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Multiscale regulatory network underlying cold exposure-induced adipose tissue remodeling: Microscopic and macroscopic perspectives

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Abstract

Cold exposure, a prototypical environmental stressor, activates the metabolic plasticity of adipose tissue (AT) by inducing extensive AT remodeling. This adaptive process not only enhances cold tolerance but also critically improves glucose and lipid (glucolipid) metabolic homeostasis through systemic metabolic reprogramming. This review synthesizes recent high-resolution sequencing studies to comprehensively examine three core dimensions of cold exposure-induced AT remodeling: tissue phenotype, cellular architecture, and metabolic function. In addition, it elucidates intercellular communication and inter-organ interactions within the multiscale regulatory networks that govern AT remodeling, thereby providing a theoretical framework for the development of intervention strategies for metabolic diseases based on mechanisms of cold-induced AT remodeling.

Keywords

cold exposure; adipose tissue plasticity; metabolic reprogramming; intercellular communication; inter-organ regulatory networks

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1 Introduction

Cold exposure represents a distinct environmental stressor whose metabolic regulatory effects, when applied as a non-pharmacological intervention, have been substantiated by both animal models and numerous clinical studies[1]. Emerging evidence further indicates that cold-induced metabolic modulation exerts pleiotropic effects. For instance, the research group led by Hanssen[2] demonstrated that a 10-day exposure to low temperatures results in a 43% improvement of peripheral insulin sensitivity in patients with type 2 diabetes, thereby enhancing overall metabolic health. In parallel, animal studies[3] have shown that exposure to 4 °C markedly suppresses tumor growth and prolongs survival in tumor-bearing animals compared with thermoneutral conditions at 30 °C. In humans, cold exposure has been reported to increase circulating levels of ω-6 and ω-3 polyunsaturated fatty acid (PUFA), which are inversely correlated with obesity, glucose homeostasis, lipid profiles, and hepatic parameters, collectively contributing to improved cardiovascular health[4].

Adipose tissue (AT), a pivotal organ in systemic energy homeostasis, exhibits a high degree of plasticity that enables the dissipation of excess energy in response to cold, with potential implications for the prevention and management of obesity and its associated comorbidities[5-7]. However, cold-induced AT remodeling involves a multitude of complex physiological processes, requiring coordinated interactions among diverse cell types within AT as well as extensive inter-organ communication. Accordingly, this review focuses on recent advances in cold-induced AT remodeling and integrates insights from high-resolution sequencing studies to systematically delineate the associated phenotypic, cellular, and metabolic alterations, as well as the underlying intercellular and inter-organ regulatory networks triggered by cold stress. This synthesis aims to provide a scientific basis and novel perspectives for enhancing adaptive thermogenesis and for identifying biomarkers and potential therapeutic targets for metabolic diseases.

2 Adipose tissue

AT is a dynamic endocrine organ composed of adipocytes and stromal vascular fractions[8]. Traditionally, AT was largely regarded as an inert energy reservoir primarily responsible for triacyl-

glycerol storage, while also providing mechanical cushioning and thermal insulation. However, advances in molecular imaging and metabolomics have progressively unveiled the multidimensional biological functions of AT. Beyond its role in energy storage, AT acts as a central regulator of adaptive thermogenesis and functions as a "metabolic sentinel", modulating systemic energy homeostasis through the secretion of adipokines and extracellular vesicles[9-10]. Based on anatomical location and functional characteristics, mammalian AT is broadly classified into two major types: brown adipose tissue (BAT) and white adipose tissue (WAT). These two depots exhibit pronounced heterogeneity with respect to embryonic origin, macroscopic tissue architecture, intracellular ultrastructure, and physiological functions.

2.1 Anatomical location and physiological functions of BAT

BAT serves as the principal effector of adaptive thermogenesis, and its activity is positively correlated with whole-body energy expenditure[11]. In rodents, BAT is predominantly located in the interscapular region. In humans, BAT develops during the embryogenesis, and its distribution, abundance, and activity change across the lifespan. Early anatomical studies suggested that BAT was present mainly in infants aged 0-3 years, distributed primarily in the interscapular, supraclavicular, and axillary regions, where it played a crucial role in maintaining core body temperature through non-shivering thermogenesis; however, these depots were thought to regress with age[12-15]. Nonetheless, the advent of 18F-fluorodeoxyglucose positron emission tomography-computed tomography (18F-FDG PET-CT) in the early 21st century provided compelling evidence for the persistence of BAT in adults, predominantly localized to the supraclavicular and paraspinal regions[16]. Notably, accumulating evidence indicates that BAT activity is closely linked to the development of obesity and related metabolic disorders, as reflected by an inverse association between BAT volume and indices of central obesity[17]. This relationship is largely attributed to mature brown adipocytes, which constitute over 90% of BAT volume. From a developmental perspective, these cells predominantly originate from Myf5+ progenitors derived from the paraxial mesoderm and differentiate under the control of multiple transcription factors. Mature brown adipocytes are characterized by a high mitochondrial density and multilocular lipid droplets[18-19]. Within these cells, uncoupling protein-1 (UCP1), which is enriched on the mitochondrial inner membrane, can be activated upon appropriate stimuli to dissipate chemical energy as heat, thereby contributing to energy balance and thermoregulation[11,20].

2.2 Anatomical location and physiological functions of WAT

WAT is the predominant adipose tissue type in healthy adult humans, accounting for approximately 20% of total body weight. Anatomically, WAT is subdivided into subcutaneous WAT (sWAT) and visceral WAT (vWAT). sWAT is primarily distributed in the anterior femoral region and within the superficial abdominal fascia, whereas vWAT surrounds internal organs and forms omental and mesenteric fat pads[21-22]. Histologically, WAT exhibits distinct morphological and cellular features distinct from those of BAT, consistent with its unique primary function in energy storage and mobilization. White adipocytes are typically unilocular, containing a single large lipid droplet, with relatively low mitochondrial content and negligible expression of UCP1. This structural organization confers a high capacity for efficient energy storage. Consequently, excessive expansion of WAT due to chronic energy surplus is widely regarded as a central pathological basis for obesity and its associated metabolic disorders[23].

However, the identification of beige adipocytes, which display morphological and functional characteristics similar to those of brown adipocytes, has challenged this traditional view of WAT. Research has demonstrated that exposure to external stimuli, such as cold or pharmacological browning agents, can induce the emergence of dispersed beige adipocytes within WAT depots, thereby promoting adaptive thermogenesis and improving metabolic homeostasis[24-25]. In addition, the discovery of numerous adipocyte-derived factors, including leptin and adiponectin, has further underscored the role of WAT as an endocrine organ involved in the regulation of systemic energy metabolism and appetite. Collectively, these findings suggest that promoting WAT browning, namely the conversion of white adipocytes into beige adipocytes, may represent a promising therapeutic strategy for the treatment of obesity and its related complications.

3 Cold exposure-induced multidimensional adaptive remodeling of AT

Low temperature represents a common environmental physical stimulus, and appropriately applied cold exposure, as a non-pharmacological metabolic intervention, may play a pivotal role in the prevention and treatment of metabolic diseases. In this context, AT, as a crucial coordinating organ of energy metabolism, has garnered significant attention. Cold exposure triggers a profound remodeling response in AT, leading to substantial alterations in tissue phenotype, cellular structure, and metabolic function. Among the various factors known to drive AT remodeling, including diet, physical exercise, and pharmacological agents, cold exposure remains one of the most classical, potent, and reproducible stimuli.

3.1 Cold-induced phenotypic remodeling of AT

AT exhibits marked phenotypic adaptability that enables it to respond to diverse environmental challenges, a feature that is readily observable at the tissue level. In BAT, cold exposure induces tissue expansion, particularly in adults, accompanied

by a color change from light pink to deep red and a clearer anatomical demarcation from surrounding interscapular tissues[26-28]. Histological analyses further reveal an increased prevalence of multilocular lipid droplets and a marked elevation in mitochondrial density within brown adipocytes.

Comparable but even more pronounced phenotypic changes occur in WAT in response to cold exposure, a process commonly referred to as WAT browning. During this process, beige adipocytes emerge within WAT depots. These cells display a morphology distinct from that of classical white adipocytes and are characterized by abundant multilocular lipid droplets and high mitochondrial content, closely resembling brown adipocytes, although their developmental origins and gene expression profiles are not identical[29-31]. As a consequence of beige adipocyte accumulation, the typically white appearance of WAT gradually shifts toward a pale pink coloration.

3.2 Cold-induced structural remodeling of AT

The functional heterogeneity and plasticity of AT are largely attributable to the diversity of resident cell populations. While BAT expansion and WAT browning reflect the de novo generation of brown and beige adipocytes, the cellular compositional changes induced by cold exposure extend far beyond adipocytes alone. Effective tissue remodeling requires coordinated interactions among multiple cell types, a process that has been elucidated by recent high-resolution approaches capable of resolving cellular heterogeneity with unprecedented precision.

For example, Song *et al.*[32], using single-nucleus RNA sequencing (snRNAseq), subdivided the previously presumed homogeneous population of brown adipocytes into subtypes with low thermogenic activity (BA-L) and high thermogenic activity (BA-H). Their findings demonstrated that cold exposure drives a progressive shift in cellular composition, characterized by a transition from BA-L to BA-H cells. In parallel, substantial remodeling occurs within the adipose stem and progenitor cell (ASPC) compartment, which directly contributes to adipocyte turnover and expansion. Although adipocytes of different lineages arise from distinct developmental programs, they can all be generated de novo from ASPCs. Importantly, ASPCs themselves are heterogeneous and exhibit pronounced spatial and temporal diversity. Current evidence suggests that ASPCs comprise at least three major hierarchical subpopulations: adipocyte stem cells (ASCs), preadipocytes (preAs), and amphiregulin-expressing cells (Aregs)[33].

Single-cell sequencing studies have further revealed that cold exposure induces dynamic shifts among these ASPC subpopulations. Specifically, exposure to 6 °C reduces the proportion of ASCs while increasing the relative abundance of preAs and Aregs[34]. This shift provides a mechanistic explanation for cold-induced thermogenic adipocyte expansion, whereby multipotent ASCs progressively commit to downstream lineages that support beige and brown adipocyte neogenesis. Moreover, sustained thermogenic activity requires coordinated vascular remodeling and enhanced sympathetic innervation, processes that are frequently accompanied by a controlled inflammatory response. Alterations in immune cell composition help establish an immunomodulatory microenvironment conducive to tissue remodeling[35]. For example, Ye *et al.* generated a comprehensive single-cell atlas of AT immune cells under cold exposure and demonstrated increased proportions of monocytes and T lymphocytes, along with a reduction in natural killer (NK) cell abundance[36].

3.3 Cold exposure-induced metabolic remodeling of AT

Cold exposure promotes a fundamental metabolic shift in AT from energy storage toward energy utilization[37]. Central to this process is UCP1, which is abundantly expressed on the inner mitochondrial membrane of brown and beige adipocytes. UCP1 facilitates proton transport across the mitochondrial membrane, dissipating the electrochemical gradient and uncoupling oxidative phosphorylation from ATP synthesis[38].

Importantly, the metabolic consequences of this process extend beyond thermogenesis and exert broad effects on systemic metabolic homeostasis. Cold-induced AT remodeling is associated with enhanced lipolysis, increased cellular uptake of glucose and fatty acids, and upregulation of upstream regulators of UCP1 expression[31,39-42]. Additionally, cold exposure augments the secretion of multiple adipokines and lipid-derived signaling molecules, including 12-HEPE, 12,13-diHOME, and N-acyl amino acids[43-46]. These factors contribute to the reduction of ectopic lipid accumulation and circulating levels of triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C)[28,47], with important implications for the prevention and amelioration of obesity, diabetes, and cardiovascular diseases. Furthermore, emerging evidence indicates that adipocytes can generate heat through UCP1-independent mechanisms, involving futile metabolic cycles such as Ca^{2+} cycling, creatine cycling, and triacylglycerol and fatty acid turnover. These alternative thermogenic pathways play complementary roles in regulating energy expenditure[5]. Collectively, these findings highlight cold-induced metabolic remodeling of AT as a promising therapeutic avenue for metabolic disorders.

4 Intercellular communication networks in cold exposure-induced AT remodeling

Cold exposure-induced AT remodeling is a complex and highly integrated systemic biological process. The dynamic changes in the abundance, state, and functional properties of multiple cell

types within AT underscore the central role of the local cellular microenvironment in orchestrating tissue remodeling. Despite substantial differences in cellular composition between WAT and BAT, accumulating evidence indicates that adipocytes serve as pivotal hubs coordinating intercellular communication in response to cold exposure[34].

4.1 Adipocyte-mediated regulation of sympathetic neural network formation

During cold exposure, activation of the BAT thermogenic program and the emergence of thermogenic beige adipocytes in WAT require extensive support from the sympathetic nervous system. Adipocyte-derived transcriptional regulators, such as PRDM16 and the endoplasmic reticulum membrane protein CLSTN3β[48-49], as well as neurotrophic factors including S100 calcium-binding proteinβ[50] and bone morphogenetic proteins (BMPs)[51-52], play crucial roles in promoting sympathetic nerve growth, branching, and innervation within AT under cold conditions.

4.2 Adipocyte-mediated regulation of angiogenesis

A dense and well-organized vascular network is essential for sustaining the thermogenic program of AT by ensuring adequate delivery of oxygen and metabolic substrates. Adipocytes act as major sources of angiogenic and vascular maintenance factors and secrete substantial amounts of vascular endothelial growth factor (VEGF) in response to cold exposure. VEGF signals through its tyrosine kinase receptors, VEGFR1 and VEGFR2, on endothelial cells to stimulate robust angiogenic responses[53-54]. In parallel, platelet-derived growth factor CC (PDGF-CC), a downstream effector of the VEGF-VEGFR2 signaling axis, facilitates crosstalk between endothelial cells and PDGFRα-positive stem cells, thereby coordinating the de novo differentiation of thermogenic beige adipocytes[55].

4.3 Adipocyte-mediated activation of the immunological microenvironment

Cold exposure induces a type 2 immune response within AT, characterized by the coordinated involvement of eosinophil chemotactic protein (CCL11), eosinophils, and alternatively activated (M2) macrophages. Under cold conditions, adipocyte-derived fibroblast growth factor 21 (FGF21) stimulates CCL11 production through autocrine and paracrine signaling pathways, leading to the recruitment of eosinophils[56]. Recruited eosinophils, in turn, exhibit increased expression of interleukin (IL)-4 and IL-13[57], thereby amplifying IL-4/IL-13 signaling within the tissue microenvironment. This signaling cascade promotes M2 macrophage polarization and catecholamine production, which contributes to the induction of AT browning[58].

In addition, M2 macrophages can secrete the glycoprotein SLIT3, which binds to its receptor ROBO1 on sympathetic nerves fibers. This interaction activates the Ca^{2+}/$CaMK^{+}$ signaling pathway, enhancing norepinephrine release and ultimately promoting adipocyte catabolism and thermogenic capacity[59]. Interestingly, cellular interaction network analyses by Liu *et al.* revealed that SLIT3 can also be secreted by endothelial cells in WAT under cold exposure[34]. Although the underlying mechanisms remain to be fully elucidated, this finding underscores the complexity and redundancy of intercellular communication networks governing AT remodeling in response to cold.

5 Inter-organ metabolic interactions during cold exposure-induced AT remodeling

Maintenance of systemic energy metabolic homeostasis is fundamental to organismal survival and physiological function. Accumulating evidence over recent decades has underscored the necessity of moving beyond a single-organ perspective to elucidate the macroscopic regulatory networks that govern energy metabolism through inter-organ communication. As a central and dynamic endocrine organ in metabolic regulation, AT undergoes extensive remodeling in response to environmental and nutritional cues, enabling flexible transitions between energy storage and energy expenditure to meet diverse systemic demands. Accordingly, cold exposure-induced AT remodeling is increasingly recognized as an intrinsically multi-organ, coordinated regulatory process.

5.1 Central nervous system-mediated initiation of adipose thermogenesis

Cold is a potent environmental stimulus that rapidly activates systemic thermogenic responses. Upon exposure to low temperatures, peripheral sensory neurons detect thermal signals and relay this information to the brain. In response, the central nervous system (CNS) activates sympathetic nerve terminals innervating BAT, leading to the release of neurotransmitters such as norepinephrine (NE), neuropeptide Y (NPY), and ATP. These signals collectively activate sympathetic signaling cascades and initiate the thermogenic program in BAT[60-62]. In parallel, hormonally mediated central pathways contribute to thermogenic regulation. For example, hypothalamic secretion of thyrotropin-releasing hormone (TRH) stimulates pituitary release of thyroid-stimulating hormone (TSH), which acts on the thyroid gland to increase the production of thyroid hormones triiodothyronine (T3) and thyroxine (T4). These hormones, in turn, promote UCP1-dependent BAT thermogenesis, lipid oxidation, and the browning of WAT[63-64].

5.2 Synergistic thermogenic metabolism of BAT and WAT

Sustained thermogenesis requires coordinated metabolic interac-

tions between BAT and WAT. WAT plays a dominant role in this process, as fatty acids released through WAT lipolysis serve as critical substrates for systemic thermogenesis. These fatty acids not only fuel thermogenic activity within WAT itself but also provide essential energy substrates for BAT-driven heat production. Consistent with this concept, genetic ablation of adipose triglyceride lipase (ATGL) or its coactivator comparative gene identification-58 (CGI-58) in brown adipocytes, which disrupts BAT lipolysis, does not impair cold-induced thermogenesis in mice[65-66]. Moreover, WAT-derived free fatty acids (FFAs) have been shown to directly enhance UCP1-mediated proton conductance, thereby facilitating activation of the thermogenic program in brown and beige adipocytes[67].

5.3 Bidirectional metabolic regulation of the liver-AT axis

In addition to WAT, the liver serves as an important supplier of metabolic fuels for thermogenic adipocytes during cold exposure. Animal studies have shown that cold stimulation enhances hepatic provision of energy substrates through the activation of gluconeogenesis, lipoprotein synthesis, very-low-density lipoprotein (VLDL) secretion, ketogenesis, and acylcarnitine production[68-69]. Concurrently, cold exposure induces hepatic secretion of endocrine factors such as Tsukushi (TSK) and fibroblast growth factor 21 (FGF21), which contribute to the regulation of thermogenesis and energy expenditure[70-71]. Intriguingly, this interaction is bidirectional: activation of BAT enhances systemic fatty acid utilization and accelerates clearance of circulating fatty acids, thereby reducing ectopic lipid accumulation in the liver and preserving hepatic health[72-73].

5.4 Regulation of thermogenesis *via* the gut-liver-AT axis

The mechanisms by which cold exposure modulate lipid metabolism and thermogenic activity extend to the gut-liver-adipose tissue axis. Cold exposure has been shown to promote hepatic conversion of cholesterol into bile acids, which are subsequently excreted into the intestine. Altered bile acid flux can reshape the composition and function of the gut microbiota. In turn, endocrine signals and microbial metabolites derived from these cold-adapted microbial communities feedback to stimulate adipocyte thermogenesis, thereby supporting sustained energy expenditure in the context of elevated plasma bile acids[74]. Notably, cold exposure itself induces pronounced changes in gut microbiome composition. Experimental studies have demonstrated that transplantation of gut microbiota from cold-exposed mice into germ-free recipients markedly enhances BAT activation and promotes beige adipocyte formation in WAT, leading to improved systemic insulin sensitivity and increased cold tolerance[75-76] (Fig.1).

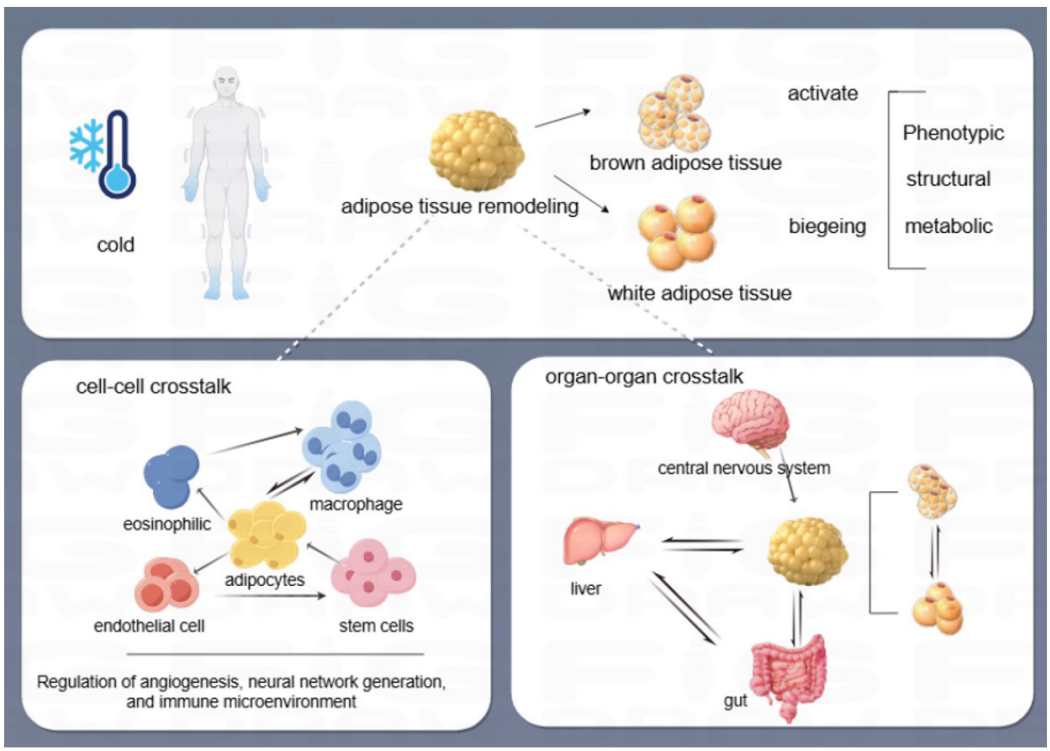

Fig. 1 Cold exposure induces adipose tissue remodeling via intercellular and inter-organ regulatory networks (Created with FigDraw, Zhejiang, China)

6 Summary and future perspectives

AT plays a paradoxical role in the pathogenesis of metabolic diseases, acting both as a contributor to pathological processes and as a promising therapeutic target. Developing strategies that modulate AT metabolic remodeling to mitigate pathogenic risks while maximizing physiological benefit is therefore of considerable scientific and clinical importance. As highlighted in this review, AT plasticity is a fundamental biological property, and cold exposure, as a prototypical environmental stressor, can activate adaptive remodeling programs within AT. These adaptations markedly enhance systemic metabolic efficiency and can attenuate metabolic dysfunction. However, cold-induced AT remodeling encompasses multidimensional biological events. At the macroscopic level, it manifests as readily observable phenotypic transitions, such as the browning of WAT. At the microscopic level, it involves complex cellular and subcellular structural remodeling, including the proliferation and functional activation of thermogenic adipocytes, which has historically been challenging to resolve. Traditional approaches, limited by technical constraints, have been insufficient to systematically interrogate these microscopic processes and their underlying mechanisms.

The advent of high-resolution sequencing technologies has provided powerful tools to dissect the spatiotemporal regulatory networks governing AT remodeling, thereby facilitating the identification of molecular targets for interventions that promote metabolically beneficial adaptations. Insights gained using these approaches indicate that cold exposure-induced AT remodeling, encompassing phenotypic, structural, and metabolic functional transitions, is characterized by pronounced spatiotemporal complexity. This process depends not only on local interactions between adipocytes and non-adipocyte populations, such as immune and endothelial cells, but also on the establishment of systemic regulatory networks linking AT with distal organs, including the brain, liver, and gut. Together, these multilevel interactions maintain energy homeostasis and enhance adaptive responses to metabolic stress. Although such multilayered regulatory architectures can buffer organisms against environmental perturbations, their heterogeneity and redundancy also substantially complicate mechanistic dissection and integrative analysis. By synthesizing current evidence, this review aims to provide new perspectives on enhancing AT adaptive thermogenic capacity and on identifying biomarkers relevant to metabolic diseases.

It is also important to recognize that cold exposure-induced AT remodeling is not permanent but exhibits a high degree of reversibility. Upon cessation of cold exposure and return to ambient or thermoneutral conditions, thermogenic capacity is markedly reduced or abolished. In WAT, this reversal is characterized by the conversion of multilocular lipid droplets in beige adipocytes back to unilocular structures, accompanied by a functional shift toward energy storage and a reduction in mitochondrial content and UCP1 expression[77]. In BAT, while brown adipocytes may partially retain their morphological features, transitions in thermogenic states, including a reduction in the proportion of highly thermogenic brown adipocytes, can still lead to diminished thermogenic and metabolic efficiency[32]. Collectively, these reversible remodeling processes adversely affect basal metabolic rate and systemic metabolic homeostasis. Therefore, exploring strategies to maintain and stabilize the beneficial metabolic effects of WAT and BAT, by understanding both the induction and reversal of AT remodeling, represents an important direction for future research.

Finally, several limitations of the current body of research should be acknowledged. Much of the mechanistic evidence derives from rodent models, whereas human AT exhibits substantial species-specific differences in cellular heterogeneity, innervation patterns, and cold acclimation capacity. Consequently, validation of clinical relevance using human-relevant systems, including organoid models, primary human adipocyte cultures, and non-invasive metabolic imaging modalities such as positron emission tomography-computed tomography (PET-CT), will be essential for translating basic research to clinical applications. Nonetheless, the continued development of advanced sequencing technologies and experimental model systems is progressively illuminating the complex regulatory networks governing AT function, opening new avenues for the precision prevention and treatment of metabolic diseases.

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Research ethics

Not applicable.

Informed consent

Not applicable.

Author contributions

Yang Y S and Zhang G Y were responsible for writing the manuscript and conducting literature searches; Yang D F and Li X performed the final review and revision of the manuscript. All authors were responsible for the final manuscript.

Use of large language models, AI and machine learning tools

No large language models, AI or machine learning tool was used for any part of the present study.

Conflict of interest

Yang D F is a member of the Editorial Board of the journal. The manuscript was handled in accordance with the journal's standard editorial procedures, and the peer review process was conducted independently of this author and her research group.

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Data availability

All relevant data are within the manuscript.

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