between the two reviewers were discussed and resolved with another author (Q.J.), and if the disagreement was not resolved, another senior reviewer (DM.W.) was consulted. For each eligible article, the following information was extracted: study type, fat donor site, recipient area, fat graft processing, follow-up time and results. The focus was on identifying key findings related to the occurrence of browning in fat grafts, the

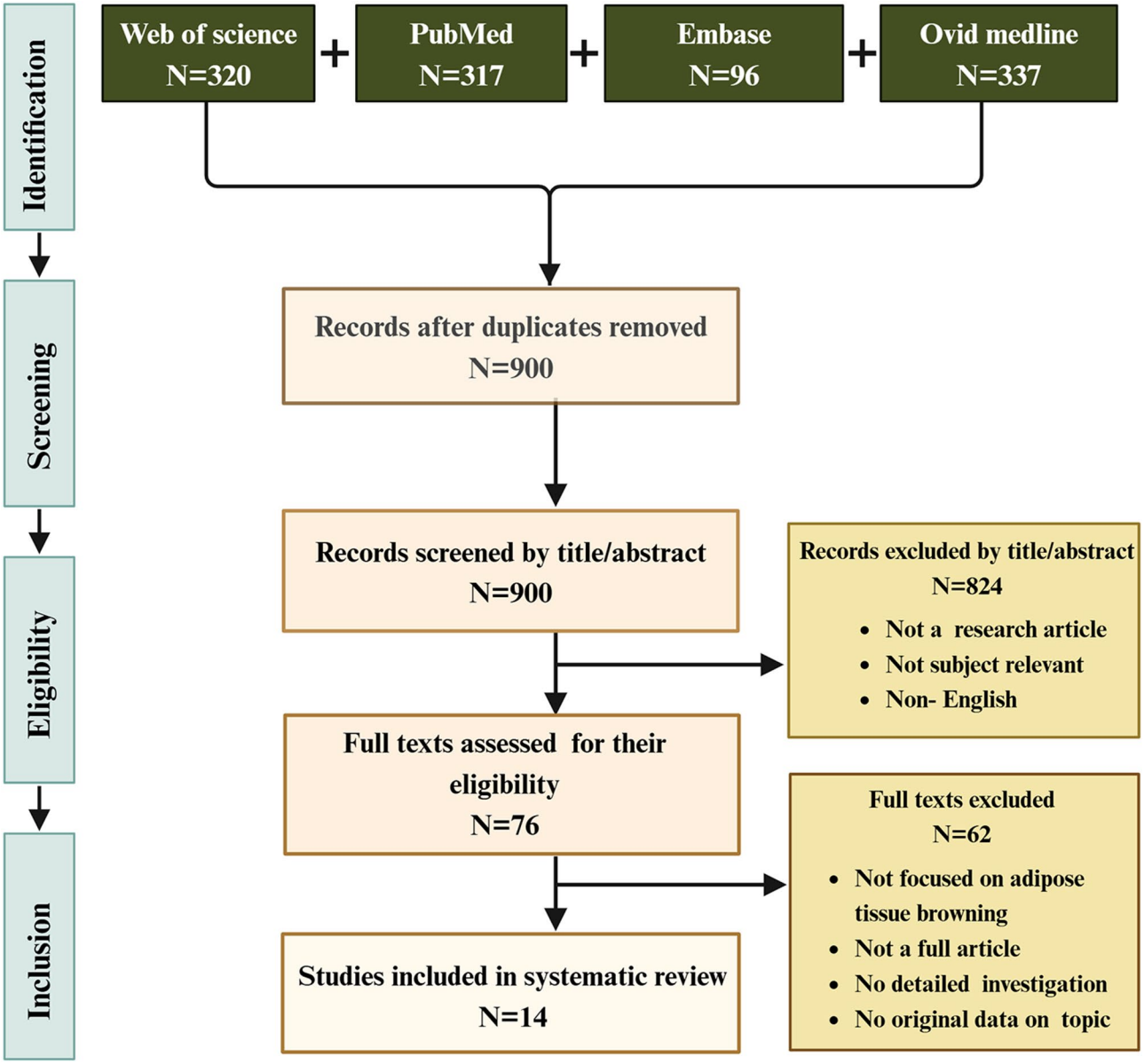

Fig. 2 Flow diagram of the retrieval strategy and study selection process

conditions under which it happens, its impact and potential mechanism on graft survival and remodeling. Data extraction and analysis were conducted in strict accordance with the PRISMA guidelines.

Results

After screening, a total of 14 studies were finally identified for inclusion in the systematic review (Fig. 2). Thirteen studies were animal studies and only one clinical report. In eligible studies, fat donor was primarily sourced from the inguinal region of mice or from the abdominal or leg areas of humans. Regarding browning conversion, four studies did not employ any induction methods, while eight studies used pharmacological agents or cold exposure for pre-transplantation browning induction. Additionally, one study involved the direct transplantation of beige adipose tissue. Based on existing datas, we outlined the critical events involved in the browning and re-whitening of transplanted fat, and discussed their role in the evolution of fat grafting.

Differentiation of white adipocytes into brown adipocytes in grafted fat

The fat grafts used for repairing and reconstructing soft-tissue defects are often free non-vascularized WAT, which may also contain metabolically active BAT. Unlike various pre-transplantation treatments aimed at activating browning in adipose tissue, spontaneous browning can occur in post-transplantation graft remnants, possibly exhibiting a certain time correlation and responsiveness to external stimuli. This physiological process switch from white to beige fat after transplantation involved the regions where browning occurs, the origins of browning cells, the time course of browning, and the transplantation factors inducing browning.

The location and origin of browning adipocytes in grafts

Studies of adipocyte fate in nonvascularized fat grafts have established that cellular survival is limited to adipocytes positioned within 300 μm of the tissue interface [21]. One finding reported that following fat transfer of human adipose cells to nude mice, brown-like adipocytes spontaneously appeared in peripheral region of the grafts [22]. Beige adipocyte accumulation in transplanted adipose tissue was predominantly observed in the regenerative zone, followed by the necrotic area, with minimal presence in the surviving region [5]. It may be attributed to the homeostasis system of self-repairing in the body, which responds to changes in the microenvironment by activating adipose-derived stromal/stem cells from either the donor or the recipient that mediated this spontaneous browning for tissue repair and regeneration. Researches further confirmed that newly formed beige adipocytes were more likely to regenerate from adipose progenitor cells of graft origin, rather than preexisting white adipocytes [19, 22]. Moreover, the precursor population that differentiate into beige adipocyte may differ from those differentiating into white adipocytes [23]. Some authors have argued that the beige adipocytes within browning fat originate from the transformation of white adipocytes [6]. However, there remains a paucity of sufficient evidence on the differentiate origin of beige adipocytes in fat grafts.

The time course of grafted fat browning

As noted by Hoppela E, a cascade of regenerative responses will occur in survival and regeneration zones of grafted fat in the short term [3]. Cell proliferation can be observed as early as the third day post-transplantation, followed by the appearance of newly formed adipocytes after day 5, and an increase in alive adipocyte area by the seventh day. Some researchers also reported that more rapid beigeing within as short as 2 days can be triggered in VEGF-A specific-expressing grafts in an interleukin-4 (IL-4) and adiponectin-independent manner [24]. On day 7 after transplantation, unilocular lipid droplet cells and a few UCP1 positive adipocytes began to occur in the grafts [5]. The accumulation of beige adipocytes reached the peak on day 14, while the graft gradually returned to the resembling state of WAT without obvious UCP1 positive fat cells on days 90. Notablely, the expression of VEGF-A in fat grafts follows a similar temporal pattern to that of browning, peaking around day 14 [5]. A similar observation was reported in a study investigating the expansion of BAT derived from grafted cells, with detectable increases as early as 2 weeks post-transplantation and sustained effects lasting up to 12 weeks [19, 25]. Considering all of this evidence, it seemed that this adaptive response of re-whitening occurred within the first three months. However, since most studies were limited to the three-month endpoint, it was absent of the long-term consideration of whitening differentiation timeline. To date, a systematic understanding of how graft browning dynamically responds to in vivo remodeling time is still lacking.

Transplantation factors associated with induction of fat browning

It has commonly been presumed that the brown differentiation is an adaptive and reversible response to stimulus (trauma, stress, cold exposure [26], hypoxia [27]), which will rapidly recruite monocytes to the injured grafted site, promote alternatively activated macrophages and enhance local metabolism. It seems possible that adipose trauma induced local and, importantly, distant adipose tissue browning [28]. Hypoxia-induced augmentation of lactate production may also stimulate the "browning" of white fat depots through recruitment of UCP1

and the development of brite adipocytes. Studies indicated that the relocation of WAT to a new environment can enhance the metabolic activity of fat grafts, with this activity being dependent on the donor and recipient area. This heightened metabolic response of the grafts may also be the result of the browning conversion of WAT [3]. But far too little attention has been paid to whether the mechanical influences caused by liposuction to the donor site will also induce browning in the donor site. Further work needs to be done to establish whether there are similar browning changes in the donor area, and even the recipient region [29].

Re-whitening differentiation of adipocytes in grafted fat

Evidence suggests that prolonged in vivo exposure to extreme hypoxia and an avascular environment may lead to mitochondrial loss, lipid accumulation, and dysfunction in beige adipocytes, potentially reducing their quantity and activity [27, 30]. Whether and when browning adipose tissue in grafted fat can re-whiten? It has been pointed out that the reciprocal conversion between white and beige adipocytes can be balanced and regulated [31]. For instance, within a 5-week period of warm adaptation, cold-induced brite adipocyte can be reversed into typical white adipocytes, which also could revert back into brite adipocytes under additional cold stimulation. It was also observed that induced beige adipocytes underwent re-whitening by 12 weeks post-grafting [7], consistent with previous reports demonstrating that tamoxifen-induced beige adipose tissue transitions into WAT [2]. Similarly, Jones also reported that the phenomenon of browning in the grafts almost disappeared at 3 months. The re-whitening for beige adipocytes phenotype seemed to be an adoptive, reversible and flexible process. This reduced energy expenditure, thereby circumventing the limitations of high energy consumption associated with the long-term survival of fat grafts. On the other hand, the number of newly formed blood vessels after transplantation was limited and their structure was imperfect, which may not suffice to meet the metabolic demands of a high proportion of beige adipocytes. This may create a vicious cycle, potentially leading to adverse outcomes such as fat necrosis. But this whitening of such cases may be a transitional phase preceding the necrosis of dysfunctional grafts.

Interestingly, obesity-associated BAT is associated with BAT "whitening" phenotype shifting, characterized by capillary rarefaction, mitochondrial dysfunction and lipid droplet accumulation [27]. The association between host overnutrition and the whitening of brown fat that may be mediated is also a new point of interest. It is unfortunate that current studies did not elucidate the precise mechanisms and potential interventions for the rewhitening of transplanted fat to avert the premature or aberrant whitening of beige fat cells.

Associations between Browning in the grafts and the effect of fat grafting

Activated beige adipocytes through "browning" or "beigeing" process of WAT can provide a local microenvironment beneficial for grafts survival, either by generating a new vascularized niche for progenitor cell proliferation and differentiation or by decreasing the level of lactate or nitric oxide during hypoxia. Such browning regulation following transplantation has been demonstrated to be conducive to improving the survival of fat grafts by the promotion of angiogenesis, resistance to inflammation and enhancement of adipogenesis (Fig. 3). This beigeing behavior also may convey systemic metabolic benefits in transplant recipients.

Inflammatory microenvironment created by the browning of white fat

It has previously been reported that the active inflammatory processes occurring in transplants could affect its white-convert-brown plasticity, disrupting the degree of browning in these fat depots and leading to the local release of vascular damage signals [32]. A limited degree of inflammatory response in the early stages of transplantation may be a contributing factor in maintaining browning. Available studies have clarified that the response of anti-inflammatory M2 macrophage recruitment from fat-grafting procedure was associated with the development of beige BT in fat grafts [24, 33, 34]. Grafts with the browning upregulation were found to be with a reduction in M1 macrophage infiltration and with superior angiogenesis and adipose structure [5]. The type of beige AT in mice demonstrated the highest retention rate 12 weeks after subcutaneous transplantation, accompanied by lower inflammation level, less fibrosis and few oil cysts than transplanted brown fat [4]. Furthermore, under hypoxic conditions, the conditioned medium from beige adipocytes shown decreased apoptosis and effectively facilitated macrophages M2 polarization. The higher distribution of the M2 macrophages were conducive to improving the retention of fat grafts [34]. Subsequent investigations further confirmed minimal inflammatory infiltration surrounding peripherally induced BAT, with a gradual reduction observed over time [25]. In addition, the incorporation of BAT in WAT was observed to inhibit the polarization of M1 macrophages and downregulate the expression of inflammatory factors such as IL-6, IL-1β, and tumor necrosis factor-β (TNF-β), while upregulating the activation CD206-positive M2 macrophages [8]. The increased proportion of M2 macrophages can further promote the regeneration of beige adipocytes, creating a positive and beneficial

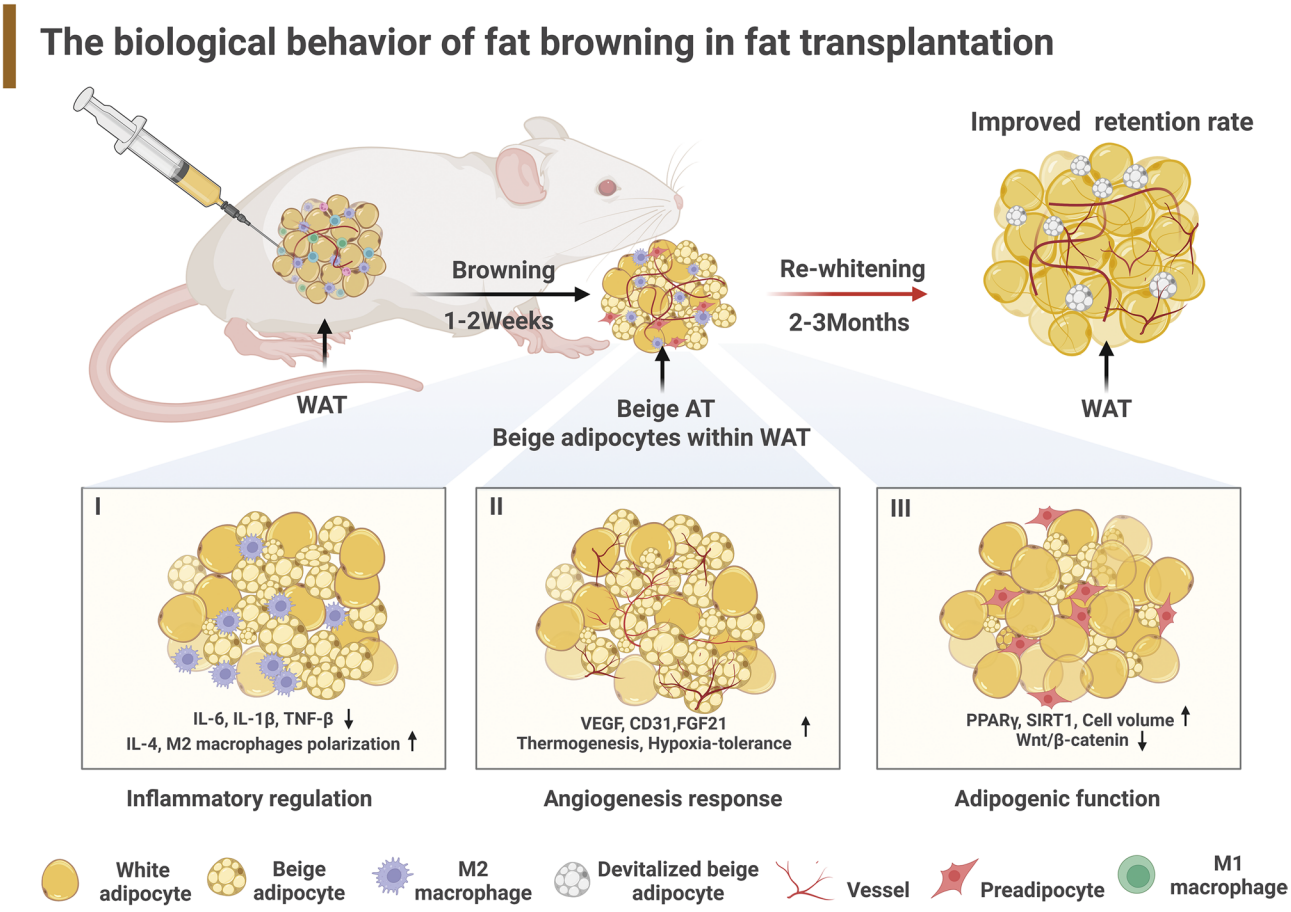

Fig. 3 The biological behavior of fat browning in fat grafting

cycle. Together, these studies indicated that early induction of browning to promote macrophage M2 polarization can improve the microenvironment of transplanted fat to some extent, serving as an effective strategy to enhance the retention rate of transplanted fat [35]. Note here that these findings conflicted with Liu T previously mentioned study which reported browning tissue in fat grafts with a higher level of pro-browning inflammatory cytokines, infiltration of M2 macrophage and necrosis [19]. Some factors of this uncertainty were the difference in grafted volumes, fat processing methods, the condition of transplants and so on. Further studies, which take these variables into account, will need to be undertaken.

Angiogenesis response from browning-related process in adipose grafts

How to promote the vascularization is crucial for the long-term retention of transferred fat. Beige adipocytes exhibit distinct morphological and metabolic features, including smaller adipocyte size, multilocular lipid droplets, and abundant mitochondria. These characteristics enhance vascularization, increase the surface-to-volume ratio, and improve tolerance to hypoxic conditions by facilitating oxygen diffusion, thereby promoting adipocyte survival [9]. Compared to WAT and BAT, transplanted beige fat were observed to be better vascularized, innervated and proliferative activity [4]. Structured vascularized adipose tissue deposition in the dorsal compartment and circulating adiponectin were observed after implantation of brown adipocyte-Matrigel composites [36]. When induced beige adipocytes were directly transplanted into mice, the fat retention rate was comparable to that adipose-derived stem cell groups [7]. Enhanced angiogenesis were observed in beige adipose grafts during the early stages post-transplantation and significantly higher than that in BAT and WAT groups. The result that induced beige adipocytes did not develop new vessels while with higher expression of VEGF-α mRNA after fat grafting can be explained in part by its paracrine effect [37]. In a relevant study where BAT improved WAT graft survival, the mixture of WAT and BAT also possessed more pronounced neovascularization with larger mass and volume than pure WAT group [8].

Adipocyte regeneration of transplanted fat regulated by fat browning

A possible positive correlation was found between browning upregulation and adipogenesis. The structure of the transplanted fat is one of the primary indicators for assessing the outcomes of fat grafting. It has been observed that the upregulation of browning can reduce oil cyst formation, inflammatory cell infiltration, and the degree of fibrosis, benefiting transplanted fat with a more superior adipose structure [5]. Many studies have adopted the strategy of inducing browning prior to graft transplantation, such as oral administration, injection agents and cold stimulation, which has shown improved fat retention post-transplantation [34, 38, 39].

Nowadays, fat grafting not only focuses on volume recovering but also pays more attention to the functional regeneration of transplanted tissues. PPAR-γ is an important transcription factor in adipogenesis via orchestrating the recruitment of adipogenic elements during preadipocyte differentiation. Relevant studies showed that BAT induced in vivo a markedly adipogenic response in WAT grafts, where a higher expression of PPAR-γ was observed. Enhanced fat regeneration capacity in BAT grafts was found to correlate with suppression of the Wnt/β-catenin signaling pathway [8]. Traditionally, the browning process, characterized by hypermetabolism, will exhibited a certain fat-reducing effect, as seen in the application of browning-focused strategies against obesity and associated metabolic disorders [40, 41]. The paradoxical relationship between browning-induced fat retention and fat reduction requires further study to elucidate its local and systemic metabolic impacts.

Discussions

The phenomenon of WAT converting to beige adipocytes with a high surface area-to-volume ratio was likely an adaptive response to early ischemia and hypoxia phase of fat engraftment. Browning seemed to be a promising route to affect transplants activity to greatly improve fat graft survival (Fig. 4**).** Currently, endogenous browning of WAT or differentiation of beige adipose tissue (AT) de novo is one of promising approaches to increase the quality or activity of beige AT. Of many means involved manipulating the browning events in vivo, diet, temperature, exercise, the augmentation of thyroid function, and beta (3)-adrenoceptors (β3-AR) activation under physiological conditions in vivo are common

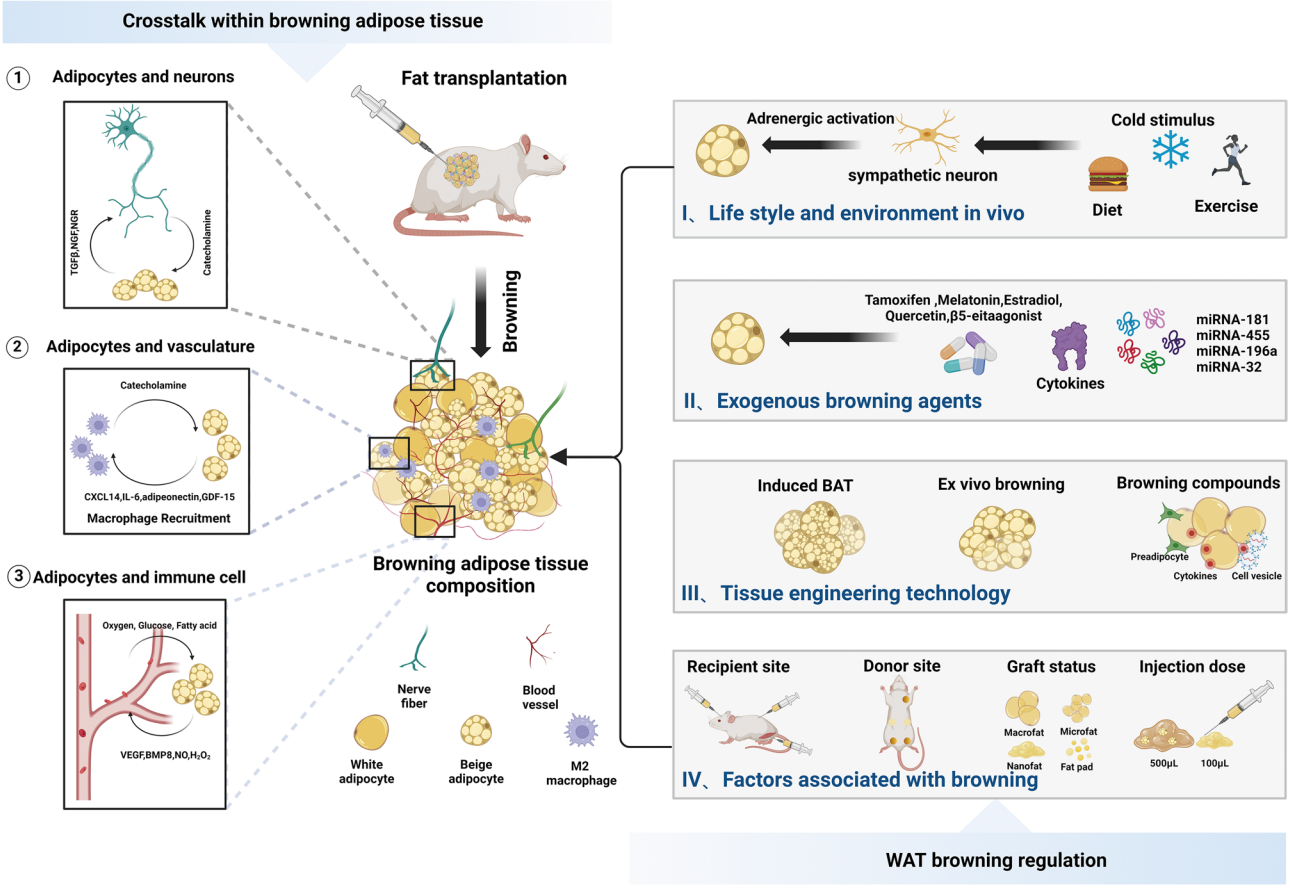

Fig. 4 The crosstalk within beige adipose tissue and regulation of browning in fat grafting

non-pharmacological pathways for harnessing WAT transdifferentiation in humans [39, 42].

Apart from above physical factors, some browning agents received before or after transplantation are also an effective manner for the browning of grafted fat. A relationship exists between catecholamine release via M2 macrophage polarization and it regulation for fat browning [43]. Extracellular vesicles [44], telmisartan [45], and interleukin-4 [46] were discovered a favorable role for activating M2-type polarity switch of macrophages. For example, 8-week oral tamoxifen pretreatment promoted beige fat conversion and improved vascularization in subsequent fat grafts [2]. However, tamoxifen treatment after fat grafting did not affect the browning of fat grafts. A strong relationship between pro-angiogenic factors and proliferation of beige adipocyte progenitor has been reported, which also shed new light on browning approaches [36]. Currently, extensive researches are being conducted to manage obesity and diabetes treatment by using various browning agents to locally or systemically activate the browning of WAT. These approaches also hold certain reference value for regulating the browning of transplanted fat, but the safety issues related to drug interventions arising from this deserve attention.

Some researchers also performed single ex vivo browning of WAT approximately 1 to 3 weeks, followed by re-implantation into the host, a process known as "ex-BAT" [47]. The phenotype maintenance of ex vivo induced BAT in vivo can maintain continuously for up to 12 weeks. This straightforward and feasible tissue transplantation strategy holds promise for circumventing the side effects associated with drug-induced approaches and boasts considerable clinical potential for enhancing functional endogenous beige AT mass [7, 47]. However, whether employing in vivo natural BAT, ex vivo induced BAT, engineered brown-like adipocytes, or beige preadipocytes for manipulating the browning of transplanted fat, all are still in the early stages of experimental research.

Both source of the graft and microenvironment of the recipient site are key factors related to the occurrence of browning. Beige adipocytes within different WAT depots exhibits donor site-specificity and variability in performance. Beige adipocytes in the subcutaneous depot have been demonstrated to originate from a specific precursor cell population, and are particularly abundant in the inguinal WAT. Inguinal WAT is more susceptible to browning compared to the WAT in epididymis [48]. Inguinal area is also a common donor site for fat grafting in clinical practice. In fat grafting, transferring such WAT to good blood supply and high metabolism of recipient area, like muscle tissue, may induce metabolic adaptations of fat browning and the long-term maintenance of browning features [49]. This not only could enhance the survival rate of the fat grafts but also may have beneficial effects on the body's glucose homeostasis, weight control and other metabolic diseases [50, 51].

Of interest, the identity of brown adipose tissues in adult humans has been proved to be composed primarily of beige adipocyte [52]. As Tran TT stated, direct transplantation of in vivo BAT may also be one of the effective strategies to simulate the browning effects [53]. Transplanting BAT with an appropriate volume ratio was recognized as a straightforward exogenous browning means in promoting the fat retention [8]. But one research indicated that the in vivo retention rate of pure transplanted BAT was substantially lower compared to grafted WAT and beige-AT [4]. It was shown that transplantation of an entire brown fat pad or large amounts of mechanically processed brown fat fragments were prone to result in extensive necrosis [54]. This view was supported that impaired vascularization of brown transplants cannot meet the high metabolic demands, potentially leading to a decrease in vascularization and survival compared to natural brown grafts [55]. It is undeniable that there may be a certain correlation between the volume of transplanted fat and the necrosis of BAT graft in large dose. Likewise, the transplantation of 500μL WAT grafts was correlated with browning-related fat necrosis, whereas not in the 100μL fat graft group. After all, clinically, the injection method of using a single point of 0.5mL of fat is rarely adopted.

Transplanted fat is a complex system where existed crosstalk among cells, tissues, and molecules from itself and the host. Notwithstanding the paucity of robust clinical evidence, current analysis reveals that browning efficacy is closely linked to clinical parameters (patient age, metabolic status) and procedural variables (harvesting technique). Regarding on these considerations, it will be more challenging to manipulate this surgery in the future to enhance beige fat functionality.

Cold exposure or β3-AR agonist stimulation induces polarization of adipose tissue macrophages toward the anti-inflammatory M2 phenotype. These M2 macrophages secrete catecholamines, which activate adipocyte β3-AR, triggering the Protein Kinase A/p38 Mitogen-Activated Protein Kinase (PKA/p38MAPK) signaling cascade. This pathway upregulates UCP1 and peroxisome proliferator-activated receptor gamma coactivator1-α (PGC-1α), enhancing mitochondrial thermogenesis and adipose tissue browning [56] (Fig. 5). Furthermore, M2 macrophages release IL-4 and IL-13, activating the STAT6 pathway in adipocytes to promote mitochondrial biogenesis [33, 57]. In contrast, pro-inflammatory M1 macrophages secrete TNF-α and IL-6, which inhibit browning, exacerbate insulin resistance, and drive tissue fibrosis. Emerging evidence suggests that browning regulators may enhance UCP1 and PPAR-γ expression by activating silent information regulator 1(SIRT1),

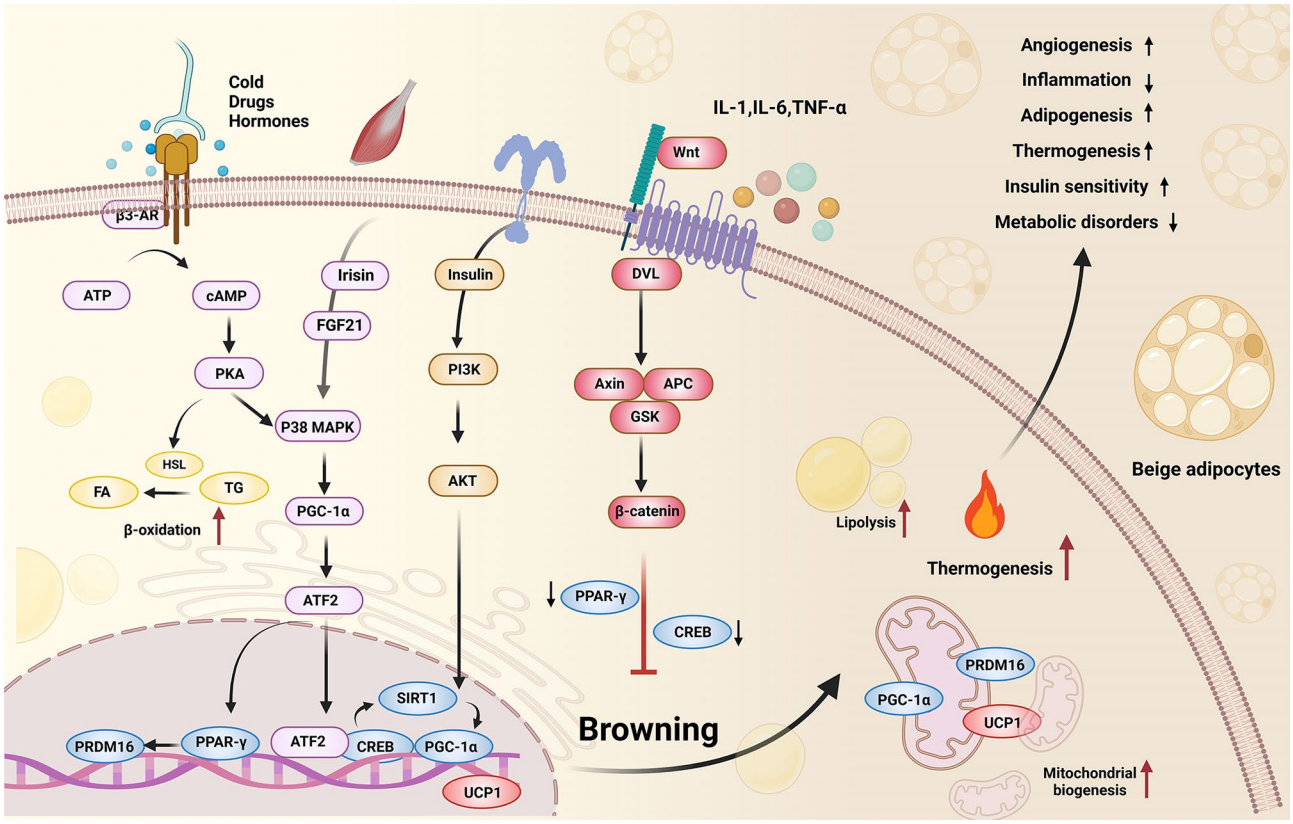

Fig. 5 Schematic diagram of the regulatory mechanism of adipose tissue browning

thereby boosting mitochondrial energy expenditure and beige adipocyte differentiation [25]. While cold exposure, mechanical stress, and pharmacological agents have been extensively studied as inducers of beige adipogenesis in WAT [52], the mechanistic details of the beigeing process within grafted WAT and how it can be re-whitening remain poorly understood.

The browning of adipose tissue improves graft survival by modulating metabolic activity and secretory profiles. UCP1, a key browning biomarker, acts as a metabolic regulator by influencing adipocyte mitochondrial function. PPAR-γ, critical for adipocyte proliferation and differentiation, is tightly linked to the Wnt/β-catenin pathway, a well-established suppressor of adipogenesis and adipose tissue function. In WAT, persistent Wnt activation promotes adipocyte dedifferentiation and apoptosis, impairing tissue viability. Recent studies demonstrate that combining WAT with BAT in subcutaneous transplants enhances graft retention via Wnt/β-catenin inhibition and subsequent PPAR-γupregulation [8] (Fig. 5**).** BAT-derived paracrine factors, such as fibroblast growth factor-21 (FGF-21), suppress Wnt signaling in adjacent WAT [58]. Intriguingly, a distinct subpopulation of Wnt^+ adipocytes that marked by active Wnt/β-catenin signaling, can transdifferentiate into thermogenically active beige adipocytes, exhibiting molecular and genomic distinctions from conventional adipocytes. These Wnt^+ adipocytes may autonomously initiate beiging or recruit $UCP1^+/Wnt^-$ beige adipocytes via insulin/protein kinase B (AKT)/mechanistic target of rapamycin (mTOR) signaling [58]. However, the therapeutic potential of targeting these pathways to enhance beige fat formation and function remains unclear.

In summary, adipose tissue browning confers beneficial effects on graft survival to a certain extent. However, sustained UCP1 activation generates Reactive oxygen species-mediated oxidative damage. Chronic thermogenesis with persistent energy demands depletes lipid reserves, resulting in adipocyte atrophy and necrosis. Furthermore, excessive browning also induces pro-inflammatory macrophage infiltration and fibrosis.

Study limitations

The cellular kinetics of the browning process with time closely related to intrinsic characteristics of the graft itself, such as the condition of receipt site, transplantation volume, the fat processing methods, and donor site source, and also the effect of graft-host interactions. It can be seen from the data in Table 1 that current researches on fat grafting browning were mainly concentrated at the animal level, with some variations in factors inducing browning and parameters related

Table 1 Included studies concerning the WAT Browning in fat transplantation

Reference	Study type	Fat donor site	Intervening measure	Follow-up period	Recipient area	Fat graft processing	Browning assessment method	Outcomes
Cai, J et al. (2018) [2]	Animal study	Subcutaneous inguinal fat pad from C57/BL6 mice	Pretreated with tamoxifen by oral gavage, for 8 weeks	Postgraft weeks 4 and 12	Sub-scalp of C57/BL6 mice	150 mg per point /Implanted through a 5 mm long skin incision	Immunohistologic staining(CD31,UCP1);Quantitative RT-PCR(UCP1,VEGF); Immunofluorescent staining(Ki67, perilipin)	Induced browning, improved fat graft survival and enhanced vascularization
Hoppela, E et al. (2018) [3]	Animal study	Epididymal, visceral, and subcutaneous fat tissue from C57BL/6 mice	None	Postgraft weeks 4 and 12	Subcutaneous or muscle tissue in nude mice	0.25 ± 0.09 mL of whole fat pad forehead; 0.13 ± 0.05 mL of fat particles for the muscle of the leg injected with 14 gauge cannula	In and ext vivo FDG-PET/CT Imaging; Gene expression analysis(UCP1);Immunohistologic staining(UCP1);HE staining	Enhanced uptaking of glucose in both receipt site and browning of fat grafts in muscle tissue
Lin, J et al. (2022) [5]	Animal study	Inguinal fat pad of C57BL/6 mice	Subcutaneously inject CL316243 at the transplantation site, for 14 days	Postgraft days7, 14, 30, and 90	Dorsal subcutaneous tissue in C57BL/6 mice	150 mg per mice / Implanted through a skin incision	Immunohistologic staining(CD31,UCP1);Immunofluorescent staining(Mac2, perilipin); Quantitative RT-PCR(UCP1, PRDM16,PGC1-α,FGF21,HIF1α, VEGF-A); Energy Eαexpenditure analysis;HE staining	Early accumulation of beige adipocytes in the center of grafts
Xia, J et al. (2021) [7]	Animal study	Abdominal region of female patients	Grafted with induced in vitro beige adipocytes	Postgraft weeks1, 4, 8 and 12	Dorsal subcutaneous tissue in nude mice	300 μL per point/ Implanted through 16-gauge needle	HE staining; Immunohistologic staining(UCP1);Immunofluorescent staining(CD31, perilipin); Quantitative RT-PCR(UCP1,VEGF-α,PPAR-γ,CEBP-β)	Enhanced angiogenesis, improved adipogenesis and decreased oil cyst formation
Yu, P et al. (2022) [15]	Animal study	Abdominal region of female patients	10% of quercetin (20μmol/L) with fat granules	Postgraft weeks 2, 4, 8 and 12	Subcutaneous layer at the forelegs or hindquarters in nude mice	0.2mL per point/ Injected by 1.0mLsyringe with a 18-gauge needle	HE staining; Immunohistologic staining(UCP1,perilipin-1);Quantitative RT-PCR(UCP1,SIRT1,PPAR-γ,VEGF-A, P16,P21,P19);Western blot analysis (UCP1,HSP60,PPAR-γ,VEGF-A)	Enhanced occurrences of peripheral fat browning and survival rate
Liu, T et al. (2021) [19]	Animal study	Abdomen or thigh region of female patients	None	Postgraft weeks2,4,8 and 12	Dorsal subcutaneous tissue in Balb/c nude mice	100 μL or 500 μL lipoaspirates/ Injected through an 18-gauge needle	Immunohistologic staining(UCP1);Western blot analysis (UCP1,human mitochondria, and apoptotic marker cleaved caspase 3, CD206); ELISA(TGF-β1, IL-10, MCP-1, TNF-α, IL-6, IL-1β);Transmission electronic microscopy	500μL graft group was associated with increased M 2 macrophage infiltration, expression of inflammatory factors and beige adipocytes than the 100μL graft
Liu, T et al. (2021) [20]	Preliminary clinical Report	Not in detail	Necrotic fat grafts were obtained from patients after fat grafting or flap grafting	Not in detail	Breast augmentation	Not in detail	Immunohistologic staining(UCP1);Western blot analysis (UCP1); Quantitative RT-PCR(UCP1);Transmission electronic microscopy	Obvious browning of white adipocytes in fat grafts with necrosis
Qiu, L et al. (2018) [22]	Animal study	Abdominal or thigh region of female patients	None	12 week after transplantation	Dorsal subcutaneous tissue in nude mice	0.5 mL per point/ Implanted through 1.0mL syringe with a 16-gauge needle	HE staining; Immunohistologic staining(UCP1,CD31,perilipin 1);Immunofluorescent staining(UCP1, perilipin)	Beigeing in the peripheral region of the grafts
Park, J et al. (2017) [24]	Animal study	Inguinal fat pad of 7week old male mice	Doxycycline -inducible VEGF-A overexpression in grafted adipocytes	At 1, 2,5, and 7 days after administration	Interscapular site of isogenic C57/BL6J male wild-type mice	200 mg fat tissue pieces implanted by surgery	Immunohistologic staining(UCP1,MAC-2,CBP/p300-interacting transactivator 1, endomucin); Quantitative RT-PCR(UCP1,CD31,VEGF-A, TNFα,IL-6,Col); Immunofluorescent staining(MAC-2);Collagen content assay; Elisa(VEGF-A)	Promoting rapid beiging, cell survival and functionality in WAT transplants

Table 1 (continued)

Reference	Study type	Fat donor site	Intervening measure	Follow-up period	Recipient area	Fat graft processing	Browning assessment method	Outcomes
Dang, J et al. (2023) [34]	Animal study	Inguinal fat tissue from C57BL/6 mice	Orally with melatonin every day for 2 weeks	At 2, 4, and 12 weeks after administration	Sub-scalp of C57BL/6 mice	0.30 ± 0.05 g per point/ Injected by 1.0 ml syringe with a 18-gauge needle	HE staining; Immunohistologic staining(CD31);Immunofluorescent staining(UCP1,CD206);Quantitative RT-PCR(VEGF)	Obvious browning, enhanced vascularization, enrichment of M2 macrophages and improved fat retention
Niu, X et al. (2022) [38]	Animal study	Inguinal fat pad of C57B/L6 mice	Fed with high-carbohydrate diet (9.3% kcal from fat, 80.1% from carbohydrate) for 4 weeks	At 4, 8, and 12 weeks after fat grafting	Dorsal subcutaneous tissue in C57B/L6 mice	0.3 mL per mice/ Injected with 1mL syringes with 21-gauge blunt needle	HE staining; Masson staining; Immunofluorescent staining (perilipin, CD34,CD31, PCNA); Quantitative RT-PCR(VEGFα, PDGFα, UCP-1);Western blot analysis (UCP1, PCNA)	Adipocyte browning, higher volume retention and reduced oil cyst formation
Luo, Y et al. (2024) [39]	Animal study	Inguinal WAT from C57/BL6 mice	Cold stimulation before transplantation for 48 h	At 8 weeks after operation	Dorsal subcutaneous tissue in C57/BL6 mice	0.2mL per point/Injected by 2.0 ml syringe with a 16-gauge cannula	Sirius red staining; HE staining; Immunofluorescent staining(CD31,UCP1,Ki67, perilipin); Apoptosis analysis; Quantitative RT-PCR(UCP1);Western blot analysis (Adiponectin, TGF-β1, HSP90,HSL, p-HSL, ATGL)	Improved the retention rate, angiogenesis, cell proliferation, and adipocytes homeostasis of fat grafts
Zhu, Y.-z et al. (2020) [44]	Animal study	Subcutaneous inguinal fat pad from C57/BL6 mice	0.2 mL extracellular vesicles derived from human ADSCs once per week for 12 weeks	Postgraft weeks 2, 4, and 12	Sub-scalp of C57/BL6 mice	150 mg of the fat pad per mice/ Implanted through 1.0mL syringe with a 19-gauge needle	HE staining; Masson staining; Immunofluorescent staining(perilipin); Immunohistologic staining(CD31,CD206,noradrenaline, UCP1)	Increased browning of grafts with higher vessel density, M2 macrophage polarization, and survival of fat grafts
Wu, S et al. (2020) [59]	Animal study	Abdominal region of female patients	Orally with estradiol (0.2 mg/g) every 3 days for 30 days	After 8 weeks of fat grafting	Sub-scalp of nude mice	0.3mL per mouse/Injected with a 19-gauge blunt needle	HE staining; Immunofluorescent staining(perilipin, estrogen receptor α.);Immunohistologic staining(UCP1);Quantitative RT-PCR(UCP1,estrogen receptor α)	Production of beige fat and high vascular density in fat graft

to transplanted fat (grafts mass, grafts source, recipient site, fat subjects sex, age, species and procedure of injection). Additionally, current evidence is largely preclinical, with insufficient human trial data to confirm browning's role in fat graft retention. Being limited to the sample size, variability among the samples and the level of current evidence, the information available on the mechanisms of browning enhancing fat survival also remains insufficient.

Subsequent researches should focus on investigating the spatiotemporal dynamics of browning in transplanted fat in vivo, coupled with longitudinal tracking and validation of browning kinetics in vitro cell models. The long-term effects (beyond 6 months) and ultimate outcomes require systematic exploration. Furthermore, further research is needed to identify the factors and mechanisms that can be modulated to optimize graft outcomes.

Conclusions

Graft fat browning, an event that might be of value for the remodeling of grafted fat, did certainly update our traditional insights into the histological changes following fat grafting. The browning event was closely associated with the effect of transplantation through affecting the inflammatory regulation, angiogenic response and adipogenic ability of the origin graft. Control of this process is therefore likely to be beneficial for fat grafting in the other metabolic diseases involved in the development of energy homeostasis, and improved energy utilization. However, these observations indicated that the interplay between adipose tissue browning and grafting survival was far more complex than what has been reported so far. The issue of regulation browning and its roles in fat graft is an intriguing one which could be usefully explored in further practice.

Abbreviations

WAT	White adipose tissue
BAT	Brown adipose tissue
AT	Adipose tissue
IL	Interleukin
TNF	Tumor necrosis factor
VEGF	Vascular endothelial growth factor
MeSH	Medical terms
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
UCP1	Uncoupling protein 1
PPAR-γ	Peroxisome proliferator-activated receptor-γ
CEBP-β	CCAAT/enhancer-binding proteinβ
SIRT1	Silent information regulator 1
PRDM16	PR domain containing
PGC-1α	Peroxisome proliferator-activated receptor gamma coactivator1-α
PKA	Protein kinase A
MAPK	Mitogen-activated protein kinase
STAT6	Signal transducer and activator of transcription 6
β3-AR	Beta (3)-adrenoceptors
FGF21	Fibroblast growth factor-21
MCP-1	Monocyte chemotactic protein-1
HIF-1α	Hypoxia inducible factor-1
PCNA	Proliferating cell nuclear antigen
ELISA	Enzyme-linked immunosorbent assay
AKT	Protein kinase B
mTOR	Mechanistic target of rapamycin

Acknowledgements

The authors acknowledge the valuable insights and timely help provided by the relevant people in conducting the literature search and review. The authors declare that they have not used Artificial Intelligence in this study.

Author contributions

He Qiu: Conceptualization, Data curation, Formal analysis, Investigation, Writing–original draft. Hang Wang: Conceptualization, Project administration, Data curation, Formal analysis. Qiang Ji: Formal analysis, Investigation, Supervision. Dongmei Wu: Methodology, Formal analysis, Investigation, Supervision.

Funding

This research received no specific financial support from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Conflict of interest

The authors declare that there is no conflict of interest in his work.

Received: 6 November 2024 / Accepted: 18 June 2025
Published online: 01 July 2025

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