



REVIEW ARTICLE

The Role of Iron in Adipose Tissue Function, Crosstalk, and Transdifferentiation

Jiamin Guo | Panpan Yu | Chenkang Li  | Guiying Nie | Wenchen Xu | Meiyi Chen | Liang Li | Tianhong Peng | Wei Xie 

Hengyang Medical School, University of South China, Hengyang, China

Correspondence: Liang Li (26002860@qq.com) | Tianhong Peng (thpeng67@163.com) | Wei Xie (weixieh@126.com)

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ABSTRACT

Brown adipose tissue (BAT) plays a crucial role in human physiology and holds significant therapeutic potential for metabolic disorders, including obesity and type 2 diabetes. White adipocytes possess the capacity to transdifferentiate into brown-like adipocytes under specific stimuli, a process termed white adipose tissue (WAT) browning. A key therapeutic strategy for metabolic diseases is to induce WAT browning, which enhances energy expenditure, improves glucose and lipid homeostasis, and reduces insulin resistance. Iron, the most abundant trace element in the body, plays a critical role in regulating adipocyte development, function, and transdifferentiation. This review critically examines the mechanisms through which iron imbalance influences adipocyte transdifferentiation and evaluates its promise as a therapeutic target for metabolic disorders.

1 | Introduction

In mammals, adipose tissue is classified into two structurally and functionally distinct types, white adipose tissue (WAT) and brown adipose tissue (BAT) [1, 2]. Recently, a third type, termed beige adipose tissue, has been identified as an intermediate between BAT and WAT. Beige adipocytes originate from white adipocyte precursors but exhibit morphological and functional similarities to brown adipocytes [3, 4]. Notably, these adipose tissues exhibit remarkable plasticity, allowing for their mutual transformation under specific physiological or environmental stimuli. In mouse models, BAT transplantation has demonstrated promising therapeutic efficacy, including improved insulin sensitivity, enhanced glucose metabolism, and even reversal of type 1 diabetes [5–7]. A process known as “WAT browning” describes the transdifferentiation of white adipocytes into beige adipocytes. This phenomenon can be triggered by diverse stimuli, including diet, exercise, cold exposure, and β -adrenergic receptor activation,

leading to the acquisition of morphological and functional features similar to those of brown adipocytes [8–10]. Importantly, WAT browning also has been shown to enhance glycolipid metabolism, reduce insulin demand, and confer protective effects against obesity and type II diabetes [11, 12]. However, BAT is also susceptible to a process known as ‘whitening,’ whereby it loses its brown characteristics and adopts a white-like unilocular morphology, a transformation influenced by factors such as high ambient temperatures, leptin receptor deficiency, impaired β -adrenergic signaling, and lipase deficiency [13, 14]. The whitening of BAT is associated with adverse metabolic consequences, comprising activation of inflammatory pathways, aberrant elevation of blood glucose concentrations, severe insulin resistance and development of hepatic steatosis [14–16].

Iron, an essential trace element, plays a critical role in maintaining human health. Iron dysregulation has been implicated

Jiamin Guo and Panpan Yu contributed equally to this work.

Summary

This review summarizes the latest research findings on the role of iron in adipose tissue transdifferentiation, as well as in the development, function, and plasticity of adipocytes, and explores the new therapeutic insights that these discoveries offer for obesity and diabetes.

in a wide range of diseases, including cancer, neurodegeneration, atherosclerosis, type 2 diabetes, osteoporosis, osteoarthritis, retinal diseases, and liver fibrosis [17–22]. Beyond its systemic effects, iron modulates adipocyte endocrine functions [23, 24] and promotes adipose tissue transdifferentiation by regulating mitochondrial activity, endocrine factors, and growth factors. This review synthesizes recent advances in understanding the role of iron in adipose tissue transdifferentiation. It specifically focuses on how iron overload and deficiency impact adipocyte development, function, and plasticity, and discusses the novel therapeutic insights these findings offer for obesity and diabetes.

2 | The Effects of Iron Transport on Adipose Tissue Transdifferentiation

In adipose tissue, iron is imported via transferrin receptor 1 (TFR1) and divalent metal transporter 1 (DMT1). Following uptake, cytosolic iron is either shunted into ferritin for storage or allocated to support various metabolic functions [25]. The expression of TFR1 in beige and brown adipocytes is essential for mediating the thermogenic response to external stimuli, such as cold exposure [26]. TFR1 deficiency impairs cellular iron uptake and storage, inducing BAT whitening via mitochondrial dysfunction characterized by diminished expression of respiratory chain complexes I, II, and V, accompanied by reduced uncoupling protein 1 (UCP1) expression [26–28]. A mouse model of systemic iron deficiency demonstrates impaired cold-induced beige adipocyte biogenesis and compromised brown adipocyte thermogenesis [27, 29]. Conversely, adipocyte-specific deletion of ferritin heavy chain (FTH) elevates labile iron levels in adipose tissue, promoting inguinal white adipose tissue (iWAT) browning through redox-dependent pathways [30, 31]. CDGSH iron-sulfur domain 1 (CISD1/mitoNEET), the primary iron-sulfur (Fe-S) cluster protein localized to the outer mitochondrial membrane (OMM) in mammals, orchestrates mitochondrial iron homeostasis and modulates cellular iron flux [32, 33]. High-iron feeding significantly upregulates CISD1 expression in murine models, driving subcutaneous white adipose tissue (sWAT) browning via transcriptional activation of thermogenic regulators, including PR domain-containing 16 (PRDM16), uncoupling protein 1 (UCP1), peroxisome proliferator-activated receptor γ coactivator-1 α (PGC-1 α), and mitochondrial cytochrome c oxidase subunit III (MT-CO3) [32, 34]. Additionally, CISD1 gene expression is significantly positively correlated with the expression of browning-related genes (PRDM16 and UCP1) in human visceral adipose tissue [34]. As a master transcriptional regulator, Forkhead box protein O1 (FoxO1) orchestrates genes governing cell cycle progression, differentiation, and mitochondrial homeostasis [35–37]. FoxO1 deficiency elicits WAT browning through upregulated expression of iron transporters DMT1, transferrin receptor 1 (TFR1), and

mitoferrin-1 (MFRN1), driving concomitant increases in cellular iron uptake and mitochondrial iron loading [38]. Interestingly, deferoxamine enhances beige adipocyte biogenesis and improves lipid metabolism through upregulation of thermogenic markers UCP1 and PRDM16 in the WAT of mice [39–41]. The iron content in epididymal fat of ob/ob mice is significantly elevated, whereas deferoxamine ameliorates obesity by reducing the high iron environment in vivo to maintain it at normal physiological levels [40]. These findings establish that supraphysiological iron transport within the homeostatic range enhances adipose beige, whereas pathological iron depletion ablates this process. The paradoxical pro-thermogenic phenotype induced by FTH deficiency characterized by elevated labile iron pools contrasts sharply with iron chelation-mediated inhibition, indicating that optimal thermogenic capacity requires iron homeostasis within a narrow physiological window.

3 | Iron Overload Inhibits WAT Browning by Exacerbating Inflammatory Response

The systemic toxicity of pathological iron overload manifests as a spectrum of complications, ranging from metabolic disorders like impaired glucose tolerance and insulin resistance to life-threatening conditions such as heart failure and liver fibrosis [42, 43]. Of particular pathophysiological significance is the role of iron in promoting adipose tissue inflammation, primarily through driving M1 macrophage polarization. In support of this, 3T3-L1-differentiated adipocytes exposed to high-iron macrophage-conditioned medium exhibit upregulated pro-inflammatory mediators including interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and monocyte chemoattractant protein-1 (MCP-1/CCL2) [40, 44–48]. Conversely, macrophage-specific FTH deletion depletes intracellular iron reserves, suppressing pro-inflammatory cytokines IL-1 β and TNF- α while concurrently activating thermogenic transcription including peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α) and PR domain containing 16 (PRDM16) in adipose tissue via paracrine signaling [49].

Tumor necrosis factor- α (TNF- α) suppresses the browning of WAT by disrupting cAMP response element (CRE)-dependent transactivation of the UCP1 promoter, mediated through extracellular signal-regulated kinase (ERK)-induced phosphorylation of CRE-binding transcription factors [50]. Similarly, in human adipocytes, concomitant activation of Toll-like receptor 4 (TLR4) and NLRP3 inflammasomes drives interleukin-1 β (IL-1 β) secretion, which abolishes beige adipogenesis through ROS-mediated repression of UCP1 transcription and mitochondrial bioenergetic collapse [51]. These findings collectively demonstrate that enhanced inflammatory response negatively regulates WAT browning. These data establish iron homeostasis as a master regulator of adipose tissue remodeling, in which iron overload creates an inflammatory microenvironment that suppresses WAT browning via M1 macrophage-polarized signaling.

4 | Iron Overload Impairs WAT Browning by Disrupting Mitochondrial Function

Family with sequence similarity 96 A (FAM96A), a cytosolic scaffold for iron-sulfur (Fe-S) cluster biogenesis, orchestrates

cellular iron homeostasis. Adipocyte-specific genetic ablation of FAM96A ablates WAT browning through hyperactivation of the mechanistic target of rapamycin complex 1 (mTORC1) signaling axis, provoking profound mitochondrial dysfunction characterized by reduced mitochondrial biogenesis, ultrastructural aberrations, diminished redox capacity and compromised metabolic capacity [52, 53]. Furthermore, adipocyte-specific FAM96A knockout mice fed high-iron diet exhibited complete ablation of WAT browning through primarily crippling mitochondrial dysfunction characterized by defective respiratory complex assembly, disrupted cristae ultrastructure, and collapsed oxidative phosphorylation, culminating in accelerated adiposity [53]. Deferoxamine provokes profound mitochondrial bioenergetic collapse including defective oxidative phosphorylation, respiratory chain complex destabilization, and ROS-mediated organellar damage, abolishing beige adipocyte differentiation *in vitro*, likely because deferoxamine lowers intracellular iron levels below the physiological threshold, thereby causing mitochondrial injury [54, 55]. These collective observations establish that precise regulation of iron homeostasis is indispensable for proper mitochondrial function and the adipose tissue browning process.

5 | Iron Deficiency Suppresses Exercise-Induced WAT Browning

Exercise increases the plasma concentration of β -aminoisobutyric acid (BAIBA) [56], a metabolite that induces a brown adipose-like phenotype and upregulates UCP1 in white adipocytes via PPAR α [57], suggesting that exercise may promote WAT browning. The exercise and cold exposure induce *Metrn1* upregulation in muscle and adipose tissue. Recombinant *Metrn1* protein promotes browning of WAT via increasing the expression of thermogenic, β -oxidation, and anti-inflammatory genes in adipose, including UCP1, DIO2, ACOX1, and IL-10 [58]. Furthermore, exercise training leads to WAT browning by enhancing the thermogenic characteristics of adipocytes in age-related obesity. Iron serves essential physiological functions in exercise metabolism, particularly in oxygen transport and cellular energy production. The pathophysiology of iron deficiency manifests through its role in oxygen transport and neuronal energy metabolism, leading to a spectrum of disorders ranging from anemia to neurocognitive and behavioral impairments [59, 60]. Clinical evidence demonstrates that iron deficiency anemia significantly impairs aerobic exercise capacity [61]. In addition, iron deficient individuals show a significant decrease in blood lactate levels during maximal exercise, indicating impaired anaerobic metabolism [62]. Endurance training promotes WAT browning by increasing the mRNA levels of Vascular endothelial growth factor A (VEGF-A) in adipose tissue [63–65]. Lactate produced by anaerobic exercise induces WAT browning by significantly increasing UCP1 and Cidea levels in differentiated adipocytes isolated from iWAT, as well as by upregulating the expression of the mitochondrial marker cytochrome c oxidase subunit 7A1 (COX7A1) and the fatty acid oxidation marker carnitine palmitoyltransferase 1B (CPT1B) [66, 67]. Therefore, iron deficiency may impair motor function, leading to suppressed release of lactate, BAIBA, *Metrn1*, and VEGF-A, which inhibits WAT browning.

6 | The Crosstalk Between Iron and Endocrine Factors Regulates the Transdifferentiation of Adipose Tissue

6.1 | Natriuretic Peptide

Natriuretic peptides (NPs), a family including atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP), promote WAT browning by enhancing mitochondrial biogenesis, which is accompanied by increased expression of PGC-1 α and UCP1 in both mouse and human adipocytes [68–70]. Notably, epidemiological evidence shows a negative correlation between circulating NPs concentration and serum ferritin and iron levels [71–73]. Therefore, we propose the hypothesis that iron deficiency may promote browning of WAT by upregulating NPs. That may represent an adaptive metabolic strategy whereby reduced iron availability stimulates the production of NPs to maintain energy homeostasis. However, when compensatory mechanisms become dysregulated, this change may be reversed, a possibility that warrants further investigation in the future.

6.2 | Adrenergic Receptor

Adrenergic receptors (ARs), which mediate catecholamine signaling, are critical drug targets for diseases including hypertension, heart failure, and asthma. Beyond their therapeutic importance, ARs are essential for systemic metabolic balance by directly regulating key processes such as lipolysis in WAT and thermogenesis in BAT [74–76]. Activation of β 3-Adrenergic receptor (β 3-AR) induces the transdifferentiation of mature white adipocytes into beige adipocytes in both mouse and human adipocytes [76, 77]. Epinephrine (Epi) can oxidize Fe²⁺ to form Epi-Fe³⁺ complexes that competitively inhibit Epi binding to adrenergic receptors and their activation during iron overload [78]. Therefore, it is hypothesized that iron overload might impair adrenergic receptor activation, consequently attenuating the browning ability of WAT. Further investigation is warranted in the future. Interestingly, adrenergic stimulation promotes the expression of thermogenic genes by upregulating iron uptake-related proteins, and this effect can be reversed by deferoxamine. This observation is explained by the fact that iron within the physiological range supports thermogenesis; however, when deferoxamine reduces iron concentrations below the physiological range, adrenergic signaling is compromised, leading to suppression of thermogenesis.

6.3 | Thyroid Hormones

Thyroid hormones (THs) are pivotal in coordinating systemic metabolism by directly acting on key metabolic tissues—including the liver, adipose tissue, and skeletal muscle—to integrate energy homeostasis [79, 80]. Iron deficiency impairs thyroid hormone synthesis by suppressing the activity of heme-dependent thyroid peroxidase (TPO) [81–83]. Thyroid hormones promote WAT browning by activating AMP-activated protein kinase (AMPK) in the hypothalamic ventromedial nucleus and by upregulating UCP1, iodothyronine deiodinase 2 (DIO2), PGC1- α , and cell death-inducing DFFA-like effector A (Cidea) in WAT [84–87]. In addition, T3 enhances BAT

thermogenesis by stimulating autophagy-dependent fatty acid oxidation and mitochondrial respiration [88]. UCP1 expression is upregulated in the WAT of mice with hyperthyroidism [89]. Furthermore, iron deficiency impairs thermogenic capacity by reducing the binding of thyroid hormones to their nuclear receptors [83]. Based on these results, it is hypothesized that iron promotes thyroid hormone generation, which could subsequently induce browning of WAT. However, the potential impacts of iron overload on thyroid hormone biosynthesis and its subsequent impact on adipose tissue browning remain to be systematically investigated.

6.4 | Leptin

Leptin is a key adipokine secreted by WAT that functions as a critical signal to the hypothalamus via the leptin receptor (LEPR), integrating central responses to suppress appetite and increase energy expenditure for body weight regulation [90]. Iron negatively regulates leptin expression by inhibiting cAMP-response element binding protein (CREB) glycosylation [91–93]. Genetic ablation of phosphatase Protein Tyrosine Phosphatase-1 B (PTP1B) and T-Cell Protein Tyrosine Phosphatase (TCPTP) amplifies leptin signaling in proopiomelanocortin neurons, driving WAT browning and increasing energy expenditure [94]. Leptin deficiency inhibits mesenchymal stem cells differentiation into brown adipocytes in vitro [95]. Experimental models of leptin deficiency or leptin resistance exhibit downregulated UCP1 expression and compromised energy expenditure and thermogenic capacity in BAT [96]. Consequently, iron overload may downregulate leptin, further attenuating WAT browning. Future experimental validation is required.

6.5 | Hepcidin

Hepcidin, a peptide hormone predominantly synthesized by the liver, is the master regulator of systemic iron homeostasis [97]. Hepcidin-deficient mice exhibit iron overload in iWAT, which significantly suppresses thermogenic transcripts (UCP1, PGC-1 α , CIDEA, and PRDM16), impairs mitochondrial respiration, and consequently inhibits beige adipocyte characteristics [98]. Notably, exogenous hepcidin reduces adipocyte iron content and inhibits beige adipocyte formation [98, 99]. In summary, hepcidin-mediated precise regulation of iron homeostasis is essential for maintaining WAT browning and differentiation potential.

6.6 | Adiponectin

Adiponectin, the most abundant adipokine, exhibits reduced circulating levels in obesity. Exogenous administration of adiponectin has been demonstrated to ameliorate insulin resistance and improve cardiovascular outcomes in preclinical models [100]. Iron overload attenuates adiponectin production in adipocytes through FOXO1 activation [101–103]. Additionally, serum ferritin levels are negatively correlated with adiponectin in humans [103]. Adiponectin promotes WAT browning through a sirtuin 1 (SIRT1)-dependent adenosine monophosphate-activated protein kinase (AMPK) activation pathway [104]. Additionally, adiponectin is

recruited to M2 macrophage surfaces via T-cadherin, enhancing AKT-mediated beige adipocyte activation and subsequent WAT browning [105]. Collectively, iron overload may inhibit WAT browning by suppressing the production of adiponectin. However, this hypothesis is solely based on the aforementioned literature and awaits further rigorous investigation.

7 | Iron Modulates Adipose Tissue Transdifferentiation via Autophagy

Deferiprone upregulates mitochondrial ferritin (FtMt) expression through the hypoxia-inducible factor 1 α (HIF1 α)-specific protein 1 (SP1) axis, thereby promoting mitochondrial autophagy in hepatocytes [106]. The genetic ablation of transcription factor E2F1, a pivotal regulator of cellular proliferation, promotes WAT browning through suppression of white adipocytes autophagy in mice [107, 108]. Overexpression of microtubule affinity regulated kinase 4 (Mark4) promotes white adipocytes autophagy and inhibits browning of WAT by activating the AMPK/AKT/mTOR signaling pathway [109]. Vitamin D3 has been shown to inhibit WAT browning by promoting white adipocytes autophagy [110]. BAT-specific deletion of Atg5 impairs thermogenic capacity by disrupting mitochondrial autophagy, leading to mitochondrial dysfunction and ROS-induced damage in BAT [111]. In addition, PTEN-induced putative kinase 1 (PINK1) knockout, a Parkinson's disease-related gene involved in selective mitochondrial autophagy, disrupts BAT function by promoting NLRP3-mediated whitening of brown adipocyte precursors (BAPs) [112]. Inhibition of mitophagy in beige adipocytes enhances thermogenesis and stimulates WAT browning by suppressing the cAMP-PKA pathway [113]. In summary, inhibiting adipocyte autophagy promotes WAT browning. However, the effect of inhibiting mitophagy on WAT browning depends on its functional role: when mitophagy disrupts mitochondrial function, its inhibition promotes WAT browning; whereas when mitophagy maintains mitochondrial function, its inhibition suppresses WAT browning. Nevertheless, whether iron deficiency influences adipose tissue transdifferentiation through modulation of adipocyte autophagy remains to be determined.

8 | Iron Influences Adipose Tissue Transdifferentiation via Growth Factors

8.1 | Bone Morphogenic Proteins

Bone morphogenetic proteins (BMPs) are potent secreted ligands that transduce signals by binding to cell-surface receptor complexes and triggering Smad protein phosphorylation, thereby initiating a key signaling cascade with broad roles in development and homeostasis [114, 115]. Iron homeostasis significantly modulates BMP signaling pathways. Iron deficiency downregulates the expression of BMP6 and BMP2 in liver endothelial cells [116–119], whereas iron overload upregulates circulating and hepatic BMP6 levels through the c-Jun pathway [120, 121]. Studies show BMP4/7 induce mitochondrial biogenesis and WAT browning via PRDM16 and UCP1 upregulation [122–124], while BMP8B promotes WAT browning by suppressing hypothalamic AMPK and activating orexin (OX) signaling [125]. Based on these findings, we propose the

hypothesis that iron deficiency inhibits the expression of BMPs, thereby suppressing the browning of WAT. Notably, BMP family members can increase hepcidin expression and reduce serum iron levels [119, 126]. These findings indicate that iron not only affects BMP expression but also that BMPs regulate iron metabolism. Although these findings suggest iron may influence adipose tissue transdifferentiation through BMP-mediated pathways, the relationship between them incompletely understood.

8.2 | Vascular Endothelial Growth Factor A

Vascular endothelial growth factor-A (VEGF-A) is the master regulator of both physiological and pathological angiogenesis. Its targeted expression is rate-limiting for the vascular expansion required for healthy adipose tissue plasticity and function [127]. Iron deficiency significantly promotes VEGF-A expression by stabilizing hypoxia inducible factor-1 α (HIF-1 α) [128, 129]. The VEGF-A promotes WAT browning by enhancing UCP1 and PGC-1 α expression in white adipocytes [63, 64]. These findings reveal that iron deficiency may facilitate WAT browning through VEGF-A-mediated transcriptional activation of thermogenic genes, but it is unknown whether this change is compensatory.

9 | Iron Influences Adipose Tissue Transdifferentiation via Other Cytokines

9.1 | 5-Hydroxytryptamine

5-hydroxytryptamine (5-HT) is an important neurotransmitter that regulates systemic energy balance through its distinct actions in the central nervous system and its separate effects in the periphery [130, 131]. Adipocyte-derived 5-HT inhibits the thermogenic effect of BAT by binding to the 5-HT receptor 3 (Htr3) [132]. Chronic 5-HT reuptake inhibitors enhance mitochondrial biogenesis and alleviate oxidative stress in BAT by upregulating the expression of PGC-1 α , PRDM16, and UCP1 [133]. These findings collectively suggest that peripheral 5-HT signaling exerts an inhibitory effect on WAT browning [134]. Interestingly, the 5-HT neuronal ablation mouse model demonstrated decreased UCP1 and DIO2 expression in BAT, impaired thermoregulation, and BAT steatosis, collectively indicating BAT whitening [135]. Activation of the M2 muscarinic acetylcholine receptor (mAChR) suppresses 5-HT neuronal activity, consequently inhibiting BAT thermogenesis [136]. Collectively, peripheral 5-HT suppresses WAT browning, whereas central 5-HT facilitates it. Given that 5-HT biosynthesis requires iron as an essential cofactor [137, 138], iron deficiency may differentially impact central versus peripheral 5-HT synthesis, thereby exerting complex effects on adipose tissue transdifferentiation.

9.2 | Adipose Triglyceride Lipase

Adipose triglyceride lipase (ATGL), the rate-limiting lipase localized on lipid droplets, catalyzes the hydrolysis of triacylglycerol to diacylglycerol. ATGL-KO mice exhibit enlarged brown adipocytes containing large lipid droplets and numerous

mitochondria with structural abnormalities. These morphological changes suggest a brown-to-white adipocyte transdifferentiation [14, 139], indicating that ATGL is essential for maintaining brown adipose tissue function. Elevated ATGL levels have been observed in both subcutaneous and visceral adipose tissue of mice fed a high-iron diet [140]. Therefore, iron-mediated upregulation of ATGL may promote WAT browning under physiological iron conditions. However, it should be noted that this browning effect may differ under iron-overloaded conditions.

10 | Concluding Remarks and Future Perspectives

Metabolic syndrome is a common metabolic disorder characterized by a cluster of conditions including non-alcoholic fatty liver disease (NAFLD), cardiovascular disease (CVD), obesity and type 2 diabetes [141, 142]. The activation of BAT and induction of WAT browning-mediated thermogenesis represent an attractive strategy for improving glucose homeostasis and insulin sensitivity, offering a novel therapeutic option for metabolic syndrome. Compared with the classic BAT which increases energy consumption, the browning in WAT may be more beneficial because its abundance in the human body is much higher. Although cold exposure, exercise, and pharmaceutical intervention represent common strategies to induce WAT browning, each is associated with significant practical limitations. A significant limitation of cold-induced BAT activation lies in its protracted timeframe to achieve desired outcomes, coupled with an unclear risk profile for individuals with cardiovascular disease [143]. Exercise-induced WAT browning is constrained by the requirement for long-term adherence, posing a significant barrier to its therapeutic utility. While pharmacological agents such as CL316243 and rosiglitazone have demonstrated efficacy in BAT activation and WAT browning, their clinical application remains limited by potential adverse effects. The precise regulation of BAT activation and WAT browning faces persistent challenges, with major impediments including inadequate targeting specificity, unresolved long-term safety concerns, and insufficient therapeutic efficacy. Consequently, there is an urgent need to identify safe and effective therapeutic interventions that can harness adipose tissue plasticity for the treatment of metabolism-related diseases.

Iron homeostasis is implicated in the pathogenesis of several Metabolism-related diseases [144–147]. Disorders of iron metabolism are highly prevalent among individuals with metabolic syndrome. Current evidence demonstrates a significant regulatory relationship between iron homeostasis and adipose tissue plasticity. A high-iron diet within the normal physiological range promotes the browning of subcutaneous WAT. However, iron overload can inhibit the browning of WAT through multiple mechanisms, including downregulating the expression of leptin and adiponectin, inhibiting adrenergic receptor signaling, triggering mitochondrial dysfunction, and promoting the activation of pro-inflammatory pathways. Conversely, iron deficiency may also inhibit WAT browning by suppressing the release of central 5-HT and weakening physical activity. Collectively, perturbations in iron homeostasis

adversely affect adipose tissue function and transdifferentiation. It is worth noting that targeted modulation of local iron concentrations through iron chelators may enable precise adipose tissue remodeling. However, the potential systemic consequences of iron depletion necessitate careful consideration, given that it poses a significant risk for the development of iron-deficiency anemia and related complications. Despite some progress in the study of iron and adipose tissue transdifferentiation, critical knowledge gaps persist regarding iron's effects on mitochondrial function, thyroid hormone metabolism, autophagy regulation, BMP pathways, and 5-HT systems etc. Therefore, future research can focus on these areas and safely and effectively induce BAT activation and WAT browning by controlling the change of body iron content. It should be noted that the vast majority of previous findings in this field are derived from mouse experiments. Only a limited number of studies have provided human serum samples or investigated human adipocytes. As a result, the relationship between iron status and adipocyte transdifferentiation in humans remains largely unknown, highlighting a substantial gap in our current understanding that necessitates future in-depth investigation. Additionally, iron exerts diverse functional effects across various cell types and organelles. The critical objective is the local modulation of iron levels within specific cells and organelles, and promotion of intercellular crosstalk to promote the directed differentiation and transdifferentiation of adipocytes. This presents a novel therapeutic approach for the treatment of metabolic diseases.

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Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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