Trends in
Endocrinology & Metabolism

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Review

Adipose tissue-targeting nanomedicines for obesity pharmacotherapy

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The increasing global prevalence of obesity presents a substantial challenge to public health. Current nutrient-stimulated hormone (NuSH)-based therapeutics are hindered by receptor desensitization, muscle loss, and weight regain. The adipose tissue, the primary organ responsible for energy storage and metabolic management, is a promising target for obesity treatment. Nanomedicine holds promise to precisely deliver medication to the adipose tissue to maximize therapeutic efficacy and minimize off-target effects; indeed, various adipose tissue-targeting nanomedicines have shown impressive anti-obesity effects by optimizing drug pharmacokinetic profiles and reducing nonspecific distribution in preclinical studies. Here we examine the current state of the art of adipose tissue-targeting nanomedicines, offering insights into recent advances, future possibilities, and the remaining challenges associated with their application in obesity treatment.

Highlights

The adipose tissue is the principal organ for energy storage and metabolic regulation, making it a promising target for obesity pharmacotherapy.

Adipose tissue-targeting nanomedicine holds promise in overcoming limitations arising from traditional obesity pharmacotherapy.

The distinct receptor profiles and physicochemical properties of the adipose tissue allow nanomedicines to target it through both active and passive strategies.

The principal approaches for adipose tissue-specific nanomedicine involve targeting adipocytes for energy balance, macrophages to reduce inflammation, and multiple cell types simultaneously to achieve synergistic effects.

Adipose tissue-targeting nanomedicine is a promising alternative for obesity treatment

Obesity has become a global issue, with projections indicating that 1.02 billion adults will be obese by 2030 [1,2]. It also raises the risk of comorbidities such as type 2 diabetes, cardiovascular diseases, and metabolic dysfunction-associated steatotic liver disease, potentially shortening life expectancy by 5–20 years [3]. Therefore, obesity is a substantial health challenge that necessitates urgent intervention.

Bariatric surgery and pharmacotherapy are the primary treatments for obesity. While bariatric surgery is highly effective for weight loss and reducing obesity-associated complications, it is costly and can lead to weight regain in about one in six patients [4]. Pharmacotherapy, by contrast, is more accessible and has become increasingly popular over the past decade. NuSH-based pharmacotherapies, represented by glucagon-like peptide 1 receptor agonists, have shown remarkable anti-obesity efficacy and more tolerable side effects, positioning them as a promising advance in obesity pharmacotherapy [5]. However, a critical issue with NuSH therapies is receptor desensitization following continuous stimulation, which hampers long-term management. Furthermore, there are concerns regarding their side effects, such as an increased risk of gastrointestinal disorders, syncope, arthritic disorders, drug-induced pancreatitis, and thyroid cancer [6,7]. Additionally, there is widespread agreement that weight regain is commonly observed on discontinuation of NuSH treatment [8]. Thus, additional, novel pharmacotherapy strategies are still needed to combat obesity.

Tissue-targeting nanomedicine offers a promising strategy to address the limitations of current treatments. This approach can improve drug bioavailability and minimize systemic toxicity by improving drug solubility, optimizing drug release patterns, precisely delivering the drug to target sites, and reducing non-target distribution [9]. The adipose tissue, the principal organ responsible for energy storage and metabolic regulation, plays an essential role in obesity and related comorbidities. Adipose tissue depots undergo pathological changes during obesity, providing a

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rationale for tissue-specific pharmacotherapy and adipose tissue-targeting nanomedicines (Figure 1).

Recently, adipose tissue-targeting nanomedicines have shown considerable advances in preclinical studies [10]. Lipid-based, polymeric, biomimetic, and photothermal nanocarriers are currently being developed for this purpose (Figure 2, Key figure). These nanocarriers, either independently or modified with targeting ligands, enable the precise delivery of therapeutic agents to the adipose tissue. Specifically, lipid-based nanocarriers, such as liposomes and nanoemulsions, possess the capability to deliver both hydrophilic and hydrophobic drugs to the adipose tissue [11,12], demonstrating excellent biocompatibility and inherent membrane affinity [13]. Polymeric nanocarriers, including self-assembled polymeric micelles and both natural and synthetic polymeric nanoparticles, are mainly used to deliver hydrophobic drugs to the adipose tissue for obesity therapy [14]. Moreover, polymeric nanocarriers containing cationic motifs can form stable complexes with anionic gene therapy products through electrostatic interactions, thereby increasing their stability and transmembrane delivery to the adipose tissue [15,16]. Biomimetic nanocarriers, such as cell membrane-camouflaged and virus-like nanosystems, mimic biological processes or intrinsic characteristics of living systems, resulting in reduced immunogenicity, prolonged half-life, and enhanced safety [17,18]. Photothermal nanocarriers, like polydopamine nanoparticles [19] and gold nanoparticles [10], have been tested in mice to induce thermogenesis and lipolysis in the subcutaneous adipose tissue, effectively preventing the progression of obesity without adverse effects. Remarkably, an adipose tissue-targeting nanoparticle co-delivering TGF-β1 siRNA and COX-2 siRNA has recently advanced to clinical trials (NCT05422378) [20], highlighting the translational potential of this strategy for obesity treatment. Building on this breakthrough, we review recent

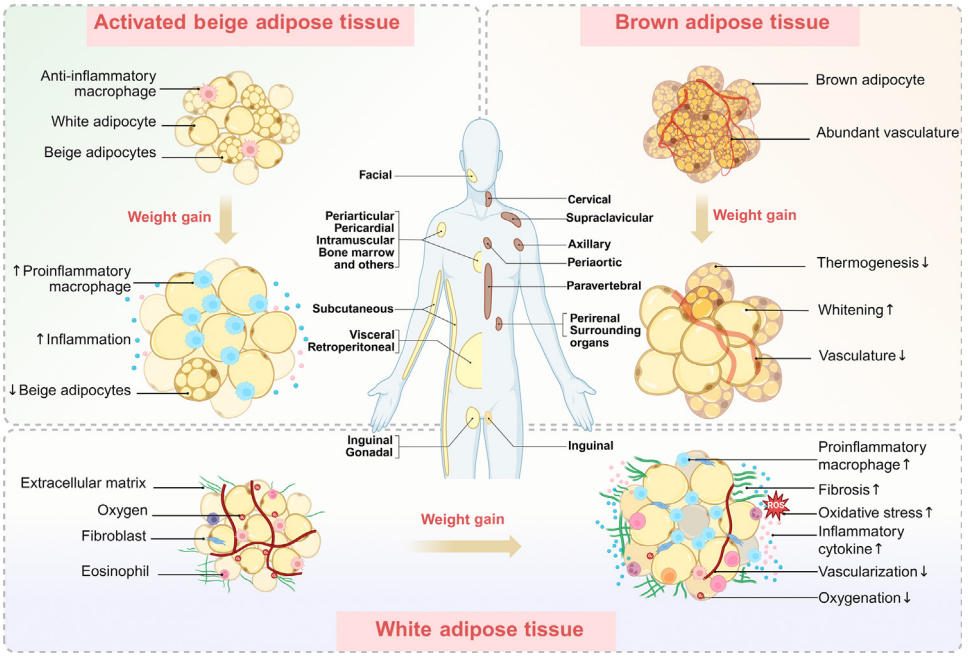

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Figure 1. Pathological changes in adipose tissues during obesity. The adipose tissue is classified into white, brown, and activated beige adipose tissue. In obesity, beige adipose tissue displays reduced brown-like adipocytes, increased proinflammatory macrophages, and inflammation. Brown fat undergoes capillary rarefaction, whitening, and thermogenesis impairment. The white fat becomes highly remodeled, suffering increased inflammation, oxidative stress and fibrosis, decreased vascularization, and poor oxygenation. Figure created using BioRender (http://biorender.com/).

Key figure

Nanocarriers used to target the adipose tissue

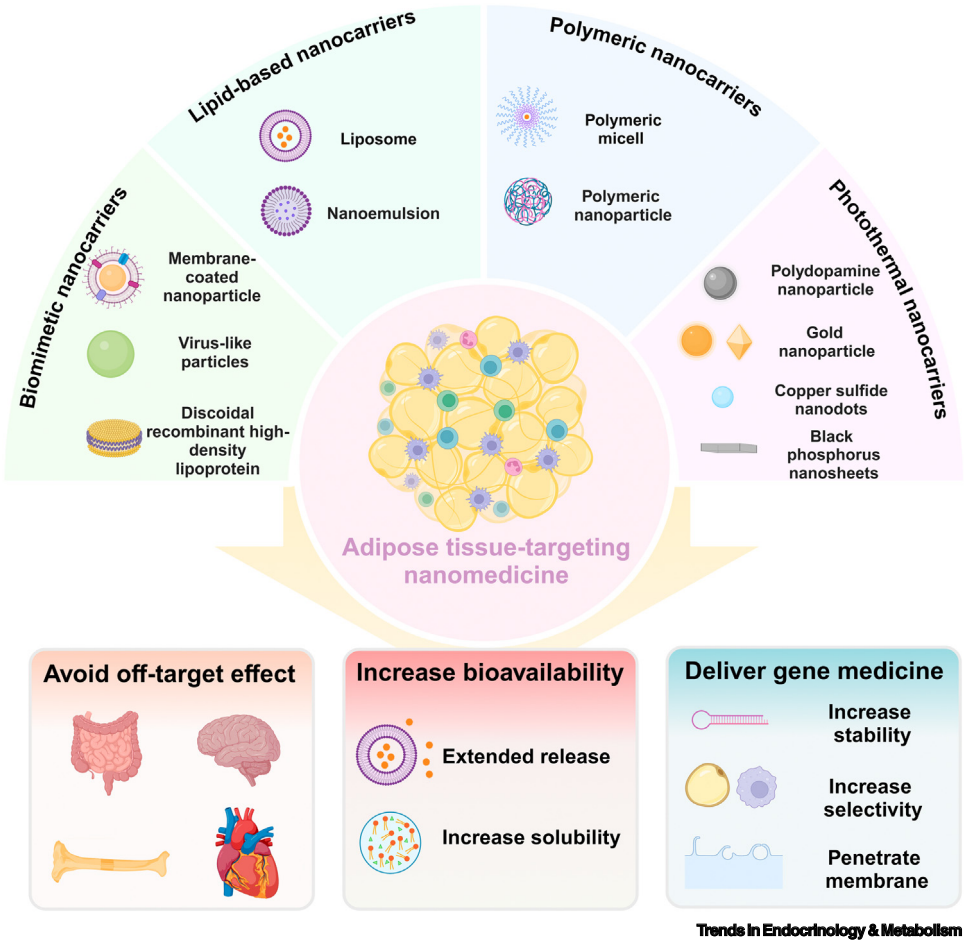

Figure 2. Biomimetic nanocarriers, lipid-based nanocarriers, polymeric nanocarriers, and photothermal nanocarriers are used for adipose tissue-targeting nanomedicines. They can improve drug bioavailability, avoid off-target effects, and improve the efficacy of gene medicine. Figure created using BioRender (http://biorender.com/).

advances in preclinical research on adipose tissue-targeting nanomedicines, aiming to provide valuable insights for future developments in the field.

Active targeting strategies

During obesity, distinct alterations in receptor expression profiles occur in various cell types in both white and brown adipose tissue depots, potentially facilitating the design of nanomedicines targeting these tissues through ligand–receptor recognition (Figure 3 and Table 1).

Endothelial cell-based targeting

The adipose tissue is highly vascularized [21]; thus, vascular endothelial cells may be promising targets for obesity treatment. Prohibitin has been identified as a vascular marker of adipose

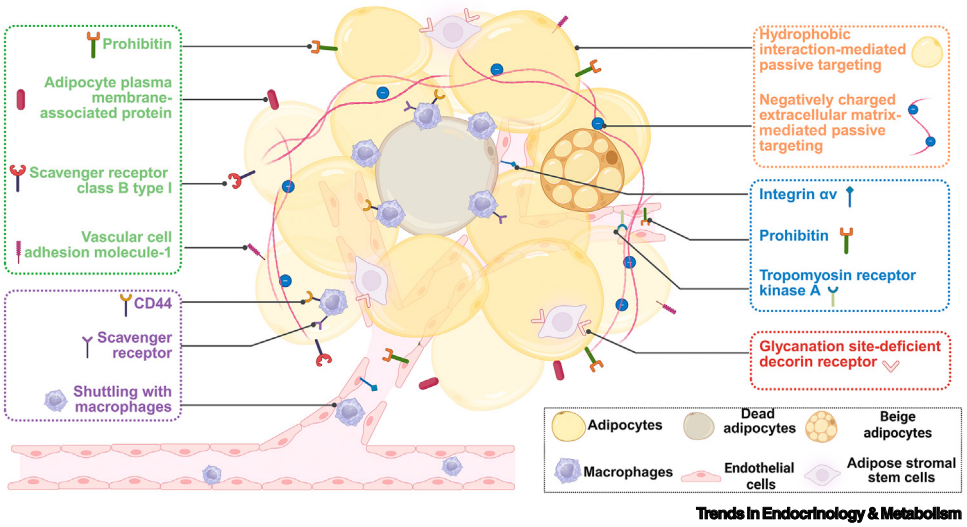

Figure 3. Delivery strategies to target the adipose tissue. Adipose tissue-targeting strategies include active and passive targeting. Active targeting strategies include adipocyte-based targeting (indicated in green), macrophage-based targeting (indicated in purple), endothelial cell-based targeting (indicated in blue), and adipose stromal cell-based targeting (indicated in red). Passive targeting strategies are indicated in orange. Figure created using BioRender (http://biorender.com/).

tissue, and the cyclic peptide CKGGRAKDC, a ligand for prohibitin, demonstrates selective accumulation in subcutaneous fat 150-fold over the peptide-free control [22,23]. Since then, CKGGRAKDC-based nanomedicines have been developed for obesity treatment, showing selective accumulation in adipose tissue depots through increased cellular uptake by endothelial cells [18,24], and used to successfully deliver gene silencing products to the adipose tissue [25–28]. Additionally, the introduction of an additional functional motif, the cell-penetrating octaarginine (R8) peptide, to GKGGRAKDGGC-modified liposomes further increased cellular uptake [29], and a dual-targeting nanosystem mediated by CKGGRAKDC and hyaluronic acid showed a greater distribution in adipose tissue than single-targeted nanomedicines [30]. Since prohibitin facilitates delivery to both mature adipocytes [27] and adipose tissue macrophages (ATMs) [25], this approach could target multiple cell types in adipose tissue depots.

Besides prohibitin, integrin αv on angiogenic endothelial cells has also been tested for adipose tissue targeting. iRGD (CRGDK/RGPD/EC), a ligand for integrin αv, is noted to have potential comparable with that of CKGGRAKDC in targeting adipose tissue [31]. Notably, integrin αv is widely distributed throughout the body, while prohibitin is exclusively expressed on the vasculature of white adipose tissue, making it more suitable for selective white fat targeting. Additionally, the truncated endothelial tropomyosin receptor kinase A is selectively expressed in brown and beige adipose tissues [32], highlighting the potential of its endogenous ligand-mimicking peptide CPATAERPC to target these depots [33]. Although several approaches targeting adipose tissue endothelial cells have been developed, their efficacy may decline with obesity progression due to ongoing vascular rarefaction in adipose tissue [34]. Specifically, the proportion of endothelial cells in adipose tissue is reduced by 50% in individuals with body mass index (BMI) > 40 [35]. Thus, further research is warranted to investigate the clinical potential of these findings.

Adipocyte-based targeting

As obesity progresses, adipocyte membrane receptors change significantly, making adipocytes another potential target for nanomedicines. Scavenger receptor class B type I (SR-BI) is notably

Table 1. Strategies for adipose tissue-targeting nanomedicine[a]

Target	Ligand	Type of nanomedicine	Experimental model	Targeting efficiency (*in vitro*/*in vivo*)	Refs
Endothelial cells – prohibitin	CKGGRAKDC	Virus-like particles	Adipose microvascular endothelial cell	Increases cellular uptake by around twofold	[18]
			ob/*ob* mice (i.v. injection)	Preferentially distributes in abdominal fat, especially mesenteric depot	
Endothelial cells – integrin αv	CRGDK/RGPD/EC	Polymeric nanoparticles	HFD-induced obese mice (i.v. injection)	Preferentially distributes in visceral fat	[31]
Adipocytes – prohibitin	CKGGRAKDC	PLGA nanoparticles	3T3-L1 adipocytes	Increases cellular uptake by around tenfold	[14]
			HFD-induced obese mice (i.v. injection)	Preferentially distributes in visceral fat	
		Liposome	Mouse primary adipocytes	Increases cellular uptake by around tenfold (5% peptide modification ratio)	[11]
			C57BL/6N mice (i.v. injection)	Preferentially distributes in white fat depots	
		Polymeric nanoparticles	C57BL/6J mice (i.v. injection)	Preferentially distributes in subcutaneous fat	[65]
		Polymeric nanoparticles	3T3-L1 adipocytes	Increases cellular uptake by around fivefold (100% feed ratio)	[68]
			HFD-induced obese mice (local injection)	Maintains in injection site (subcutaneous fat) after 72 h	
	CKGGRAKDC-9R	Nanocomplex	HFD-induced obese mice (i.v. injection)	Preferentially distributes in visceral fat	[28]
		Nanocomplex	HFD-induced obese mice (i.p. injection)	Preferentially distributes in visceral fat	[81]
		Nanocomplex	HFD-induced obese mice (s.c. injection)	Preferentially distributes in both visceral and subcutaneous fat	[26]
	GKGGRAKDGGC + R8	Liposome	3T3-L1 adipocytes	Increases cellular uptake by around tenfold	[29]
	CKGGRAKDC + macrophage membrane	Liposome	3T3-L1 adipocytes	Increases cellular uptake by around twofold	[17]
			HFD-induced obese mice model (i.v. injection)	Preferentially distributes in subcutaneous fat	
Adipocytes – VCAM1	Anti-VCAM-1 antibody	Polydopamine	3T3-L1 adipocytes	Increases cellular uptake by 3.8 times	[41]
			HFD-induced obese mice (local injection)	Increases distribution in subcutaneous depots by 1.9 times	
Adipocytes – SR-BI	rHDL	rHDL nanoparticle	C57BL/6J mice (p.o.)	Preferentially distributes in intestine, visceral fat, and liver	[38]
Adipocytes – APMAP	Aptamer adipo-8	Liposome	C57BL/6J nude mice (i.p. injection)	Preferentially distributes in liver	[43]
		Polymeric nanoparticles	3T3-L1 adipocytes	Increases cellular uptake by 2.7 times	[82]
		DNA micro-nanoflowers	C57BL/6J mice (i.p. injection)	Preferentially distributes in liver and visceral fat	[83]
Macrophages	CKGGRAKDC-9R	Nanocomplex	ATMs	Increases cellular uptake by fourfold	[25]
			HFD-induced obese mice (i.p. injection)	Preferentially distributes in visceral fat	
Macrophages – SR	Dextran	Polysaccharide nanocarrier	HFD-induced obese mice (i.p. injection)	Preferentially distributes in visceral fat	[45]

(continued on next page)

Table 1. (continued)

Target	Ligand	Type of nanomedicine	Experimental model	Targeting efficiency (*in vitro*/*in vivo*)	Refs
Macrophages – CD44	Chondroitin sulfate	Micelle	*db*/*db* mice (i.v. injection)	Preferentially distributes in subcutaneous fat	[46]
Macrophages – Dectin-1	Laminarin	Self-assembled nanoparticle	RAW 264.7 cell line	Increases cellular uptake by around ninefold (at 2 h)	[48]
			HFD-induced obese mice (p.o.)	Preferentially distributes in subcutaneous fat	
Macrophages	Yeast	Microcapsule	NA	NA	[47]
ASCs – ΔDCN receptor	CSWKYWFGEC	Lipid nanoparticle	ΔDCN-transduced 3T3-L1 cell	Increases cellular uptake by around 4.7 times	[51]
			ASC from mice inguinal fat	Increases cellular uptake by 3.4 times	
			C57BL/6 J mice (i.v. injection)	Preferentially distributes in white fat depots	
		Gold nanobipyramid	NA	NA	[10]
Passive targeting – electrostatic interaction	Cationic polymer	Polymeric nanoparticles	HFD-induced obese mice (i.p. injection)	Preferentially distributes in visceral fat	[54]
Passive targeting – hydrophobic interaction	Phosphatidylcholine, medium-chain triglyceride, and α-tocopherol	Nanoemulsion	HFD-induced obese mice (i.v. injection)	Preferentially distributes in liver	[12]
			HFD-induced obese mice (i.p. injection)	Preferentially distributes in liver	
			HFD-induced obese mice (local injection)	Preferentially distributes in subcutaneous fat	

[a]Abbreviations: HFD, high-fat diet; i.p., intraperitoneal; i.v., intravenous; NA, not available; p.o., oral; s.c., subcutaneous.

more expressed in white fat than other tissues, and its expression rises with obesity [36]. Biomimetic discoidal recombinant high-density lipoprotein (rHDL) with high specificity for SR-BI was constructed for delivery to adipocytes [37–39]. After oral administration in mice, rHDL highly accumulated in adipose tissue and liver, indicating that SR-BI-targeting nanomedicines do not exclusively accumulate in the fat but show potential to simultaneously improve hepatic steatosis and target the adipose environment. Obese adipose tissue overexpress vascular cell adhesion molecule-1 (VCAM-1) [40] and polydopamine nanoparticles conjugated with anti-VCAM-1 antibody selectively accumulated in adipocytes both *in vitro* and *in vivo* [41]. However, adipose tissue distribution of VCAM-1-targeting nanomedicine increased only by 1.5 times, probably indicating the low expression of VCAM-1 in adipocytes despite its relative upregulation during obesity. Adipo-8, an aptamer with high affinity for adipocyte plasma membrane-associated protein (APMAP) *in vitro* [42], failed to facilitate the accumulation of conjugated nanoparticles in adipose tissues *in vivo* [43], perhaps due to its instability under physiological conditions, as it comprises 87 nucleotides. Therefore, monitoring the stability of ligands during preparation and under physiological conditions is important. Notably, since APMAP plays a key role in adipogenesis, adipo-8 acts as both a targeting motif and an antagonist to reduce fat accumulation. Given that APMAP is more highly expressed in white adipose tissue than in other tissues [44], exploring more stable APMAP-targeting ligands may advance adipose tissue-targeting nanomedicines.

Macrophage-based targeting

ATMs constitute about 40–50% of total cells in the obese adipose tissue and shift to a proinflammatory state, being therefore a potential target for nanomedicine. For instance, proinflammatory

ATMs overexpress dextran-binding C-type lectins and scavenger receptors (SR), allowing preferential accumulation of dextran conjugates, particularly those of 500 kDa molecular weight, in the visceral fat of obese mice [45]. CD44, also overexpressed in obese adipose tissue, serves as a target to deliver nanomedicines to ATMs [46]; compared with bare counterparts, nanoparticles coated with hyaluronic acid, a ligand for CD44, demonstrated a twofold increase in cellular uptake by macrophages and an eightfold enhancement in distribution within the visceral adipose tissue. Other approaches have explored using migrating macrophages to deliver nanomedicines to the adipose tissue during inflammation; since intestinal macrophages can migrate from the gut to other inflammatory sites, nanomedicines have been developed to target these macrophages via nonpathogenic yeast–macrophage [47] and laminarin–Dectin-1 [48] recognition following oral administration. Notably, macrophages play a pivotal role in immune defense and surveillance [49]; therefore, macrophage-targeting nanomedicines for obesity treatment could offer therapeutic benefits but may also trigger immune-related side effects. Identifying specific ATM populations involved in obesity could enhance the precision of this approach.

Adipose stromal cell (ASC)-based targeting

ASCs constitute 15–30% of adipose cells and function as mesenchymal progenitors in the white adipose tissue. The peptide CSWKYWFGEC was demonstrated to specifically targets ASCs by binding to the non-glycanated decorin isoform (ngDCN) on their surface in both rodents and humans [50]. Compared with non-targeted nanoparticles, CSWKYWFGEC peptide-conjugated nanoparticles accumulated 3.4 times more in ASCs of inguinal adipose tissue while overall accumulation in inguinal fat increased only 1.8 times [51], suggesting that targeting of other cell types like adipocytes and macrophages might be more effective. Notably, a different study suggested that the CSWKYWGFEC peptide can also be recognized by mature adipocytes [10].

Hydrophobic interaction- and electrostatic interaction-mediated passive targeting

The unique physicochemical properties of the obese adipose tissue offer opportunities to reach this organ via passive targeting mechanisms. As obesity advances, lipid droplets and excess extracellular matrix endow the adipose tissue with a lipophilic and anionic character, aiding in targeting through hydrophobic and electrostatic interactions. Recently, a nanoemulsion comprising phosphatidylcholine, medium-chain triglyceride, and α-tocopherol was developed to target adipose tissues. Following subcutaneous injection in obese mice, 87.28% of the nanoemulsion accumulated in the subcutaneous fat, likely due to the natural affinity of adipocytes for lipid-like nanoemulsions [12]. Another study found that esterified 2,4-dinitrophenol, due to its higher lipophilicity, exhibited increased permeability and affinity in various adipose tissue depots [52]. Similarly, lipid-coated mesoporous silica nanoparticles showed strong retention in subcutaneous fat even 48 h post-injection [53]. On the other hand, the cationic dendrimer polyamidoamine's third generation (P-G3) and branched polyethyleneimine were preferentially distributed in the visceral fat of obese mice via electrostatic interactions following intraperitoneal injection. Lipophilic nanoparticles comprising P-G3 derivative showed increased distribution to the adipose tissue and reduced liver distribution, highlighting the benefits of combining cationic and lipophilic properties [54]. Notably, linear polyethyleneimine with weak cationic charges showed a reduced yet present visceral fat preference, indicating that the targeting efficiency depends on the charge density and molecular structure of cationic carriers [54]. However, electrostatic targeting poses a higher safety risk than hydrophobic targeting, as strong cationic charges can harm biological membranes. Thus, the balance between efficacy and toxicity needs careful future assessment. Alternatively, modifying nanoparticle surface properties, such as electrical charge and hydrophilicity/lipophilicity, may offer promising potential for the development of optimal nanocarriers for adipose tissue-targeting obesity treatment.

Anti-obesity efficacy and potential mechanisms of adipose tissue-targeting nanomedicines

Activating thermogenesis

Traditional anti-obesity drugs aim to restore energy balance by targeting the intestines or central nervous system to reduce energy absorption and intake, often causing serious side effects [55]. Several drugs, like AMPK and PPARγ agonists, and endogenous hormones, promote beige fat browning to boost energy expenditure [56], but their clinical use is limited by poor effectiveness and systemic toxicity. As a therapeutic alternative, adipose tissue-targeting lipid nanoparticles can address the challenges of the low aqueous solubility and limited bioavailability of resveratrol, resulting in an approximately twofold enhancement in thermogenesis induction via the AMPK/SIRT1 signaling pathway (Figure 4) [51]. Similarly, CKGGRAKDC-decorated liposomes loaded with rosiglitazone effectively facilitated browning by activating PPARγ, achieving an efficacy more than three times greater than that of free rosiglitazone [29]. Furthermore, adipose tissue delivery of triiodothyronine is more effective in promoting white adipose tissue browning, reducing adiposity, and nearly completely mitigating systemic side effects, including cardiac toxicity, bone loss, and

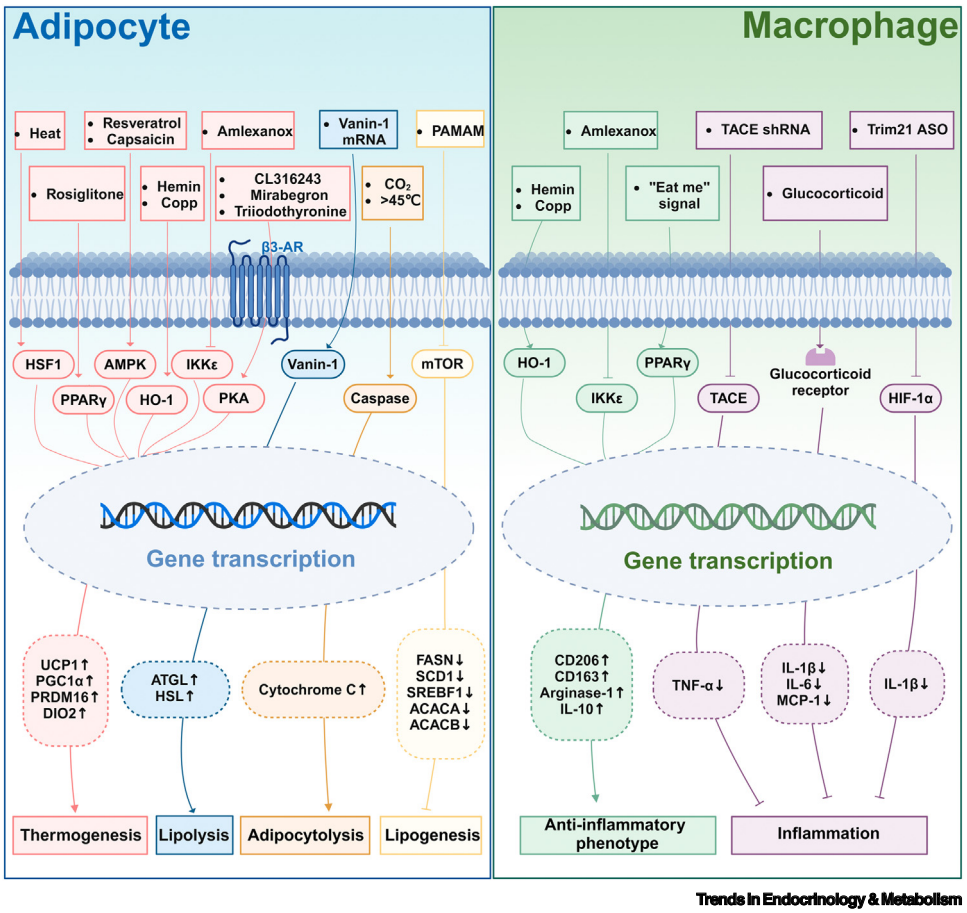

Figure 4. Therapeutic mechanisms of adipose tissue-targeting nanomedicines. Nanomedicines regulate energy homeostasis by targeting adipocytes to influence thermogenesis, lipolysis, adipocytolysis, and lipogenesis through the regulation of multiple signaling pathways. Moreover, relieving inflammation by targeting macrophages to promote an anti-inflammatory phenotype or inhibit inflammation could efficiently inhibit obesity. Abbreviations: AMPK, AMP-activated protein kinase; HIF-1α, hypoxia-inducible factor 1-alpha; HO-1, heme oxygenase-1; HSF1, heat shock transcription factor 1; IKKε, I kappa-B kinase epsilon; mTOR, mammalian target of rapamycin; PPARγ, peroxisome proliferator-activated receptor gamma.

neuroendocrine circuit disruption [11]. Beyond pharmaceutical approaches, triggering thermogenesis through local hyperthermia (41 °C) in beige fat may also pose a therapeutic approach [19]. Likewise, photothermal agents in the near-infrared region (NIR-I) like polydopamine nanoparticles [57] and IR780-loaded nanoparticles [58,59] have been locally used to raise the temperature of inguinal white fat to 41–45°C to induce browning. However, NIR-I light has limited tissue penetration [60]; using copper sulfide nanodots with high NIR-II photothermal efficiency has been shown to induce browning of subcutaneous adipose tissue up to 6 mm deep [61]. Similarly, magnetic induction hyperthermia induced by gold nanoclusters with high penetration significantly increased *Ucp1* and *Prdm16* mRNA expression in adipocytes [62]. Remarkably, applying local hyperthermia to the supraclavicular fat depot in human volunteers also enhanced thermogenesis, highlighting its clinical translation potential [19]. Future research should focus on creating nanomedicines with precise temperature control and/or adipocyte-specific targeting to minimize side effects on other organs and cells.

While gene regulation for thermogenesis may be another option to induce browning, gene editing in mature adipocytes is difficult due to their high lipid content and limited ability to proliferate. To overcome this challenge, a lipid-tolerant fluoropolypeptide was synthesized to condense TLE3 siRNA, effectively knocking down the TLE3 gene and boosting thermogenic gene expression in mature adipocytes [16]. Unlike nucleic acid-based gene editing, hydrophobic small molecules with gene-regulating abilities are more stable and tend to remain in the adipose tissue for sustained stimulation. For instance, iron and cobalt protoporphyrin IX, strong inducers of heme oxygenase-1 (HO-1), were delivered to adipose depots via CKGGRAKDC-modified PLGA nanoparticles, significantly boosting HO-1 expression and the downstream thermogenic transcriptional cascades, doubling browning effects compared with free drugs. [14]. Adipose tissue-targeting amlexanox also showed promise in increasing UCP1 expression by modulating the I kappa-B kinase epsilon (IKKε) and TANK-binding kinase 1 (TBK1) pathways. Additionally, new browning strategies, like using menthol to activate cold sensors on white adipocytes [63] and nitric oxide injections to stimulate brown fat [64], are gaining interest.

Inducing lipolysis

Lipolysis is another approach to regulate energy homeostasis through noncytolytic and cytolytic methods. Noncytolytic lipolysis mobilizes lipids without harming adipocytes. Vascular noninflammatory molecule-1 (Vanin-1), an oxidative stress sensor, is a potential target for its connection to lipolysis. Overexpression of Vanin-1 using adipose tissue-targeting polymeric nanoparticles significantly enhanced lipolysis in mouse abdominal white fat, thereby reducing body weight and fat mass [65]. While noncytolytic lipolysis is safe, its fat reduction effect is temporary. Conversely, cytolytic methods permanently destroy fat cells, although they cause severe side effects like edema and bruising. Therefore, targeting strategies are essential. Adipose tissue-targeting nanomedicines are often used to reduce fat by triggering photothermal and photodynamic damage. For example, CKGGRAKDGGC-decorated hollow gold nanospheres were used for transdermal photothermal lipolysis to target subcutaneous fat with reduced side effects [66]. CSWKYWFGEC- and phosphatidylserine (PS)-decorated gold nanobipyramids induced macrophage-mediated apoptosis and NIR laser-mediated thermal damage in adipocytes [10]. Aggregation-induced emission luminogens (AIEgens), which naturally bind to lipid droplets, were also used to reduce subcutaneous depots via photodynamic therapy [67]. In addition, calcium carbonate-loaded nanoparticles with adipocyte-targeting peptide can induce adipocytolysis by generating carbon dioxide in late endosomes/lysosomes without significant changes in hematological or serum biochemical parameters [68]. However, these cytolytic methods often trigger local inflammation even with targeting approaches, necessitating combination use of anti-inflammatory strategies. Thus, noncytolytic and cytolytic methods should be carefully selected based on a thorough evaluation to balance therapeutic efficacy and safety.

Relieving inflammation

The adipose tissue environment is key to obesity progression and associated disorders, making it a promising therapeutic target. Chronic low-grade inflammation on obesity, driven by an imbalance between proinflammatory and anti-inflammatory signals, is a known contributor to metabolic disorders. Direct suppression of proinflammatory mediators and stimulation of endogenous pro-resolving pathways is being explored to relieve inflammation [69]. To reduce proinflammatory mediators, CKGGRAKDC-conjugated chitosan nanomicelles and ATS-9R-based nanocomplex have been developed to selectively deliver TNF-α shRNA, MCP-1 shRNA [70], and MCP-1 siRNA [71] to the adipose tissue, significantly reducing inflammatory cytokines, improving glucose intolerance and insulin resistance. Dual cytokine-targeting therapies exhibited greater potential than single-target treatments [70,72]. Multi-mechanism anti-inflammatory drugs like glucocorticoid have shown limited clinical benefits in obese patients due to side effects like Cushing's syndrome. Adipose tissue-specific glucocorticoid delivery via dextran nanocarriers reduced the therapeutic dose from 5 mg/kg to 0.7 mg/kg, improving therapeutic outcomes with minimal side effects after prolonged treatment. Additionally, inhibition of inflammatory cytokine production and their downstream pathways present alternative targets. Nanomedicines loaded with short hairpin RNA targeting TNF-α-converting enzyme [25] and antisense oligonucleotides for E3 ubiquitin ligase tripartite motif-containing 21 [73] were applied to inhibit TNF-α and IL-1β production. Anti-VCAM-1 antibody-decorated nanoparticles loaded with amlexanox selectively block TNF-α-activated IKKε and TBK1 pathways in adipocytes, restricting the downstream effects of TNF-α [41]. Alternatively, supplying anti-inflammatory cytokine by IL-10-conjugated liposomes also significantly inhibits inflammation [74]. Notably, the inflammatory microenvironment in the adipose tissue is regulated by multiple biomolecules from various cells, not just single cytokines. Thus, targeting cells involved in inflammatory responses may offer a more effective treatment.

To mimic natural pro-resolving pathways, converting proinflammatory macrophage in the obese adipose tissue to an anti-inflammatory phenotype may pose a potential strategy. PS-liposomes, mimicking apoptotic cells with an 'eat me' signal, can be engulfed by macrophages and induce this polarization [10], altering the balance between pro- and anti-inflammatory macrophages, reducing body weight in obese mice by 24.4% and minimizing weight regain, highlighting the importance of immunomodulation in obesity treatment. Furthermore, gene editing can switch macrophage phenotypes. Targeted induction of HO-1 or inhibition of IKKε and TBK1 in adipose tissue depots significantly shifts the macrophage balance towards anti-inflammatory phenotypes [14]. Adipocytes also influence the inflammatory environment via cytokine secretion and interaction with macrophages; thus, future strategies should target both adipocytes and macrophages to better manage inflammation.

Regulating endothelial cells

Obesity is associated with impaired blood flow, endothelial dysfunction, and reduced vascular density, causing hypoxia, inflammation, and fibrosis in adipose tissue [34]. Targeting vascular development could treat obesity, but it is unclear whether antiangiogenesis or angiogenesis is more effective. Some research focuses on using proapoptotic agents to destroy blood vessels of adipose depots and limit fat growth [22,75,76], while others propose increasing capillary density to enhance oxygen supply and energy expenditure [17,31]. We believe angiogenesis strategies are safe and more efficient for delivery, as they are less prone to off-target effects than antiangiogenesis, which may cause hypoxia and inflammation. Additionally, well-vascularized adipose tissue resembles a healthy state and offers better opportunities for tissue-targeting nanomedicines.

Combined treatment strategies

As obesity progression is associated with various pathological changes at the adipose tissue, combined therapeutic strategies targeting multiple dysfunctions may offer better management. Nanomedicine approaches with dual functional modules addressing different adipose tissue dysfunctions outperform single treatments. Recently, a nanosystem was developed to simultaneously alleviate endoplasmic reticulum and oxidative stress in adipocytes, achieving anti-obesity efficiency comparable with FDA-approved 10% deoxycholic acid in mice [12]. Likewise, combining reactive oxygen species (ROS) scavenging with rosiglitazone-induced browning resulted in significant weight loss and glucose intolerance improvement [77]. Moreover, combining hyperthermia-induced lipolysis with inflammation relief [30] or thermogenesis activation [78] also exhibited synergistic anti-obesity effects. Thus, the potential of combining multiple antiobesity strategies with synergistic effects is worth further research.

Concluding remarks and future perspectives

The adipose tissue acts as both an energy reservoir and an endocrine organ by releasing adipokines, significantly influencing obesity and its associated comorbidities. Recently, nanomedicines targeting the adipose tissue to promote browning and reduce inflammation have effectively restored metabolic balance with minimal side effects in preclinical studies. However, the targeting efficiency and tissue distribution of adipose tissue-targeting nanomedicines are often inconsistent. Thus, it is necessary to elucidate the predominant factors that govern their tropism and retention, including nanocarrier type, ligand density, and particle size (see Outstanding questions). Furthermore, future studies should also focus on other pathological alterations in the obese adipose tissue, such as fibrosis, oxidative stress, and hypoxia. Exploring the interactions between these pathological changes can offer insights for the development of synergistic strategies. Furthermore, cellular targets like mitochondria and the endoplasmic reticulum, whose disorders underlie pathological changes in the adipose tissue, are also worth exploring for obesity treatment.

Adipose tissue-targeting nanomedicines currently present several challenges, particularly scalability and quality control, which need to be addressed urgently. Simplifying their fabrication or isolating natural bioactive vesicles is preferable, and establishing standardization guidelines is essential. Furthermore, the full extent of the effects of nanomedicines on the body is unclear due to complex immunological and biological factors. Future studies should evaluate the therapeutic effects and adverse events of nanomedicines using standardized animal models. Additionally, due to genetic diversity and varying obesity etiology among patients, personalized strategies are expected in the development of adipose tissue-targeting nanomedicine. Despite numerous challenges, we propose that adipose tissue-targeting nanomedicines represent a superior alternative to conventional pharmacotherapy for obesity treatment; for instance, targeting the regulation of adipose tissue shows promise in mitigating rebound weight gain, as adipose tissue remodeling is a critical factor favoring this process [79]. Notably, ARO-ALK7, an adipose tissue-targeting siRNA delivery system, demonstrated dual benefits of reducing body weight while preserving lean mass [80], thereby addressing a key limitation associated with NuSH-based therapeutics. Furthermore, we anticipate that combining adipose tissue-targeting nanomedicines with pharmacological therapies could present a novel therapeutic paradigm, as evidenced by coadministration of ARO-ALK7 with tirzepatide inducing synergistic weight loss without compromising lean mass[i]. Expanding adipose tissue-targeting nanomedicines options, particularly focusing on gene editing and oral delivery, is crucial for broader patient access and improved efficacy.

Outstanding questions

Since obesity is a chronic condition requiring prolonged treatment, can adipose tissue-targeting nanomedicines effectively manage obesity on a large scale over an extended period in a cost-effective and patient-friendly manner?

How can these adipose tissue-targeting nanomedicines optimize the use of existing anti-obesity medications with maximized efficacy and minimized side effects? Can they work synergistically with current treatments?

Can organ crosstalk mechanisms be harnessed to regulate whole-body energy homeostasis via adipose tissue-targeting nanomedicines therapies, beyond just aiding weight loss?

Will adipose tissue-targeting nanomedicines retain their specificity and effectiveness in larger mammals or humans? What strategies can address the challenges of translating these preclinical therapies into clinical use?

Can adipose tissue-targeting nanomedicines be tailored to the pathophysiology of different obesity stages, and can biomarkers like metabolic signatures and genetic profiles guide their selection?

Acknowledgments

This work was supported by the National Natural Science Foundation of China (82370869, 82170874, and 82025007) and Youth Foundation from Sichuan Province (2023NSFSC1541 and 2023NSFSC1543).

Declaration of interests

The authors declare no competing interests.

Resources

[i]https://ir.arrowheadpharma.com/static-files/d8586ad7-50f8-4973-9576-e49542a893e7

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