Regulatory mechanism of white adipocyte browning and research advances

Zihan Wang*

Jinan Foreign Language School, Jinan, 250108, China

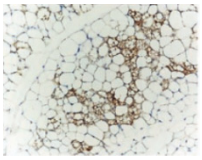
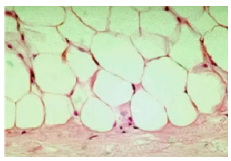
Abstract: Adipose tissue has energy storage and metabolic functions, and its content is highly correlated with an individual's obesity status. The relative proportions of white adipocytes, brown adipocytes, and beige adipocytes are also important in regulating individual metabolic levels. White adipocytes function as energy stores, Brown adipocytes can consume energy through heat production. It has indicated that under certain stimulus conditions, some white adipocytes can exhibit characteristics similar to those of brown adipocytes, a process known as browning of white adipocytes, leading to the production of beige adipocytes. Activating browning of white adipocytes is an effective way to control obesity. This article describes the research progress related to the browning of white adipocytes, focusing on the mechanisms of transcriptional regulation, hormones, mitochondrial morphology-associated proteins, and local thermal stimulation on cell browning. Regulating the composition ratio of adipocytes improves the individual metabolic level and thus provides some theoretical basis for the treatment of obesity.

1. Introduction

Obesity is a widely recognized problem in our society today and is prevalent among adolescents, young adults, and middle-aged and older adults. Since obesity can cause many complications, such as hyperlipidemia, hypertension, diabetes, heart disease, and other diseases, research on obesity control and treatment methods is particularly relevant. Not only is it conducive to improving the health of the entire population, but it can also reduce the burden on society.

Obesity is closely related to adipocyte function, and different types of adipocytes play significant roles in physiologic or disease conditions. In individuals, there are mainly three kinds of adipocytes, including brown adipocytes, white adipocytes, and beige adipocytes (Table 1).

Table 1. Main characteristics of the three types of adipocytes

Adipocyte type	Morphological	Appearance location	Origins	Hallmark expression	Critical transcription factors	Activation condition
Beige adipocytes		Clavicle, groin and neck	Myf5– cells, Pdgfr-α+cells	Cd137, Tbx1, Tmem26, Cited1, Shox2	C/ebpβ, Prdm16, Pgc-1α	Cold Thiazolidinediones Natriuretic peptides Fgf21, Irisin
White adipocytes		Subcutaneous tissue and around the internal organs	Myf5+ cells	–	PPARγ, C/EBPα, FGF21, PRDM16	–

Brown adipocytes, which contain multihomed cytoplasmic lipid droplets and a large number of functional mitochondria, are key cells for heat production in mammals and are filled with mitochondria containing UCP1 (Uncoupling protein 1). When UCP1 is activated, it drives ATP, which burns energy through non-fibrillatory heat production. White adipose tissue (BAT) is stored mainly in the abdominal cavity, also found in the greater omentum, mesentery, thighs, and buttocks. One of the characteristics of white adipocytes is monolocular lipid vacuoles, which squeeze around the nucleus and squeeze mitochondria to the thin edge around lipid

*Corresponding author's e-mail: service@zkycedu.com

droplets. White fat cells do not help produce heat in the body. Enhanced lipolysis of some white adipocytes in response to beta-adrenergic receptor agonists or in response to cold stimulation. Those cells have elevated UCP1 expression and exhibit characteristics similar to brown adipocytes, and this intermediate taxon between white and brown adipocytes is called beige adipocytes. Beige adipocytes are adipocytes that have thermogenic capacity during the development of white adipose tissue and express UCP1.Beige adipocytes can be formed from white adipocytes by through mitochondria, cellular autophagy, hormones, transcriptional regulation, inflammatory and nutrient signaling pathways; In addition, beige adipocytes also be generated directly by preadipocytes, stem cells (Figure 1).

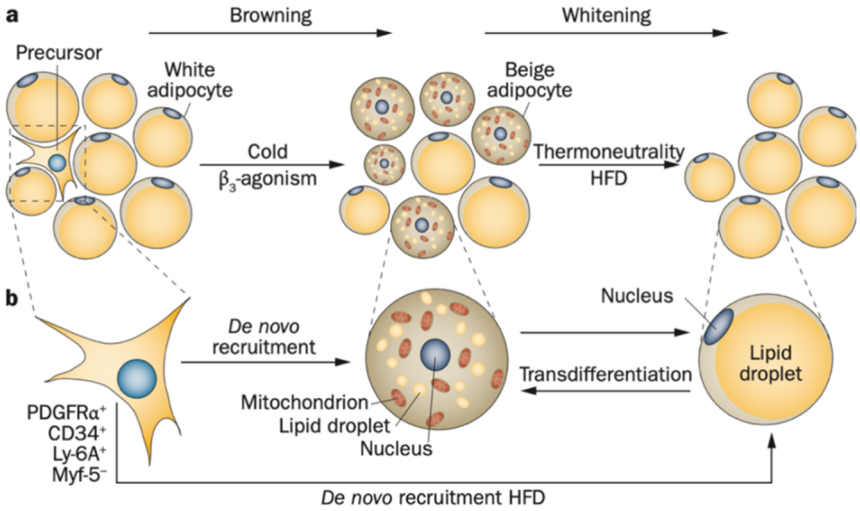


Fig.1. Reversibility of Adipose Tissue Browning and Origin of Beige Adipocytes

a. Specific pools of white adipocytes can produce large numbers of beige adipocytes (browning of white adipocytes), a process determined by environmental stimuli such as low temperatures and β3-adrenergic receptor agonists leading to browning.

b. In the adipocyte population, there is a population of bi-directional potential precursor cells that express PDGFRα, CD34, Ly-6A but not Myf-5, and can differentiate into beige or white adipocytes depending on environmental stimuli; Differentiated cells can also differentiate again into white or beige adipocytes after a white or browning stimulus.

Since beige adipocytes can perform some of the functions of brown cells and have beneficial aspects for human health, exploring the conversion of white adipocytes into beige adipocytes, i.e., the process of browning white fat, is of particular importance for the prevention and treatment of obesity.

The process of adipocyte browning, where white adipocytes acquire brown-like characteristics, presents a promising avenue for metabolic research. It offers a natural mechanism to enhance energy expenditure and potentially reverse obesity-related metabolic dysregulation. However, the molecular underpinnings of this process are complex and not yet fully understood. Understanding the regulatory mechanisms of adipocyte browning is crucial for harnessing its therapeutic potential. This article will summarize the regulatory mechanisms and major research advances in the browning of white adipocytes and delve into the current research landscape, highlighting the significance of adipocyte browning and its implications for the development of innovative obesity treatments.

2. Ucp1 Expression Regulation

UCP1 is an inner mitochondrial membrane transporter protein responsible for thermogenesis, which promotes thermogenesis in brown and beige fats by uncoupling oxidative phosphorylation from ATP synthesis and converting the energy generated by substrate oxidation into heat. Brown adipose tissue (BAT) is filled with mitochondria containing UCP1. When UCP1 is activated, it drives the electrochemical gradient short circuit of ATP synthesis, thereby stimulating the activity of the respiratory chain. Heat is produced by the burning of available substrates and distributed to other parts of the body through cycles; There is no UCP1 expression in white adipocytes, which can not produce heat in the human body; beige adipocytes have UCP1, so they can play some functions of brown adipocytes, such as heat production.

The expression of UCP1 is affected by many biological factors, such as Crfr2, Dlk1, Ikbke, Rip140, Prkcb, Prkcb, Tnfrsf1a, Prdm16 and so on. Crfr2 increases glucose tolerance and UCP1 expression in BAT, and Dlk1 increases PGC-1α and UCP1 expression in WAT, Ikbke can increase the number of UCP1 transcripts and proteins in WAT. Rip140 can recruit chromatin modifiers such as DNA methyltransferase and histone methyltransferase to weaken UCP1. The presence of Prkcb will increase the expression of β1 and β3 adrenergic receptors in WAT and lead to increased expression of PGC1α and UCP1 mediated by p38 MAPK. The presence of Tnfrsf1a can help increase UCP1 in BAT, leading to increased oxygen consumption, and PRDM16 in adipocytes can help increase intracellular beige fat.

The expression and function of UCP1 are tightly correlated with the function of the three adipocyte cell types, and thus regulation of UCP1 expression can mediate transitions in type and function among adipocytes.

3. Transcriptional Regulation Mediates Browning of White Adipocytes

3.1. PPARγ

PPARγ is a ligand-activated transcription factor that belongs to the nuclear hormone receptors. PPARγ is necessary for adipocyte formation and function in vivo and in vitro and is involved in the regulation of adipogenesis, lipid metabolism, inflammation, and metabolic homeostasis through PPARγ-responsive regulatory element binding.PGC-1α can bind to the complex of PPARγ and retinoid X receptor (RXR), which activates UCP1 expression for thermogenesis by binding to the PPAR response element in the UCP1 promoter. When adipocytes were treated with PPARγ or RXR agonists, the transcription level of UCP1 also increased. Ectopic expression of PGC-1α in white adipocytes activates the expression of UCP1 and key mitochondrial enzymes of the respiratory chain (e.g. Cox4) and increases mitochondrial biogenesis. Besides, K268ac and K293ac of PPARγ can be deacetylated and regulated in a ligand-dependent manner by SIRT1, whereas deacetylation of PPARγ reduces metabolic abnormalities caused by a high-fat diet, which induces browning alterations in white adipose tissue [1].

3.2 C/EBPα

Like PPARγ, CCAAT / enhancer-binding protein α (C/EBPα) is also a major regulator of adipogenesis. C/EBPα has an essential role in cellular insulin sensitivity but is not required for brown adipocyte differentiation. SHOX2 protein is highly expressed in mouse and human inguinal WAT, and its role is to inhibit C/EBPα activity and lipolysis in adipocytes. Specific knockdown of the Shox2 gene in mouse adipocytes increased browning and lipolysis of inguinal WAT and increased β-adrenergic receptor levels [2]. In addition, the role of C/EBPα, including PPARγ mentioned above, is also regulated by a large group of pre-dipole or anti-dipole transcriptional cofactors, such as GATA transcription factors, liver X receptors and sterol regulatory element binding protein 1C.

3.3 PRDM16

PRDM16, a key transcriptional regulator controlling BAT development, also plays an important role in PPARγ-mediated leukocyte browning. Studies have shown that PPARγ ligands need to be fully excited to preferentially induce brown fat-related gene expression in subcutaneous white fat, and these effects require the expression of PRDM16.PRDM16 knockdown attenuates the effect of rosiglitazone, an agonist of PPARγ, on brown adipose gene-induced expression. In contrast, PRDM16 and rosiglitazone were able to synergistically activate brown adipose gene expression in vivo, and this synergistic effect was closely associated with increased accumulation of PRDM16 protein. This suggests that compounds capable of stabilizing PRDM16 protein expression may represent a novel avenue for the treatment of obesity and diabetes.

On the other hand, microRNAs can modulate PRDM16 to regulate the process of white adipocyte browning. MicroRNAs are a class of evolutionarily conserved non-coding small RNA, which have the function of regulating genes at the translation level to affect the browning of fat. Inhibition of miR-133 expression in adipocytes by cold exposure will result in increased protein expression of PRDM16 and increased expression of downstream thermogenic target genes. Mice lacking miR-133 expressed higher levels of PRDM16 in WAT and developed more beige adipocytes compared to wild-type mice. miR-133 was also highly expressed in mouse adult muscle stem cells while inhibiting PRDM16 expression. Reduction of miR-133 in regenerating muscle leads to ectopic development of brown adipocytes and associated increased energy expenditure.

4. Effect Of Hormones on Browning of White Adipocytes

4.1. γ-aminobutyric acid (GABA) and β-aminoisobutyric acid (BAIBA)

GABA affects the infiltration of macrophages in adipose tissue, and through this process the degree of whitening of brown adipocytes is reduced, which allows for the maintenance of thermogenesis in brown adipocytes. BAIBA is also a PGC-1α-mediated and exercise-triggered non-adrenergic activator of white fat browning, which can mediated through PPAR α increased gene expression specific for brown fat in white cells and help induce the phenotype of brown cells in pluripotent stem cells in humans.

4.2. Thyroid hormone

Thyroid hormone can promote the differentiation of preadipocytes into white adipocytes, promote fat synthesis and catabolism, and accelerate the rate of fat metabolism, which plays an important role in regulating fat metabolism and adipocyte transformation. Thyroid hormones on the one hand release T3, which directly regulates UCP1 expression, and also act as sympathetic activators inducing UCP1 expression at the central level, which increases fatty acid oxidation and mitochondrial respiration, and can modulate autophagy, thus promoting increased thermogenesis in brown fat; adipocytes also catalyze the conversion of thyroid hormones via DIO2.

4.3. FGF21

Fibroblast growth factor 21 (FGF21) is a peptide hormone that is synthesized by several organs and is capable of regulating energy homeostasis, and the liver is thought to be the primary site of FGF21 production and release into the bloodstream. FGF21 is involved in the regulation of hepatic lipid metabolism, blood glucose, and pancreatic β-cell function, and can help brown adipocytes and beige adipocytes produce heat. FGF21 plays a key regulatory role in the browning of white adipocytes. It has been shown that FGF21 and FGF receptors and their co-receptors interact with each other, and the activated receptors subsequently activate the p38/MAPK pathway, which in turn increases the expression of UCP1, enhances brown adipose activity and promotes the process of browning of white adipocytes. Also, brown adipocytes can transcriptionally regulate FGF21 via the cAMP-mediated signaling pathway after thermogenic activation, resulting in an autocrine effect on brown adipocytes.

4.4. Bone morphogenetic protein (bmp)

Studies have found that BMP can participate in the development and differentiation of adipose tissue.BMP4 induces adipocyte precursors and adipose stem cells to express PGC-1α, which promotes angiogenesis and beige adipocyte development.BMP7 is an important factor involved in brown fat differentiation, as BMP7 stimulates the expression of PRDM16 and PGC-1α, early regulators of brown fat, and thereby promotes UCP1 synthesis. Furthermore BMP8B, although not affecting fat browning, plays a crucial role in maintaining altered browning; Because BMP8B is dependent on ovarian estradiol levels, the thermogenic effect in white and brown fat is only present in the female body.

5. Effect of Mitochondria on the Browning of White Adipocytes

Mitochondria, the energy metabolism center of the cell, also play an important role in the browning process of white adipocytes. As a highly dynamic organelle, dynamic changes in shape and morphology can regulate energy conversion processes, thereby altering respiratory efficiency and nutrient utilization. Changes in mitochondrial morphology are mainly regulated during two processes, fusion and division, regulated by MFN1/2, Opa1, which mediates mitochondrial fusion, and Drp1, which mediates fission, respectively. Among other things, Opa1 is responsible for anchoring proteins into the inner mitochondrial membrane during mitochondrial fusion and can regulate the morphology of the mitochondrial cristae and the stability of the respiratory chain complex. It has been shown that the knockdown of Opa1 in BAT was able to stimulate WAT browning by inducing the expression and secretion of FGF21, suggesting that mitochondrial fusion can influence the browning process in adipocytes [3], but the exact mechanism of action and its role in the transformation of white to beige cells remains to be investigated. It has also been reported that Opa1 expression promotes both thermogenesis in brown adipocytes and browning of white cells, this process is mainly regulated using the urea cycle, linking changes in mitochondrial dynamics, nutrient utilization, and metabolic regulation [4]. Specifically, Opa1 can increase the concentration of cAMP in cells by regulating Ca2+ levels, while multiple signaling pathways of cAMP and calcium-regulated protein kinases can phosphorylate and activate CREB. In cells, Cps1 mainly controls nitrogen sources to influence urea synthesis, while activated CREB stimulates Cps1 to carry out the urea cycle and promotes the accumulation of fumaric acid. Fumaric acid can drive the expression of demethylase Kdm3a-dependent Ucp1, which in turn leads to browning of white fat. These studies have demonstrated the role of mitochondrial morphology in promoting the browning of adipocytes, suggesting a new direction for obesity treatment.

6. Thermal Stimulation Promotes Browning of White Fat Cells

Thermal stimulation is a commonly used method for the treatment of metabolic diseases, which can improve the metabolic state of cells, to achieve the purpose of treating diseases. Recent studies have shown that thermal stimulation has also been shown to promote the browning of white fat and stimulate thermogenesis in beige adipocytes [5]. Local thermal stimulation increased the expression levels of UCP1 and PGC1a in cells and mouse white adipocytes, and this process was independent of the action of norepinephrine. The authors found through experimental investigation that thermal stimulation activates HSF1, a heat shock transcription factor that coordinates cellular responses to various stresses. The ability of thermogenesis and browning of white fat was significantly reduced in HSF1 knockout mice compared with non-knockout mice. Next, the author identified an RNA-binding HSF1 protein target-Hnrnpa2b1 (A2b1) through ChIP-seq. Overexpression of A2b1 in HSF1-knockout mice can help mice to produce heat and attenuate the decrease in heat-producing gene expression. It is concluded that the HSF1-A2b1 axis can regulate the browning of white fat and reduce metabolic disorders.

This innovative study shows that thermal stimulation plays an important role in stimulating white fat browning and beige fat thermogenesis, providing a scientific basis for the treatment of obesity and various metabolic diseases. The HSF1-A2b1 pathway can be used as a potential target for the treatment of obesity, and it is expected that drugs based on this target can show great potential in clinical practice.

7. Conclusion

Enhancement of brown adipocytes and beige adipocytes is very effective in the treatment of obesity and related metabolic diseases. Although there are still quite a few unsolved problems, a growing body of research is now

pointing to specific genes or pathway alterations that can increase the relative proportions of brown fat cells and beige fat cells. It has the potential to become a therapeutic target for obesity and related metabolic diseases. One potential application lies in the development of pharmacological agents that mimic the effects of hormones known to induce browning, such as thyroid hormone and FGF21. These drugs could be designed to activate the expression of key browning regulators like PRDM16 and UCP1, thereby converting white adipose tissue into more thermogenic beige or brown adipocytes. Gene therapy represents another frontier, where precise manipulation of the genome could enhance the browning process. Techniques such as CRISPR/Cas9 may be utilized to upregulate or stabilize proteins like PRDM16, facilitating the transition of white to brown adipocytes. Moreover, lifestyle modifications, including increased physical activity and a diet rich in thermogenic nutrients, could be tailored to promote endogenous browning mechanisms. For instance, cold exposure, known to activate browning pathways, could be incorporated into treatment regimens. It is believed that with further research, the therapeutic idea of white adipocyte browning will have a broad application prospect.

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