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REVIEW

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Innovative gene therapy strategies for tackling obesity

Motahareh Sheikh-Hosseini[1], Mohammad Moarefzadeh[2], Alyaa Abdulhussein Alsaedi[3,4], Ahmed M. Amshawee[5], Sahar Kareem Al-Mozani[6], Ahmed Yaseen Abed[7], Mostafa Neissi[8,9*] and Peyvand Parhizkar Roudsari[10]

Abstract

Obesity is characterized by an excessive accumulation of body fat, resulting from an imbalance where biochemical processes related to fat synthesis outpace those responsible for energy expenditure. Genetic predisposition plays a significant role in the susceptibility to obesity. In this context, gene therapy presents a promising approach to address obesity as a global health concern by modulating gene expression to favor energy consumption and lipolysis, leading to fat reduction and the restoration of energy homeostasis. Recent advancements in gene therapy for obesity have leveraged novel vectors and delivery systems. Emerging approaches also use zinc finger proteins, small interfering RNAs, and self-cleaving ribozymes to modulate gene expression. Despite significant progress, several challenges remain in optimizing gene therapy for obesity. Key considerations include the selection of appropriate target genes, understanding long-term effects, ensuring the safety of gene transfer methods, conducting comprehensive preclinical studies, and developing strategies to mitigate potential side effects such as the random insertion of virus-borne transgenes and associated toxicity. Ongoing research and technological innovations will be essential in overcoming these challenges and translating gene therapy into a viable clinical solution for managing obesity.

Keywords Genes, Gene therapy, Novel approach, Obesity, Therapeutic strategy

Introduction

Obesity encompasses a diverse group of conditions and is a complex, multifactorial disorder characterized by an imbalance between caloric intake and expenditure, resulting in excessive fat accumulation. Therefore, obesity is defined as an increase in fat mass that negatively impacts health. Genetic factors and behavioral habits are closely linked to obesity [1].

Obesity can be classified into primary and secondary types. Primary obesity is generally attributed to lifestyle and behavioral factors, while secondary obesity is associated with medical conditions such as endocrine disorders, medications, or genetic syndromes [2]. Genetic obesity can be further divided into monogenic forms (e.g., leptin or melanocortin-4 receptor (MC4R) deficiencies) and syndromic forms (e.g., Prader–Willi syndrome) [3]. These genetic variants interfere with the energy balance pathways, contributing to severe early-onset obesity.

*Correspondence:
Mostafa Neissi
iammostafaneissi@gmail.com
[1] Pediatric Cell & Gene Therapy Research Center, Tehran University of Medical Sciences, Tehran, Iran
[2] Lorestan University of Medical Sciences, Lorestan, Iran
[3] Department of Microbiology, Collage of Veterinary Medicine, University of Al-Qadisiyah, Al Diwaniyah, Iraq
[4] School of Industrial Technology, University Sains Malaysia, Penang, Malaysia
[5] Department of Radiology, College of Health and Medical Technology, University of Hilla, Babylon, Iraq
[6] Department of Biology, University of Misan, Misan, Iraq
[7] Department of Medical Laboratories Techniques, College of Health and Medical Technology, University of Al Maarif, Al Anbar 31001, Iraq
[8] Department of Genetics, Khuzestan Science and Research Branch, Islamic Azad University, Ahvaz, Iran
[9] Department of Genetics, Ahvaz Branch, Islamic Azad University, Ahvaz, Iran
[10] Tehran University of Medical Sciences, Tehran, Iran

Patients with genetic obesity often show inadequate responses to conventional treatments such as diet, exercise, or pharmacotherapy [4]. Gene therapy provides a promising targeted approach by addressing specific genetic abnormalities. For example, MC4R gene therapy [5] and leptin gene therapy [6] are critical interventions for reestablishing metabolic balance in patients with inherited obesity syndromes.

Multiple genes regulate the expression of proteins and enzymes responsible for metabolic homeostasis, and defects in these genes can contribute to obesity [4]. Environmental factors, such as increased food intake and reduced energy expenditure, also significantly influence obesity risk. Dietary habits, including high-carbohydrate intake, low physical activity, and sedentary behaviors like television watching, along with sociocultural influences, all elevate the risk of obesity. Additionally, restrained eating, as a psychosocial factor, appears to play a role in the etiology of obesity [1].

Research shows that obese individuals face a higher risk of health complications compared to those with normal weight [2]. Obesity is associated with numerous disorders, including cardiovascular diseases (e.g., hypertension, coronary heart disease, cerebrovascular disease, varicose veins, and deep venous thrombosis) and respiratory conditions (e.g., sleep apnea, breathlessness, and hypoventilation syndrome). Additionally, obesity contributes to metabolic disorders (e.g., hyperlipidemia, diabetes, insulin resistance, and menstrual irregularities), gastrointestinal issues (e.g., fatty liver, cirrhosis, hemorrhoids, hernia, colorectal cancer, and gallstones), and various malignancies (e.g., breast, endometrial, prostate, and cervical cancers) (Fig. 1) [7]. Obesity also negatively affects psychological well-being and cognitive function, with recent studies showing links to mood disorders, particularly depression [8].

Obesity can be assessed through various methods, including anthropometry, bioelectrical impedance analysis, densitometry, and imaging, with body mass index (BMI) being the most widely used [2]. Higher BMI levels are associated with increased risks of hypertension, type 2 diabetes, and cardiovascular diseases [3]. Treatment strategies for obesity include dietary and physical activity modifications, pharmacotherapy, and bariatric surgery [2]. Measuring BMI and waist circumference helps evaluate risk factors, guiding the most suitable treatment approach [7].

Dietary therapy is the primary approach for most individuals, except in cases such as pregnancy, lactation, or osteoporosis. Low-calorie diets (LCDs) and very-low-calorie diets (VLCDs) are common calorie-restriction methods. Meal replacement programs like Optifast and Medifast are also available and are considered safe for

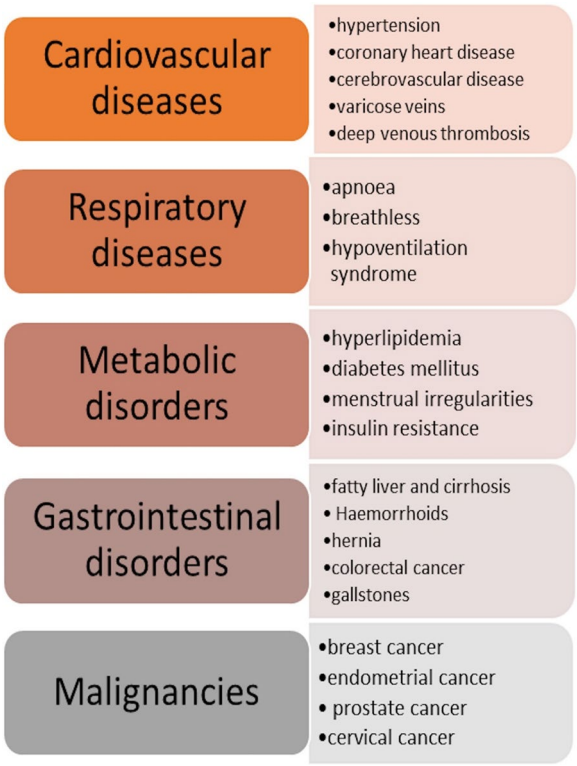

Fig. 1 Related diseases to obesity. Some related diseases to obesity include: cardiovascular diseases (hypertension, coronary heart disease, cerebrovascular disease, varicose veins, deep venous thrombosis), respiratory diseases (apnea, breathless, hypoventilation syndrome), metabolic disorders (hyperlipidemia, diabetes mellitus, menstrual irregularities, insulin resistance), gastrointestinal disorders (fatty liver and cirrhosis, hemorrhoids, hernia, colorectal cancer, gallstones), and malignancies (breast cancer, endometrial cancer, prostate cancer, cervical cancer)

weight reduction [7]. Diets high in protein, with low glycemic and fat indices and lower carbohydrate content, aid in maintaining weight loss. Adherence to these diets is essential for long-term weight management, and they should promote lasting health benefits [2].

Physical activity plays a key role in boosting energy expenditure, reducing fat storage, and supporting energy balance. Studies indicate that regular exercise improves cardiovascular fitness and mental well-being [7]. Gradual increase in aerobic activity is recommended for obese patients, as exercise also lowers the risk of diabetes and cardiovascular disease. For long-term weight maintenance, 60–90 min of daily exercise may be necessary. Exercise is one of the most effective strategies for obesity prevention, helping to reduce mitochondrial dysfunction by balancing mitochondrial dynamics and mitophagy, though the exact mechanism remains unclear [9].

Drug treatment is another strategy for managing obesity, recommended as an adjunct to diet and exercise for

moderate- to high-risk patients [2]. FDA-approved medications for long-term weight management include Orlistat, lorcaserin, liraglutide, diethylpropion, phentermine, phendimetrazine, benzphetamine, phentermine–topiramate extended release, and naltrexone–bupropion sustained release. These medications primarily aid in dietary adherence, although only Orlistat and cetilistat specifically support low-fat diets. If a 4–5% reduction in body weight is not achieved within three months, the drug should be discontinued in favor of alternative strategies [2].

Gastric partitioning and gastric bypass are surgical procedures used to treat obesity, typically recommended when other methods have failed and BMI is excessively high. These surgeries can positively impact lipid levels, diabetes, and hypertension associated with severe obesity. However, they may also lead to complications such as nutritional deficiencies and intractable vomiting. Late complications can include gallstone formation in about 10% of patients, hair thinning, and excess skin [10].

Additional strategies for treating obesity are under investigation, including precision drugs, antibody therapies targeting mediators, bioactive compounds for metabolic effects, oxygen therapy to modulate appetite, and gene therapy [2].

Gene therapy, a novel treatment with potential benefits across various medical fields, can correct altered genes and enable site-specific modifications for therapeutic purposes [11]. Advances in understanding the molecular basis of obesity and related diseases position gene therapy as a promising strategy. It aims to increase or decrease gene products, resulting in fat reduction and improved energy homeostasis [4].

Obesity arises from biochemical processes involving enzymes and genes that regulate metabolic homeostasis and occurs when fat synthesis and accumulation exceed energy expenditure. Gene transfer aims to produce essential proteins that maintain metabolic balance by blocking fat accumulation and enhancing energy expenditure [4].

Literature search strategy

A comprehensive literature review was performed using the PubMed, Scopus, and Google Scholar databases to identify English-language articles published till November 1, 2024. The search strategy incorporated key terms, including Obesity, Gene therapy, Gene transfer techniques, Novel therapeutic strategies, Genes, Biomarkers, and Therapeutic applications. Abstracts were screened for relevance, and the full texts of eligible studies were retrieved and analyzed. To ensure a thorough review, the reference lists of selected articles were also examined to identify additional pertinent publications (Fig. 2).

An overview on obesity as a disorder of energy homeostasis

Two major environmental factors closely associated with obesity are diet and lifestyle. High-fat diets (HFDs) often lead to excessive energy intake due to their appealing taste, particularly when combined with insufficient physical activity. Biochemically, obesity is characterized by fat storage exceeding permissible limits, resulting from processes involving enzymes and genes that regulate metabolic homeostasis. Obesity develops when fat synthesis and accumulation outpace energy expenditure [12]. Genetic defects in the coding or regulatory sequences of proteins responsible for lipid accumulation and consumption contribute to obesity. Consequently, current trends in treatment focus on blocking lipid accumulation and increasing energy expenditure. A gene therapy-based approach aims to transfer coding or non-coding sequences to produce essential proteins that help re-establish and maintain metabolic homeostasis [13].

Role of genetic factors in highly variable individual susceptibility to weight gain

Obesity is influenced by complex interactions among developmental, behavioral, genetic, and environmental factors. Evidence from family, twin, and adoption studies indicates a significant genetic component, with heritability estimates for BMI ranging from 0.71 to 0.86. Heritability reflects the proportion of total phenotypic variance attributable to genes within a specific environment, and these estimates can vary over time and between populations [3]. A study involving 45 twin cohorts from 20 countries, aged 0.5 to 19.5, confirmed that environmental factors shared by co-twins influence BMI during childhood; however, their impact diminishes by late adolescence. The findings indicate that genetic factors predominantly contribute to BMI variation in adolescence across populations of diverse ethnicities, even when exposed to varying obesity-related environmental factors [14]. Although the high heritability of obesity-related phenotypes underscores the genetic influence, it does not clarify the number of genes involved or their interactions with environmental factors [3].

Pathways of key genes in regulating energy homeostasis

Leptin as a main regulator of energy homeostasis

Human studies have demonstrated a strong positive correlation between leptin mRNA concentrations in adipose tissue and serum leptin levels with fat mass, indicating that leptin primarily signals increasing energy stores [6]. However, many individuals exhibit resistance to both endogenous and exogenous leptin. In fact, leptin's physiological role in humans and mice appears to signal

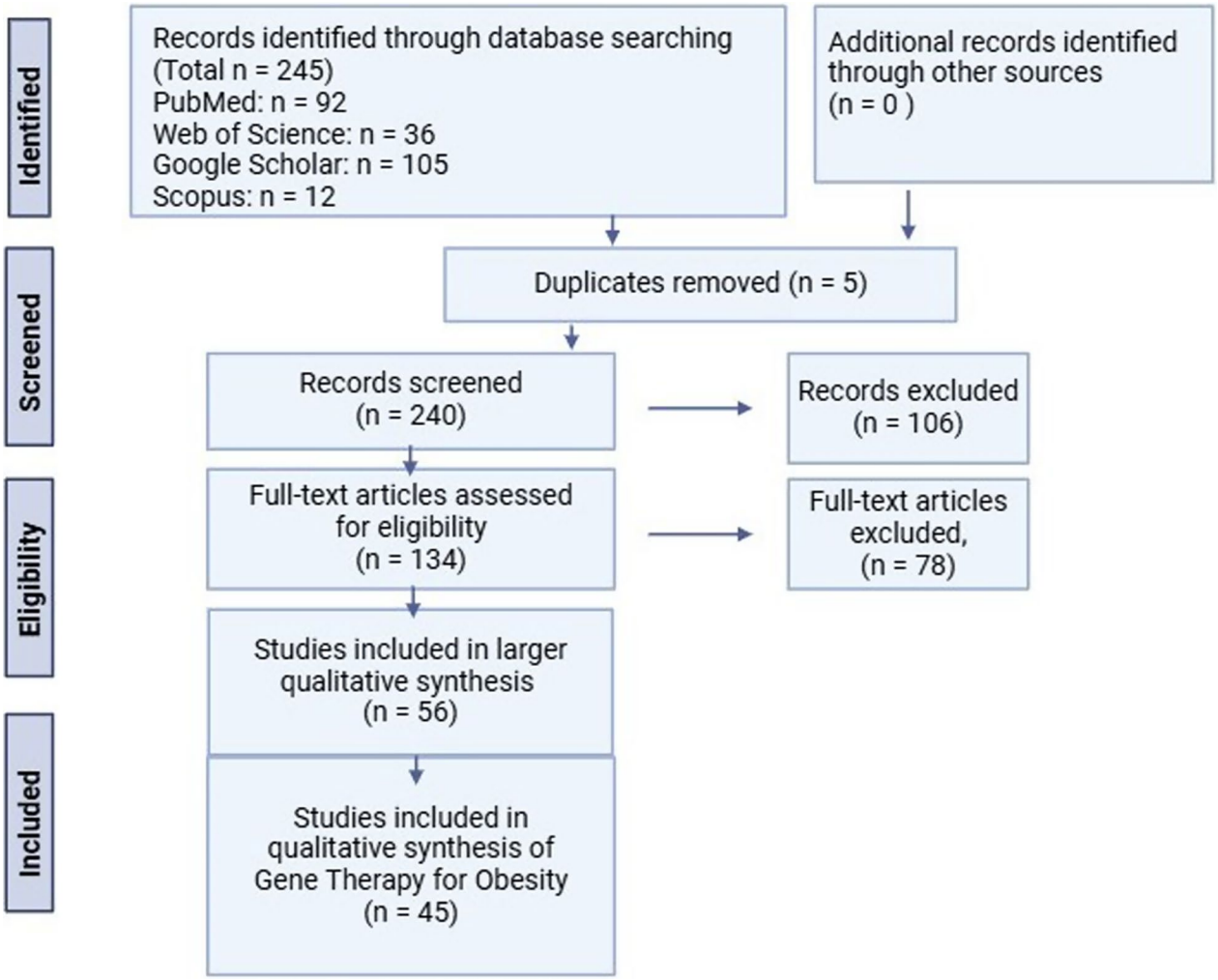

Fig. 2 A PRISMA diagram illustrating the process of identifying the articles that were included in the study

nutritional deficiency; for instance, fasting or weight loss leads to decreased leptin levels, which subsequently triggers changes in energy expenditure, energy intake, and neuroendocrine function to maintain energy homeostasis [15] (Fig. 3).

Melanocortin peptides and their receptors

Leptin activates primary neurons in the hypothalamus that express pro-opiomelanocortin (POMC). This precursor is post-translationally processed to produce melanocortin peptides, including alpha, beta, and gamma melanocortin-stimulating hormone (MSH), which act as agonists at melanocortin 3 and 4 receptors (Mc3r and Mc4r) on second-order neurons. Leptin signaling influences energy balance through both melanocortin-dependent and melanocortin-independent pathways. These hypothalamic pathways interact with other brain regions to regulate energy intake and expenditure [16].

The role of critical genes in obesity

Genes involved in controlling food intake

Balanced activity among genes that code for proteins and enzymes regulating food intake, fat storage, and metabolism is crucial, along with the genes that control their expression. Numerous genes are associated with susceptibility to human obesity, including leptin, leptin receptor, POMC, Mc4r, and proprotein convertase subtilisin/kexin, all of which play significant roles in appetite regulation (Fig. 4) [17].

Leptin, a protein hormone produced by adipose tissue, indicates adipose mass and regulates appetite by inhibiting neuropeptide Y and agouti-related peptide while promoting the action of alpha MSH. Leptin signaling influences energy intake to maintain energy homeostasis, and dysfunction in this pathway can trigger a strong urge to eat. Leptin binds to its receptor and regulates hunger sensations [16]. It stimulates primary neurons

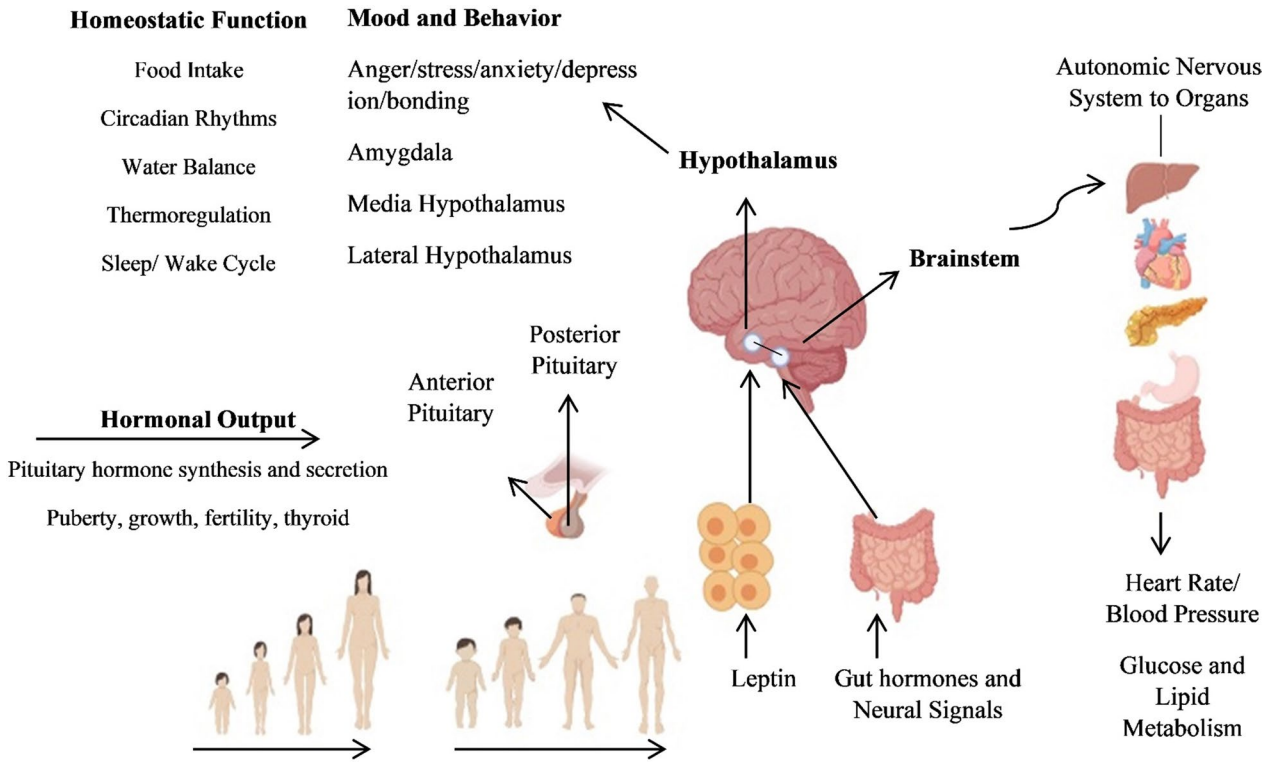

Fig. 3 Leptin as a Main Regulator of Energy Homeostasis. Leptin signals nutritional depletion and initiates changes in energy expenditure, intake, autonomic nervous system tone, and neuroendocrine function to conserve energy. The hypothalamus coordinates these processes, regulating circadian rhythms, temperature, sleep, and behaviors such as anger, stress, anxiety, and aggression via connections to the amygdala and periaqueductal gray (PAG). Through direct and indirect pathways to the brainstem and cortex, hypothalamic neurons modulate ANS tone, influencing metabolic processes in the liver, heart, pancreas, and gut. Beyond energy homeostasis, leptin also plays critical roles in immune function and puberty

in the arcuate nucleus of the hypothalamus that express POMC, which produces melanocortin peptides such as adrenocorticotropic hormone (ACTH) and alpha, beta, and gamma MSH [18]. These peptides act as agonists at Mc3r and Mc4r, regulating energy through both melanocortin-dependent and independent pathways. These pathways interact with other brain centers to coordinate energy intake and expenditure. Impairments in the POMC gene can lead to severe early-onset obesity [18]. Additionally, the synergic effect of single nucleotide polymorphism (SNP) risk alleles in obesogenic genes, such as the fat mass and obesity-associated protein (FTO) and Mc4r, influences the obese phenotype in Greek children and adolescents [19]. Targeted disruption of the Mc4r gene has been linked to obesity in mice, while a frameshift mutation in Mc4r is associated with inherited obesity in humans [5]. Furthermore, adipose tissue-driven macrophage chemotaxis promoted by proprotein convertase subtilisin/kexin type 3 can exacerbate obesity [20]. Proprotein convertase subtilisin/kexin 1 (PCSK1) is essential for the post-translational processing of POMC, and defects in PCSK1 can lead to obesity. The genes mentioned are crucial in regulating eating behavior and food intake, and any defects or imbalances in their expression can result in severe obesity in humans [20].

Genes involved in energy expenditure

Numerous studies have identified critical genes associated with energy expenditure, particularly those encoding uncoupling proteins (UCPs) and adrenergic receptors (Fig. 4) [21].

UCPs are mitochondrial carrier proteins that transport fatty acid anions, facilitating a process that reduces ATP generation during fuel oxidation [22]. UCP1 plays a crucial role in adaptive thermogenic responses, while UCP2 and UCP3 have been linked to metabolic rates, making them valuable targets for obesity therapies [22]. Activation of UCP2 can reduce insulin secretion, and UCP3, expressed in skeletal muscles, is associated with early obesity [21]. Certain polymorphisms in UCP genes, such as the UCP1-3826A/G variant, have been connected to increased obesity susceptibility [21]. Additionally, UCP1 genetic polymorphisms may lower resting energy expenditure and disrupt energy balance. For therapeutic

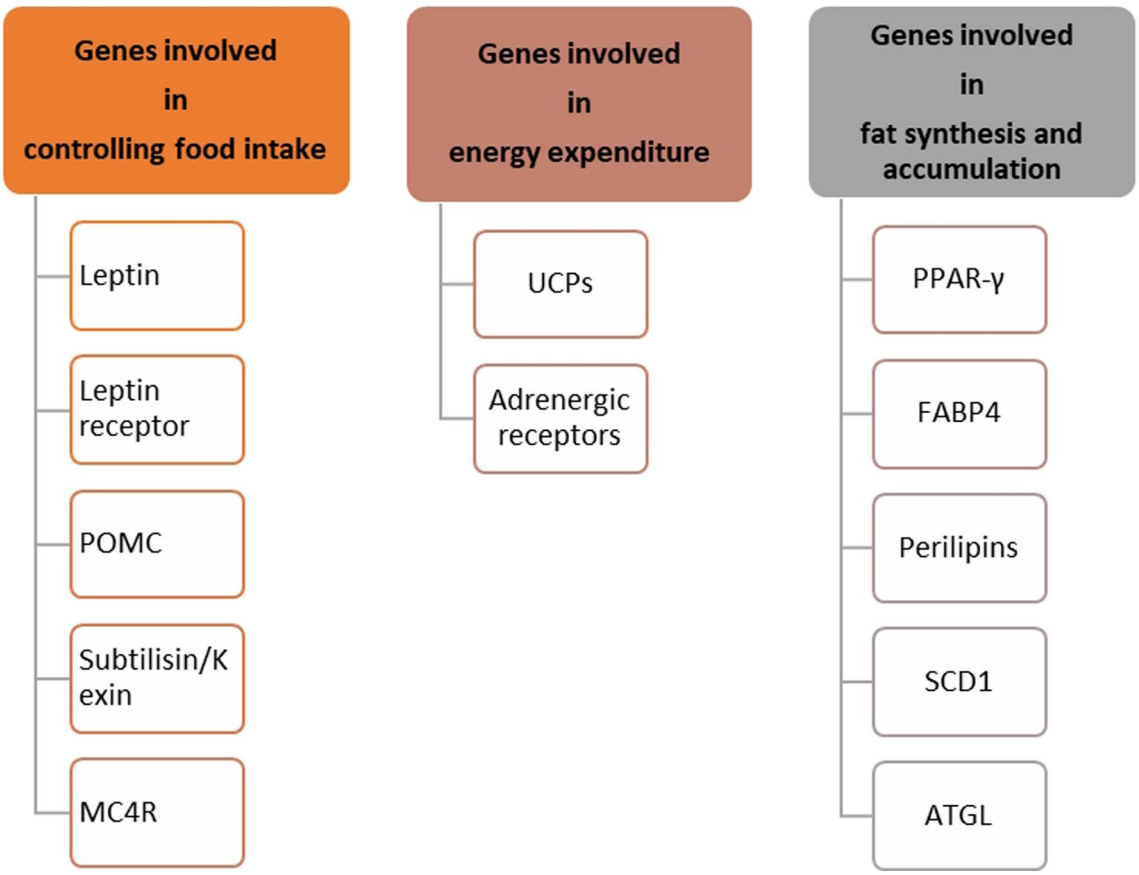

Fig. 4 Genes with certain roles in obesity including: Genes involved in controlling food intake (leptin, leptin receptor, pro-opiomelanocortin (POMC), subtilisin, and Melanocortin-4-receptor (Mc4r); genes involved in energy expenditure (uncoupling proteins (UCPs) and adrenergic receptors); genes involved in fat synthesis and accumulation (peroxisome proliferator-activated receptor (PPAR-γ), fatty acid-binding protein 4 (FABP4), perilipins, Stearoyl-coenzyme A desaturase 1 (SCD1), adipose triglyceride lipase (ATGL))

purposes, utilizing UCP1 to generate heat and increase energy expenditure is being investigated [22].

Adrenergic receptors also play essential roles in regulating energy expenditure. Variants of the β-adrenergic receptor (β-AR), including polymorphisms such as Gly389Arg in beta(1)-AR, Gln27Glu in beta(2)-AR, and Trp64Arg in beta(3)-AR, have significant associations with obesity [23]. Research indicates a relationship between the Gly389Arg polymorphism in the beta(1)-adrenoceptor gene and obesity, with the Arg allele linked to higher BMI in Caucasian women [24]. Beta 3-adrenergic receptor motifs are crucial for lipid metabolism, as catecholamine activation of beta 3-AR enhances lipolysis in adipose tissue [25].

Genes involved in fat synthesis and accumulation

Several other genes play crucial roles in fat synthesis and accumulation (Fig. 4). One key gene is the peroxisome proliferator-activated receptor (PPAR), a member of ligand-dependent receptors. There are three isoforms: PPAR-α, PPAR-β, and PPAR-γ, each significantly influencing metabolism [26]. PPAR-γ is particularly important for regulating genes involved in glucose metabolism, lipid storage, and inflammatory responses. PPAR-γ ligands enhance fatty acid storage and regulate the expression of hormones secreted by adipocytes, which also impacts glucose homeostasis, thereby improving insulin sensitivity [27]. Additionally, PPAR-γ ligands can help prevent adiposity and play a vital role in the treatment of type 2 diabetes mellitus [26].

The fatty acid-binding protein 4 (FABP4) gene is highly expressed in adipose tissue and its expression is regulated by PPAR-γ. FABP4 is associated with eight interacting genes—acp1, ext2, insr, lipe, ostf1, sncg, usp15, and vim—all of which contribute to lipid metabolism [28]. In obesogenic conditions, FABP4/aP2 is released, which decreases insulin secretion. Although insulin levels typically increase in obesity, feedback regulation inhibits FABP4 release, leading to disrupted FABP4 patterns in severely obese patients. Genetic

disruption of FABP4 has also been shown to cause obesity in mice on HFDs [29].

Perilipins are adipocyte proteins whose expression is also regulated by PPAR-γ in adipose tissue. There are two isoforms: perilipin A and perilipin B, both of which inhibit lipolysis by protecting triglycerides from degradation by lipase [30]. Variations in the perilipin gene have been linked to obesity, with the PLIN 6 polymorphism potentially increasing obesity risk in adolescents [31].

Stearoyl-coenzyme A desaturase 1 (SCD1) is a rate-limiting enzyme that regulates fuel metabolism by catalyzing the synthesis of monounsaturated fatty acids (MUFAs), such as oleate and palmitoleate, from saturated fatty acids. MUFAs play a vital role in weight regulation and are considered potential therapeutic targets for obesity and type 2 diabetes. SCD1 serves as a homeostatic checkpoint between glucose and lipid metabolism [32].

Adipose triglyceride lipase (ATGL) is another crucial enzyme in fat synthesis and hydrolysis, playing an essential role in adipogenesis. Research indicates an independent association between ATGL levels and waist-to-hip ratio, as well as overall body fat content, highlighting the close relationship between ATGL and obesity [33].

Gene-based approaches to obesity prevention

Gene therapy strategies have significantly advanced in treating and preventing obesity. These strategies primarily focus on two approaches: transferring therapeutic genes to provide functional gene copies and knocking down endogenous genes to reduce the production of obesity-related gene products [34].

Metreleptin, a recombinant form of human leptin, is effective in patients with congenital leptin deficiency and generalized lipodystrophy. However, its efficacy is limited in more common obesity cases due to lipid tolerance or resistance. Consequently, combining leptin with other agents may enhance its weight loss effects [35]. Studies have shown that recombinant adenovirus (Ad)-mediated leptin gene transfer can positively impact obesity and diabetes [6]. In experiments with adult mature mice, administering recombinant adeno-associated virus (AAV) encoding the leptin gene into the third cerebroventricle helped protect against weight gain, increasing energy expenditure while decreasing food intake. This approach resulted in improved body weight homeostasis, reduced adiposity, and lowered insulin and triglyceride levels, indicating its potential for long-term obesity treatment strategies. In addition to leptin therapy, ciliary neurotrophic factor (CNTF), a cytokine from the IL-6 family, has been tested to bypass leptin pathways [36].

AMP-activated protein kinase (AMPK) is a key gene-activated downstream of leptin signaling, playing a crucial role in regulating metabolism, food intake, and energy expenditure through its interactions with various hormones, including leptin, adiponectin, and ghrelin [37].

Adiponectin, a polypeptide hormone secreted by adipose tissue, exemplifies upstream targeting of AMPK signaling pathways. This adipocytokine is significant in obesity and has two receptor isoforms, AdipoR1 and AdipoR2, that mediate its effects. Studies have shown that adiponectin administration can lead to weight reduction, suggesting that adiponectin replacement therapy may be an effective strategy for treating obesity [38]. For instance, research involving HFD-fed obese mice (C57BL/6J) demonstrated a lentiviral vector under adiponectin promoter gene delivery improved insulin sensitivity, metabolic activity, vascular function, and decreased adipocyte size, fibrosis, inflammation, and oxidative stress markers [39].

Stearoyl-CoA desaturase (SCD1) plays a significant role in leptin signaling and AMPK activation. Disruption of the SCD1 gene in mice leads to diet-induced obesity and increased insulin sensitivity, suggesting that SCD1 downregulation could be a promising target for obesity treatment [40]. Research has shown that hepatic SCD1 knockdown can effectively mediate lipid and glucose metabolism [32].

Skeletal muscles also regulate metabolism through engineered respiratory uncoupling. Mice with enhanced expression of UCP1 demonstrated improved insulin sensitivity and resistance to obesity, indicating that partial respiratory uncoupling may be beneficial for obesity treatment [41].

Glucagon-like peptide-1 (GLP-1) is an incretin hormone that reduces food intake and stimulates insulin release. GLP-1 receptor agonists are available for treating obesity in prediabetic and type 2 diabetes (T2D) patients [42]. Exendin-4, a GLP-1 receptor agonist, is used as an injectable treatment for T2D. Initially developed for short-term use, a helper-dependent adenoviral (HDAd) vector has been employed to achieve long-term expression of Ex4 [43]. Studies have shown that transferring the Ex4 gene can effectively treat obesity in mice on HFD, with additional benefits in reducing fat synthesis [44].

Brain-derived neurotrophic factor (BDNF), a member of the "neurotrophin" family, plays a key role in regulating food intake and addressing obesity in specific mouse model [45]. Research has shown that intraperitoneal and subcutaneous administration of BDNF reduces food intake and significantly improves obesity in mice [45]. Moreover, delivering the AAV-mediated BDNF gene in mice has shown promise in preventing age-related weight gain, enhancing glucose tolerance, and reducing inflammation. This is achieved through the suppression of pro-inflammatory genes in both the hypothalamus and adipose tissue, highlighting its potential as a therapeutic

strategy for managing metabolic and inflammatory conditions associated with aging [46].

Fibroblast growth factors (FGFs), particularly FGF19, FGF21, and FGF23, play essential roles in metabolic regulation. FGF19 is involved in cholesterol and bile acid synthesis, while FGF23 regulates phosphate and vitamin D metabolism. Knock-in and knock-out studies have shown that FGF21 is critical for glucose and lipid metabolism. Transgenic FGF21 mice exhibit lower levels of insulin, serum cholesterol, and triglycerides and demonstrate resistance to both age- and diet-induced obesity [47]. Studies demonstrated that the administration of AAV-FGF21 in mouse models of obesity, whether induced by diet or genetics, resulted in notable metabolic improvements. These benefits included a reduction in body weight, a decrease in adipocyte size, and diminished inflammation, as well as a mitigation of hepatic steatosis and fibrosis [48, 49] (Fig. 5).

Moreover, FGF21 gene transfer via hydrodynamic delivery in obese C57BL/6 mice on a high-fat diet (HFD) reduced adiposity, improved glucose regulation, and modulated the expression of genes involved in thermogenesis and adipogenesis [49].

Irisin, a cleaved and secreted fragment of fibronectin type III domain-containing 5 (FNDC5), plays a critical role in metabolic regulation and is controlled by peroxisome proliferator-activated receptor-γ coactivator-1 (PGC1)-α. FNDC5/irisin has been shown to improve glucose and lipid metabolism and insulin resistance in obese mice. It utilizes the cAMP-PKA-HSL/perilipin pathway to enhance lipolysis, making it a promising target for therapeutic interventions [50, 51]. Additionally, irisin's activation of p38 mitogen-activated kinase and extracellular signal-regulated kinase pathways, which upregulate UCP1, contributes to obesity regulation and supports glucose homeostasis [52].

Hypoxia-inducible factors (HIFs) are key regulators of cellular responses to hypoxia, crucial for cell survival and energy homeostasis. HIF-1α, a significant sensor for energy balance, also influences food intake and lipid/glucose metabolism. Hypothalamic inhibition of HIF-1α affects obesity, making it a promising therapeutic target for obesity and type 2 diabetes [53].

Chronic inflammation is linked to obesity, largely due to adipose-infiltrating macrophages. Depleting these macrophages can improve metabolism in C57BL/6 mice on a HFD [54]. IL-10 gene transfer enhances glucose metabolism and may also help suppress chronic inflammation [54].

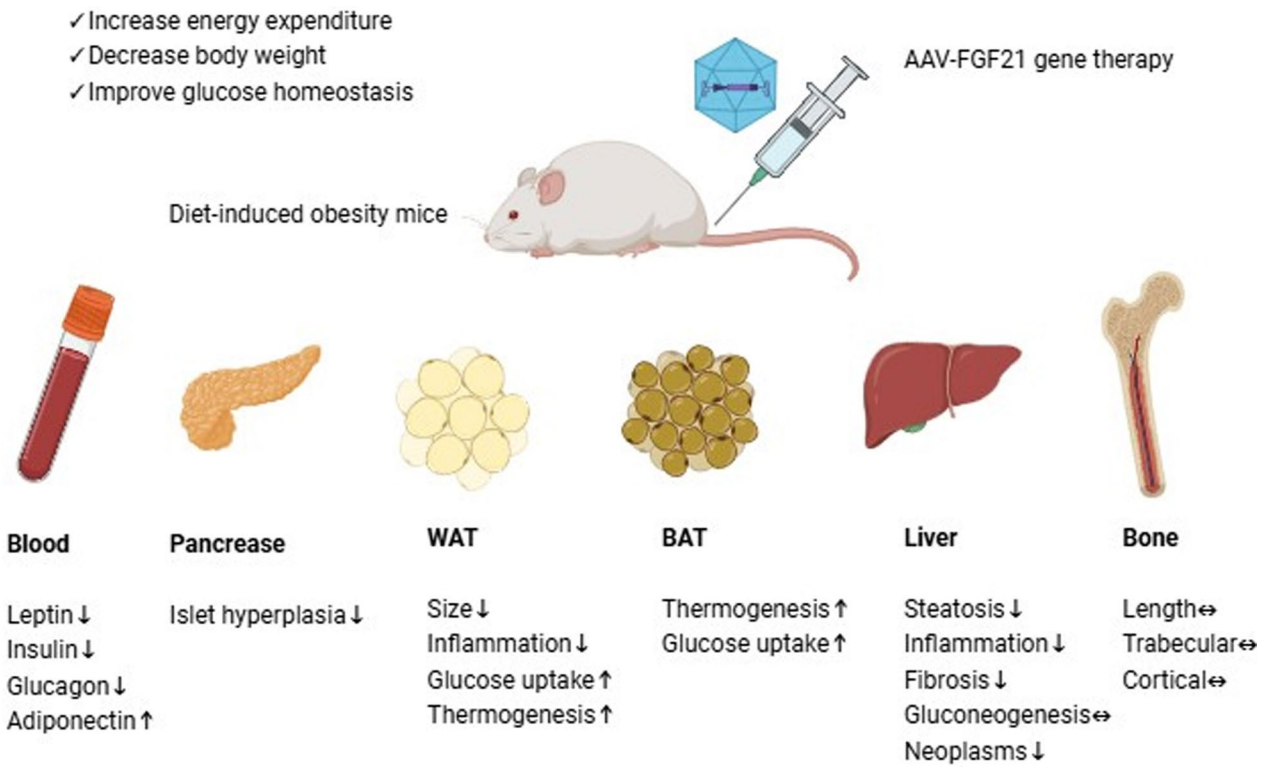

Fig. 5 AAV-FGF21 gene therapy enhances metabolic health in diet-induced obese (DIO) mice. Adeno-associated virus (AAV)-mediated FGF21 expression delivers the following metabolic benefits across targeted tissues. BAT: brown adipose tissue, WAT: white adipose tissue

Obesity is closely linked to insulin resistance. c-Jun amino-terminal kinases (JNKs) influence insulin action, and their activity increases with obesity [55]. The absence of JNK1 improves insulin sensitivity and reduces adiposity, suggesting JNK as a potential therapeutic target for obesity. In HFD-induced and genetically obese mice, Ad-mediated JNK1 shRNA reduces JNK1 expression, lowering insulin concentration. This JNK1 knockdown strategy shows promise in treating obesity [56]. Obesity-induced insulin resistance can lead to pancreatic β-cell apoptosis. Beta-trophin plays a crucial role in pancreatic β-cell proliferation, and its overexpression via hydrodynamics-based methods enhances glucose tolerance. These findings suggest beta-trophin as a potential therapeutic target for obesity [57].

Gene therapy as a new approach in modern medicine

A historical overview of gene therapy

Gene therapy uses genes to treat or prevent disorders. Initially focused on life-threatening conditions like cancer, it is now recognized for its potential to improve non-life-threatening conditions affecting quality of life. Advances in vectors, mechanisms, and approaches have enabled more effective treatments [58].

Gene therapy began developing in the 1960s and early 1970s, marked by the uptake and expression of exogenous DNA in mammalian cells and discoveries about RNA tumor viruses and reverse transcription. In the 1980s, ethical discussions emerged, and by 1983, phenotype correction studies began [59]. The first approved clinical trial in 1990 targeted adenosine deaminase deficiency, followed by trials for chronic granulomatous disease (CGD) in the late 1990s. Numerous trials have occurred since, though early results were sometimes unsuccessful [60].

Gene therapy initially targeted monogenic defects, with successful trials expanding its scope to cancer, heart failure, Parkinson's, diabetes, and other conditions [61].

In 1999, the death of Jesse Gelsinger, who had ornithine transcarboxylase deficiency, temporarily hindered gene therapy development due to his adverse reaction to an adenovirus carrier. Progress resumed in 2002 with SCID treatment in children, and in 2003, gene transfer into the brain was achieved using polyethylene glycol-coated liposomes, bypassing viral vectors that cannot cross the blood–brain barrier. This approach holds promise for treating Parkinson's disease [61]. In 2005, an adenovirus vector was successfully used to repair deafness in guinea pigs, alongside advancements in treating myeloid cell-related diseases and inherited retinal conditions [62]. Early trials faced severe side effects in some patients. However, with advanced tools and Phase I/II trials, gene therapy has achieved strong clinical results, establishing it as a clinical reality [61].

The therapeutic effects of gene therapy

After a 50-year journey, gene therapy has become a promising treatment for various disorders. Although early studies encountered severe side effects, advances in vector engineering have improved its safety [63]. AAV and lentiviral vectors offer good safety and moderate efficacy, particularly in delivering transgenes to the brain. Oncolytic viruses have been used to target cancer cells, and adenoviral vectors of simian origin are being explored for their potential in immune response induction through vaccination [64].

Ex vivo gene therapies have shown effectiveness in treating adult and pediatric acute lymphoblastic leukemia, diffuse large B cell lymphoma, chronic lymphocytic leukemia, and multiple myeloma, primarily through T cell applications. Conditions like β-thalassemia, sickle cell anemia, and Wiskott–Aldrich syndrome are being targeted using hematopoietic stem and progenitor cells (HSPCs). Current in vivo gene therapy trials are advancing treatments for Parkinson's disease, spinal muscular atrophy, hemophilia A and B, Hunter's syndrome, lipoprotein lipase deficiency, and inherited retinal dystrophy [63].

Gene therapy has shown promise in treating blindness, neuromuscular diseases, hemophilia, immunodeficiency, and cancer. Engineered T cells, in particular, have benefited patients with lymphoid malignancies. While these advancements offer significant improvements, challenges remain, including the prevention of genotoxicity, off-target genome editing, and immune responses [63].

Recent genome-editing strategies using engineered or bacterial nucleases have advanced the field considerably. While gene addition relies on viral vectors, gene editing enables gene addition, ablation, and correction, allowing precise modifications in eukaryotic genomes by introducing DNA double-strand breaks (DSBs) [65]. Liver-directed gene therapy exemplifies in vivo applications of gene editing [64].

Current trends of gene therapy

Recent developments in gene therapy and our growing understanding of its mechanisms offer optimism for the future. Advances using recombinant adeno-associated viruses (rAAV), novel vectors, and insights into microRNAs and CRISPR/Cas9 technology enhance the potential for treating genetic and infectious disorders. Current studies focus on the biodistribution of vector components and the associated risks of carcinogenesis. CRISPR/Cas9 and RNA interference (RNAi)-based therapies demonstrate greater potential for treating certain genetic

disorders compared to older strategies, particularly for autosomal dominant diseases. CRISPR/Cas9 can repair genes in situ while preserving the necessary elements for normal physiological regulation [66]. Although it appears to be a permanent solution for correcting genetic disorders, concerns about efficacy and safety remain. A key goal of gene therapy is to control gene expression. Compounds like tetracycline and estrogen/progesterone receptor modifiers have shown promising results in regulating genes in cell cultures and animal models. However, immune responses to transcriptional activator domains have hindered clinical application. Two-component RNA-based systems have been developed, offering specific features that may help narrow the therapeutic windows of expression in gene therapy [67].

Tissue engineering is rapidly advancing, particularly in the realm of meniscal repair, where previous limitations have been addressed through ongoing research. This progress offers promising new avenues for utilizing tissue engineering and regenerative medicine to effectively treat meniscal lesions [68].

In human orthopedic regenerative medicine, gene therapy using viral vectors plays a vital role in enhancing the intrinsic repair capabilities of orthopedic tissues. The integration of viral gene vectors with tissue engineering strategies presents a significant opportunity to improve in vivo applications and overcome existing challenges. As preclinical data expand, biomaterial-guided viral gene therapy may unlock exciting potential in this field [69].

Significant efforts have been made to engineer recombinant viral vectors for therapeutic gene delivery, with nanotechnology enhancing drug delivery solutions. Oral gene therapy, due to its advantages, has shown considerable promise in treating conditions that were previously difficult to address with older methods [70].

Targeted diseases by gene therapy strategies

Today, gene therapy is an effective strategy for treating autoimmune diseases, thanks to a better understanding of the immunological basis of these disorders. Its goals include regulating pro-inflammatory cytokine levels, controlling lymphocyte infiltration, and modulating gene expression to maintain immune tolerance [71].

Gene therapy also shows promise for patients with sickle cell disease, which is caused by a homozygous missense mutation in the β-globin gene that leads to hemoglobin S polymerization. Treatment using lentiviral vector-mediated antisickling β-globin has successfully corrected disease hallmarks without recurrence of sickle cell crises [72].

In the context of Alzheimer's disease (AD), a leading cause of dementia, gene therapy offers new approaches for studying and potentially treating neurodegenerative disorders. Recombinant adeno-associated viruses are particularly suited for both basic research and therapeutic applications due to their transduction specificity and long-term gene expression capabilities. They can be precisely injected into specific brain regions at various life stages, enhancing their therapeutic potential [73].

Gene therapy has shown significant promise in treating Pompe disease (PD), a monogenic disorder caused by mutations in the acid alpha-glucosidase gene (GAA) [74]. While enzyme replacement therapy (ERT) has improved PD prognosis, it has its limitations. Gene therapy offers a potential long-term solution through sustained Gaa gene expression, presenting hopeful prospects for additional therapeutic options [74].

Inherited retinal diseases also benefit from gene therapy. Trials using AAV vectors have demonstrated encouraging safety and efficacy results [75].

Advancements in genetic modification through gene therapy hold great promise for cancer treatment [76]. Preclinical models have shown tumor regression and reduced metastasis [77].

Breast cancer is the most prevalent cancer among women [78], and advancements in gene therapy are showing promise in its treatment [76]. Researchers are exploring the use of various viral vectors to deliver therapeutic genes, including adenovirus, AAV, lentivirus, poxvirus, reovirus, baculovirus, and herpesvirus [76]. Each vector offers unique advantages in targeting cancer cells and enhancing therapeutic efficacy [76].

Perspective on gene therapy in obesity and associated disorders

Mutations in human genes related to energy expenditure and food intake can contribute to obesity, highlighting the importance of genetic factors. Overexpressing a transcription factor to suppress genes responsible for fat accumulation may inhibit lipogenesis and reduce fat storage [79]. Animal studies have demonstrated the effectiveness of gene transfer of BDNF, irisin, and FGF, resulting in reduced fat mass [45, 46, 50]. While gene therapy shows promise for treating obesity, further studies are needed to evaluate its safety before clinical trials can proceed [79]. In addition to the previously mentioned genes, discovering new genes that block lipogenesis or enhance energy expenditure could help maintain metabolic homeostasis, even in the presence of excessive energy intake [79].

Three methods are used to regulate gene expression: viral vectors, nonviral vectors, and physical methods [61]. While viral vectors are the most prevalent, synthetic vectors offer improved safety, albeit with lower efficiency [61]. In addition to hydrodynamic gene transfer, research is focused on developing more effective gene delivery

systems to address the limitations of current methods [61]. Advancements in human genome sequencing and mapping of obesity-related genes are expanding the druggable gene pool, enabling targeted interventions at the nucleic acid level [79]. Moreover, innovations in vector technology may facilitate the long-term expression of therapeutic genes [80].

Promoter analysis and vector engineering advancements are fostering optimism about overcoming gene silencing challenges [80]. Selecting the appropriate gene for obesity treatment is crucial; although obesity itself is not lethal, it can lead to serious complications, necessitating assurance of the therapeutic gene's safety. Innovations in gene therapy that focused on regulating metabolism have the potential to enhance the quality of life [4].

Obesity also increases cancer risk, particularly for prostate cancer (PCa), which appears to correlate with rising obesity rates [81]. Diagnosing PCa can be challenging due to lower levels of prostate-specific antigen (PSA) in obese men. Leptin's molecular, endocrinological, and genetic characteristics link it to PCa development. Elevated leptin levels, influenced by obesity and genetic variants of the leptin gene, may drive androgen-independent PCa progression. This presents a significant challenge: blocking peripheral lipid action without disrupting its physiological functions [81].

Currently, gene therapy remains an underdeveloped approach to treating diseases. However, advancements in molecular therapeutics are shifting focus from pharmaceutical companies to genetic therapeutic strategies for obesity and its associated conditions [79].

Gene therapy approaches for treatment and prevention of obesity

Gene-editing techniques

The ability to control gene expression is crucial for the long-term success of gene therapy. Over the years, various systems have been developed and tested, most of which rely on engineered transcription factors (TFs) that bind to specific DNA sequences to either activate or suppress transgene expression. While some of these systems allow functional control, limitations have prevented their adoption in clinical gene therapy applications [61]. Table 1 presents key gene therapy strategies and their outcomes for the prevention and treatment of obesity.

Zinc finger proteins (ZFPs), due to their ability to recognize specific DNA sequences, have significant therapeutic potential. The ZFP transcription factor (ZFP TF) system addresses many limitations. ZFPs contain a DNA-binding domain that recognizes specific sequences and another domain that activates or suppresses the target gene. Engineered based on natural transcription factors, ZFPs can also be combined with domains from integrases and other proteins to create useful tools [82]. ZFP 423 plays a crucial role in maintaining white adipose cell function. Although its levels remain unchanged during adipogenesis, ectopic expression of ZFP 423 in non-adipogenic murine cells can activate the gene encoding peroxisome proliferator-activated receptor γ (Pparγ), enhancing the adipogenic potential of these cells [82].

Another approach to gene expression regulation is RNAi, initially discovered in nematode worms as a sequence-specific response to double-stranded RNA (dsRNA) that triggers mRNA degradation. This technology has expanded opportunities for in vivo gene knockdown, particularly for preclinical target validation [83]. During RNAi, long dsRNA generates small interfering RNAs (siRNAs), which inhibit target gene expression. A study demonstrated the role of exosomal miRNA in regulating glucose and lipid metabolism in mice [84]. However, the disease state may influence the efficacy of specific RNAi delivery methods, presenting a potential limitation [83].

Genetic modulation requires precise methods to alter target genes. Tools such as engineered DNA-binding proteins (e.g., ZFPs and transcription activator-like effector (TALE) proteins) and RNAi enable genetic modification, but ZFPs and TALEs are challenging and costly to design and develop [72].The CRISPR (clustered regularly interspaced short palindromic repeats) system offers precise genetic engineering across various cell types. Combining CRISPR interference (CRISPRi) with a targeted nonviral gene delivery system shows promise for treating obesity and obesity-induced type 2 diabetes (Fig. 6). For instance, the targeted delivery of CRISPRi against Fabp4 to white adipocytes could reduce body weight safely and effectively [85]. CRISPR, combined with AAV, also shows significant potential for treating genetic disorders. A study demonstrated CRISPR's success in addressing obesity caused by haploinsufficiency in a murine model, offering hope for broader therapeutic applications [86].

RNA-based gene technology is another regulatory system that incorporates sequences encoding self-cleaving ribozymes into the transcriptional region of a transgene. This approach eliminates the need for protein transactivator expression or promoter elements [87].

Vectors used in gene therapy for obesity

Obesity is a chronic condition, and for gene therapy to be effective, therapeutic transgene expression must persist long-term, matching the enduring nature of obesity. According to the body weight (BW) set-point hypothesis, BW tends to return to its original level once stimuli like dieting or exercise are removed. Therefore, whether through integration into the host cell chromosome or episomal expression, sustained transgene

Table 1 Key gene therapy strategies and their outcomes in the prevention and treatment of obesity

Gene	Gene transfer method	Administration method	Animal model	Outcome	References
Leptin	Lentiviral vector	Systemic administration	Adult male Sprague Dawley rats	Weight loss, a reduction in food intake and blood glucose levels, Treatment of T1D	[13]
	rAAV	Intracerebroventricularly	leptin-deficient ob/ob mice	The reduction in marrow adipose tissue	[91]
Exendin-4	Plasmid vector	Hydrodynamic transfer / pEAT plasmids were transfected into HEK293T cells	ob/ob mice	Suppress body weight gain, maintain metabolic homeostasis, and block fatty liver development	[44]
BDNF	Genetic engineering via crossbreeding	Targeted hypothalamic gene transfer	Mice (including heterozygous BDNF-knockout, NF-L conditional knockout, and double knockout models)	Reduction in aging-associated weight gain, improved glucose tolerance, suppression of inflammatory genes in the hypothalamus and adipose tissues, and alleviation of obesity symptoms	[45]
FNDC5 (precursor of irisin)	Plasmid transfection (pVAX1-mFNDC5 vector for overexpression) and siRNA for knockdown experiments	Cell transfection with plasmid DNA or siRNA in 3T3-L1 preadipocytes; recombinant irisin was also administered to the culture medium	NP, study conducted on 3T3-L1 mouse preadipocyte cell line	1. FNDC5 overexpression inhibited adipogenesis, reduced lipid accumulation, and downregulated key adipogenic transcription factors (PPARγ, C/EBPα, and FABP4) 2. Irisin treatment increased Wnt signaling, which disrupted adipogenesis 3. Knockdown of FNDC5 reduced Wnt expression but did not significantly impact adipocyte differentiation	[50]
Adiponectin (HO-1)	Lentiviral vector under adiponectin promoter	Retro-orbital vein injections	Obese mice (C57BL/6J)	Improved insulin sensitivity, metabolic activity, vascular function; decreased adipocyte size, fibrosis, inflammation, and oxidative stress markers	[39]
Interleukin 10	Recombinant protein	Subcutaneous injection (50 µg/kg)	C57BL/6J wild-type and IL-10 knockout (KO) mice	IL-10 administration mitigated atrial remodeling, fibrosis, lipidosis, and atrial fibrillation induced by a HFD	[53]

Table 1 (continued)

Gene	Gene transfer method	Administration method	Animal model	Outcome	References
FGF21	AAV	Intravenous (IV)	HFD-fed mice	Reduced body weight, decreased white adipose tissue hypertrophy, improved insulin sensitivity, reversed hepatic steatosis, inflammation, and fibrosis	[48]
			ob/ob mice	Reduced body weight, decreased adiposity, improved glucose tolerance, enhanced insulin sensitivity, reduced hepatic steatosis, and inflammation	
		Intra-depot (epididymal WAT)	ob/ob mice	Reduced body weight gain, improved insulin sensitivity, increased circulating FGF21 levels, and enhanced energy expenditure	
JNK	Chemical inhibitor (SP600125)	Intraperitoneal injection	HFD-fed rats	Suppression of autophagy, improved insulin signaling, reduced markers of liver function injury (ALT, AST), decreased serum levels of cholesterol, triglycerides, TNF-α, free fatty acids, and insulin; alleviation of NAFLD symptoms in rats	[54]
SCD1	None (gene expression modulated by DEX)	Intraperitoneal injection (100 $\mu g \cdot kg^{-1}$ Dexmedetomidine)	HFD-fed mice	Decreased body weight, reduced liver fat accumulation, improved insulin sensitivity, decreased liver injury markers (ALT, AST), reduced inflammation through MAPK/NFκB signaling pathways	[40]

T1D: Type I diabetes, rAAV: recombinant adeno-associated virus, EAT: The fusion gene encodes a protein with **e**xendin-4 peptide placed at the N-terminus of human α−1 **a**nti**t**rypsin, BDNF: Brain-derived neurotrophic factor, HFD: High-fat diet, NP: Not applicable, FGF21: Fibroblast growth factor 21, JNK: c-Jun N-terminal kinase, SCD1: Stearoyl-CoA desaturase 1

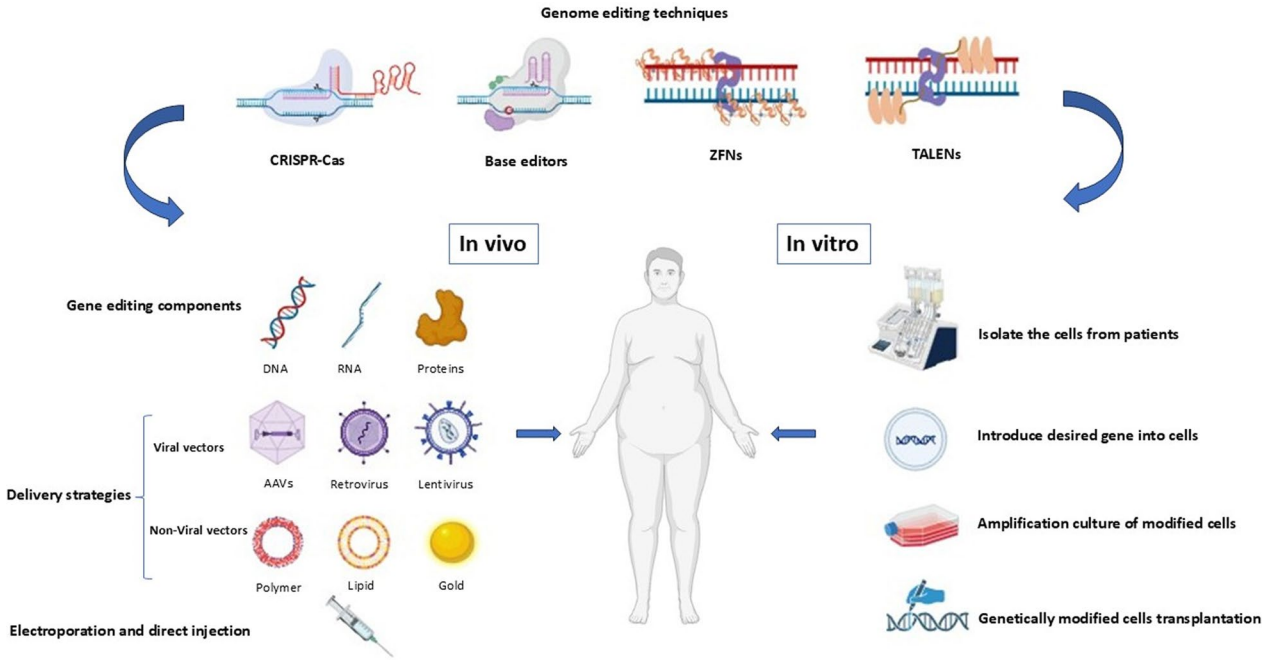

Fig. 6 In vitro and in vivo therapeutic gene-editing strategies for obesity treatment. Gene-editing therapeutics are categorized into two primary approaches: in vivo and in vitro. In vivo gene-editing strategy (left): This method involves directly delivering vectors containing the desired gene cargo and editing machinery into targeted tissues or organs, enabling on-site gene modifications. In vitro gene-editing strategy (right): This approach consists of four key steps: (1) Cell isolation and culture: Collect the required cells from the donor and culture them in vitro. (2) Genome editing: Use an appropriate gene-editing platform (e.g., TALENs, ZFNs, or CRISPR) to modify the cell genome. (3) Cell expansion: Cultivate and expand the edited cells in vitro. 4) Cell transplantation: Inject the edited cells back into the patient to achieve therapeutic effects. AAV: adeno-associated virus, TALENs: transcription activator-like effector nucleases, ZFNs: zinc finger nucleases

expression is essential [61]. Past efforts have introduced three primary delivery methods: viral vectors, nonviral vectors, and physical or synthetic vectors. Current research focuses on developing more efficient delivery systems and addressing the limitations of existing approaches [4, 80].

Despite safety concerns surrounding viral vectors, they remain the most widely used method for gene delivery. Physical methods, while safer, are generally less efficient. Among nonviral approaches, hydrodynamic gene transfer stands out for its higher efficiency [80].

Viruses can transfer their genes to host cells, making them powerful tools for gene delivery. rAAV vectors are particularly attractive for gene therapy due to their ability to transduce differentiated cells, lack of pathogenicity, and broad host range. Studies have shown that rAAV administration is associated with minimal toxicity [80]. The long-term safety profile of rAAV has made it a cornerstone in advancing gene therapy approaches such as gene knockdown, gene editing, and more [80]. For instance, studies have demonstrated that continuous hypothalamic overexpression of glial cell line-derived neurotrophic factor (GDNF) via AAV2 leads to significant weight loss in aged rats [88].

Mutations in the Mc4r are a common cause of severe early-onset obesity. In the energy balance regulation pathway, BDNF acts downstream of Mc4r, and studies have shown that AAV-mediated hypothalamic BDNF gene transfer can help alleviate obesity. This gene therapy prevents obesity development and impacts food intake, hyperleptinemia, and energy expenditure, without causing cardiovascular side effects. These promising results make BDNF gene therapy a viable option for treating Mc4r-deficient obese patients [89].

Hydrodynamic delivery is another effective method used in gene therapy studies due to its high efficiency and simplicity, providing a near-perfect approach for in vivo intracellular DNA delivery. This method requires only the essential DNA sequences to be injected into a targeted blood vessel, helping to mitigate some of the concerns associated with other vector types [90]. Two examples of its applications are as follows:

1. FGF21 plays a critical role in glucose and lipid metabolism. Using hydrodynamic delivery to transfer the FGF21 gene increases its mRNA levels in the liver, leading to higher blood levels of FGF21, which can help alleviate HFD-induced obesity [91].

2. The fusion gene of exendin-4 and α1-antitrypsin, known as EAT, is designed to combat obesity and related metabolic disorders such as fatty liver. This gene encodes a protein with the exendin-4 peptide at the N-terminus of human α1-antitrypsin. Hydrodynamic transfer of the EAT gene to mice prevents HFD-induced obesity [44].

Challenges, limitations, and advantages

Challenges with targeting critical genes in obesity

Gene therapy is a promising treatment for single-gene disorders, although it faces several challenges. One such challenge is gene silencing, which can occur in many biological systems, hindering sustained expression of the transgene. To address this, significant progress has been made in promoter analysis and vector engineering to minimize gene silencing [61].

Another critical challenge is selecting the appropriate gene for obesity treatment. Unlike cancer or single-gene deficiencies, obesity is a chronic condition that, while not lethal, can lead to various medical complications. Therefore, it is essential to ensure that the effects of gene transfer are long-lasting and safe, with careful consideration of the long-term safety of gene expression [61].

Obesity typically manifests similarly among patients, but the underlying causes of fat accumulation can vary. When leptin replacement is administered both peripherally and centrally, it initially leads to weight reduction [15]. However, over time, leptin resistance develops, and understanding the specific mechanisms of this resistance is crucial. There are two approaches for the peripheral administration of leptin gene therapy, although leptin insensitivity remains a challenge. While successful in some obese patients, showing improvements in treating metabolic abnormalities, leptin therapy alone does not offer a viable long-term solution. Alternative methods are needed to effectively treat the majority of obesity patients [15].

Large-scale genome-wide studies have identified numerous loci associated with adiposity traits, and the number of these loci will continue to grow as larger population studies are conducted. The value of genome-wide association studies lies in the discovery of new genes involved in both known and novel pathways. While pinpointing the specific genes within each locus remains a challenge, advancements in approaches and methods may help integrate this data. Collaboration between geneticists and physiologists is essential to identify the causal genes, which is a crucial step [92].

Safety concerns also present challenges. For example, while adiponectin (Acrp30) replenishment may reduce body fat, further research on the safety of gene therapy strategies is needed. Another challenge is translating laboratory methods to clinical applications, such as the efficient delivery of siRNA. Although there have been successes in vector-mediated siRNA delivery both in vitro and in vivo, challenges remain [84].

Gene therapy shows promise for obesity treatment, but safety studies, including pharmacokinetics, biodistribution, and toxicity assessments in large animal models, are essential before clinical implementation. Despite the challenges, gene therapy has the potential to significantly improve the regulation of metabolism and enhance the quality of life [4].

Benefits and limitations of applying gene-editing techniques in clinical practice

Gene editing, as a new technology, enhances our ability to alter human traits both physically and mentally [93]. While the therapeutic potential of gene editing is advancing, it is crucial to consider the safety and specificity of this method in each editing process. Since gene therapy has permanent effects on cell function, safety is a critical factor. Unintended modifications can result in long-lasting consequences that alter cell function. Furthermore, a lack of specificity may increase the risk of random gene integration, posing safety concerns [94]. The development of artificial endonucleases with tailored specificity offers hope for preventing random insertions, allowing for the correction of mutated genes at a targeted locus. This approach differs from other gene therapies that rely on random insertions into various pathways [61].

Genome editing technologies, with their precision akin to a scalpel, can overcome many challenges associated with viral vector-mediated semi-random genomic insertions. Gene editing can be performed ex vivo on cells or through in vivo delivery of the editing machinery (Fig. 6). It is anticipated that numerous clinical genome editing trials will be conducted in the coming years [63].

Despite some limitations, gene therapy and its tools play a crucial role in genetic modification and are becoming essential for targeted genome alterations. These tools are customizable, easy to target, and can be used to create desired mutations in specific genes. They are poised to revolutionize industries such as food, biopharmaceuticals, and the treatment of various genetic diseases [95].

Unlike viral vectors, which are limited to gene addition, gene editing provides a precise approach for gene addition, gene ablation, and gene correction. It is crucial to foster greater involvement from the biotechnology and pharmaceutical sectors to accelerate the delivery of these treatments to patients. Despite its efficacy, gene editing faces challenges, such as genotoxicity and off-target effects, and improving gene transfer and its efficacy to therapeutic levels remains essential [63].

CRISPR/Cas9 is a genome editing method that allows for the correction of genomic errors. It also enables the activation or silencing of genes in cells and organisms quickly and cost-effectively. This technology has been used to repair defective DNA in mice with genetic disorders, and as mentioned, it holds potential for treating obesity and obesity-induced type 2 diabetes by performing precise genetic engineering in a variety of cells [66].

Initially, gene therapy was considered primarily for life-threatening disorders such as cancer and inborn defects [61]. However, it is now being explored for a broader range of conditions, including those that negatively impact the quality of life. Over the past decade, various vector and delivery methods have been developed, and to maximize the potential benefits of gene therapy, it must be efficient, persistent, and low in toxicity [96].

Conclusion and future outlook

In recent years, obesity has garnered significant attention from both the media and the medical community. However, despite increased awareness, the sedentary lifestyle persists. Although many major pharmaceutical companies have developed various weight-maintenance drugs, no single drug has proven to be safe and effective for treating obesity. As a result, recent advances in molecular therapies have shifted the focus of pharmaceutical companies toward genetic approaches for obesity treatment. Human genome sequencing and the identification of genes linked to a higher risk of obesity will significantly expand the pool of druggable targets, allowing for the development of treatments that target macromolecules at the nucleotide level. Additionally, advancements in vector generation have brought us closer to the technological reality of targeting metabolically active tissues and achieving long-term expression of therapeutic genes. One major obstacle in implementing reliable gene therapy protocols and controlling gene expression will soon be addressed by applying the gene therapy techniques discussed in this review.

Abbreviations

AAV	Adeno-associated virus
ACTH	Adrenocorticotropic hormone
AMPK	AMP-activated protein kinase
AAV	Adeno-associated virus
AdipoR1/AdipoR2	Adiponectin receptor 1/2
ATGL	Adipose triglyceride lipase
BAT	Brown adipose tissue
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
CRISPR	Clustered regularly interspaced short palindromic repeats
CNTF	Ciliary neurotrophic factor
DIO	Diet-induced obese
dsRNA	Double-stranded RNA
DSBs	DNA double-strand breaks
ERT	Enzyme replacement therapy
FGF	Fibroblast growth factor
FNDC5	Fibronectin type III domain-containing 5
FABP4	Fatty acid-binding protein 4
FDA	Food and Drug Administration
HFD	High-fat diet
HDAd	Helper-dependent adenoviral vector
HSPCs	Hematopoietic stem and progenitor cells
IL-10	Interleukin-10
JNK	C-Jun N-terminal kinase
Mc3r/Mc4r	Melanocortin-3/4 receptor
MUFAs	Monounsaturated fatty acids
MSH	Melanocyte-stimulating hormone
PAG	Periaqueductal gray
PGC1-α	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PPAR	Peroxisome proliferator-activated receptor
POMC	Pro-opiomelanocortin
RNAi	RNA interference
rAAV	Recombinant adeno-associated virus
SCID	Severe combined immunodeficiency
SCD1	Stearoyl-coenzyme A desaturase 1
siRNA	Small interfering RNA
T2D	Type 2 diabetes
TALENs	Transcription activator-like effector nucleases
TALE	Transcription activator-like effector
UCPs	Uncoupling proteins
VLCD	Very-low-calorie diet
WAT	White adipose tissue
ZFNs	Zinc finger nucleases
ZFPs	Zinc finger proteins

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