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Review

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Brown adipose tissue and its therapeutic application

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Abstract In addition to white adipose tissue (WAT) that stores energy, human and small mammals also have brown adipose tissue (BAT) that dissipates chemical energy for thermogenesis. BAT contains multilocular lipid droplets and much higher numbers of mitochondria than WAT. The mitochondria in BAT uncouple large amounts of fuel oxidation from ATP for heat generation. Accumulating evidences have demonstrated that increased activity and/or amount of BAT can reverse obesity and improve insulin resistance, which highlights that BAT plays an important role in energy metabolism. In this review, we summarized recent findings that shows advantageous effects of BAT activation in metabolic diseases. In addition, we presented the function and role of brown and beige fat cells and regulatory factors for them. Finally, we discussed the potential application of brown adipocytes-based therapy and pharmacological intervention to increase BAT activity for the treatment of obesity and related diseases including insulin resistance, cardiovascular diseases and type 2 diabetes.

Keywords Brown adipose tissue · Lipid metabolism · Therapeutic application

SPECIAL TOPIC: Lipid Metabolism and Human Metabolic Disorder

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1 Introduction

Obesity is a major risk factor for metabolic syndromes, including insulin resistance, type 2 diabetes mellitus, cardiovascular diseases and some types of cancer [1]. The long-term dysregulation of energy balance leads to the occurrence of obesity. Recent anti-obesity approaches are aimed at reducing energy absorption, however, the outcome is not satisfactory. After active BAT has been 're-discovered' in adult humans [2–6], increasing energy expenditure has brought much attention for the treatment of metabolic syndromes since increasing energy expenditure can be achieved either by muscle with physical activity [7] or brown adipose tissue (BAT) with non-shivering thermogenesis (NST). Compared with white adipose tissue (WAT) which stores energy, BAT dissipates energy as heat. In rodents, BAT can be found in interscapular, cervical, axillary and perirenal regions, however, BAT are mainly found around neck and also in interscapular region of newborns in human [8]. Brown adipocytes consist of multilocular lipid droplets and more mitochondria than WAT. BAT specific protein, uncoupling protein 1 (UCP1) dissipates the proton gradient from oxidative phosphorylation to generate heat [9]. UCP1 positive adipocytes that have thermogenesis capacity are also found in WAT depots after cold exposure, which is called brown in white (brite)/or beige adipocytes [10]. Similar to brown adipocytes, beige adipocytes are packed with multiple small lipid droplets and a large number of mitochondria and they contribute to energy metabolism. Either increase of BAT activity [11, 12] or recruitment of beige adipocytes within white adipose tissue [8, 13, 14] is regarded as an alternative option for the treatment of obesity and its related diseases.

2 Metabolic benefits of activating BAT

2.1 Contribution of active BAT to whole body energy expenditure

In rodents, BAT contributes to up to 60 % of resting energy expenditure (REE) during cold acclimation [9, 15]. It is estimated that BAT mass range from ~30 to 300 g in human which could contribute to 20 % of daily REE [3, 16]. The amount of active BAT in adult humans is rather heterogeneous due to different experimental conditions. For example, acute cold exposure leads to increased energy expenditure of 0.8 kcal $d^{-1}g^{-1}$ of BAT [11]. On the other hand, fully activated BAT could account for increasing energy expenditure of 1.5 kcal $d^{-1}g^{-1}$ of BAT [5]. Therefore, average 1 kcal $d^{-1}g^{-1}$ of BAT is assumed to generate 50 kcal/d and might decrease 2 kg of fat mass yearly, if adult human has average 50 g of BAT. The browning of WAT also improves thermogenic function by burning glucose and fat to produce heat, resulting in a reduction of adipocity [17, 18].

2.2 Role of BAT in lipid metabolism

Accumulating evidences have demonstrated that fatty acids (FAs) are the main fuel for UCP1 mediated BAT thermogenesis [9]. Along with this line, it was recently illustrated that prolonged activation of the β3-adrenergic receptor (β3-AR) increases fatty acid β-oxidation and lipolysis in both WAT and BAT [19]. The activation of BAT provokes phosphorylation of adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL), which rapidly induce intracellular lipolysis and eventually lead to FAs release from lipid droplets. In rodent studies, it was demonstrated that cold exposure could decrease plasma triglyceride (TG) level and improve hyperlipidemia [20]. In addition, short-term and/or prolonged cold exposure leads to transient reduction in plasma TG level in humans [21, 22]. Similarly, metformin treatment also decreases plasma TG level by increasing BAT activity [23]. Therefore, triglyceride hydrolysis and re-synthesis are a critical factor for BAT mediated lipid metabolism. It is further supported by the evidence that acute cold exposure for 6 weeks elevates FAs uptake dramatically in BAT, not muscle or WAT [24]. Taken together, the activation of BAT is now considered as an encouraging therapeutic strategy to treat hypertriglyceridemia and obesity [25].

2.3 Role of BAT in glucose metabolism

BAT also possesses massive glucose dissipation ability [9]. Indeed, BAT utilizes large amount of glucose. In lean subjects, the glucose uptake rate of cold stimulated BAT exceeds that of insulin-stimulated skeletal muscle [26, 27]. Glucose uptake by BAT might be mediated by insulin-dependent and insulin-independent manner [9]. In addition, BAT participates in glucose uptake and further contributes to whole-body glucose metabolism. We and others have demonstrated that BAT transplantation ameliorates glucose intolerance in diet induced and genetic obese *Ob*/*Ob* mice [28–30]. Moreover, β3 adrenergic agonist induced BAT activation increases glucose disposal rate and improves insulin sensitivity both in mice [31] and humans [32–34]. Consistent with these findings, cold exposure increases insulin sensitivity in humans with active supraclavicular BAT [35]. Above results highlight that BAT plays predominant role in glucose homeostasis and insulin sensitivity.

3 Activators of BAT

As BAT has an important role in glucose and lipid metabolism, it is urgently demanded to find safe and specific BAT activators to prevent obesity and its related diseases.

3.1 Cold exposure

Cold exposure is a well-known safe way to activate BAT. Physiologically, cold exposure stimulates sympathetic nervous system which increases norepinephrine turnover, thereby increasing thermogenic function of BAT [36–38]. Mechanistically, norepinephrine enhances transcriptional factor mediated UCP1 expression by activating PKA and p38-MAPK signaling pathways [39]. Interestingly, it was reported that PET-CT positive biopsies from supraclavicular area displays more similar gene signatures with beige cells rather than classical brown adipocytes in adult human [13]. More recently, it has been demonstrated that cold exposure activates eosinophils and type 2 cytokines that stimulates M2 macrophages to secrete catecholamines and finally induces WAT browning [40, 41]. Indeed, it has been reported that acute mild cold exposure activates BAT and increases total energy expenditure in human subjects [24].

3.2 Exercise

Exercise increases metabolic activity of BAT and activation of thermogenic programs as well as browning in the visceral fat [42, 43]. Interestingly, just 7 d of aerobic exercise (60 min/d) upregulates mitochondrial UCP1 expression in BAT and reduces body weight in mice [44]. Also, the browning effect was found in subcutaneous WAT after 12 weeks of training in human subjects [45]. In contrast, a case-controlled study demonstrated significant reduction in BAT activity as well as browning of subcutaneous WAT in endurance trained group compared with

their sedentary counterpart [46]. Thus, exercise might activate and recruit human BAT through activation of sympathetic nervous system (SNS), yet, further studies including exercise mode, duration and intensity are needed to investigate the role of exercise in BAT metabolism.

3.3 Natural components

Oral administration of capsinoids that derived from chili pepper has been shown to increase acute energy expenditure and BAT activity in adult human [47]. Berberine (BBR) treatment showed increased energy expenditure and BAT activity in obese rodent model [48]. In addition, we demonstrated that the mulberry extract (ME) and mulberry wine extract (MWE) which contain large amount of anthocyanin such as cyanidin 3-glucoside (C3G) and rutin, increase mitochondrial function during the brown adipogenesis [49]. *Kaempferia parviflora* extract (KPE) administration significantly decreases body weight gain and intra-abdominal fat accumulation, which suggested that KPE increased energy expenditure by BAT activation [50].

3.4 Growth factors

Fibroblast growth factor 21 (FGF21) is secreted from BAT and it shows a promising therapeutic potential in obese rodent model [51, 52]. Indeed, FGF21 treatment increases energy expenditure via BAT activation [53]. A large number of evidences suggest that plasma FGF21 shows strong positive correlation with energy expenditure. In addition, cold exposure increases FGF21 level together with elevated BAT activity [54, 55]. FGF21 is also known to participate in beige formation in WAT [56]. Recently, a clinical study demonstrated that FGF21 mimetic treatment shows modest body weight reduction and robust lipid clearance without effect on glucose homeostasis [57]. Future systemic investigation of therapeutic effect of FGF21 and its mimetics on BAT mediated whole body energy metabolism are needed in the future. BMP7, a member of the BMP family, is essential for BAT development and whole body energy balance mediated by BAT [58]. In addition, BMP8b also enhances BAT mediated thermogenesis [59]. In other hand, it has been reported that both BMP4 and BMP7 orchestrate beige formation [60]. Furthermore, growth differentiation factor 5 (GDF5), another BMP family member, induces beige formation in WAT and increases systemic energy metabolism [61].

3.5 Other factors and hormones

The class of β3-AR agonists stimulates BAT activity in rodent [62, 63]. Recently, the novel β3-AR agonist, mirabegron shows to stimulate human BAT thermogenesis [64]. Also, several adipocyte specific β3-AR agonists, such as L-796568 [65] and TAK-677 [66], increase energy expenditure without meaningful weight loss in either case. The growing evidences indicate that several factors and hormones participate in whole body energy metabolism via beige formation. Recent studies show that meteorin-like (METRNL) [67], β-aminoisobutyric acid (BAIBA) [68], cardiac natriuretic peptides (CNPs) [69] and prostaglandins (PGs) [70] increase energy expenditure by inducing beige formation. Bile acids (BAs) treatment up-regulates BAT function, thereby increasing energy expenditure [71]. In addition, fexaramine (Fex), a agonist of farnesoid X receptor (FXR) that is a sensor of BAs, promotes beige formation and raises energy expenditure [72]. Interestingly, bile acid chenodeoxycholic acid (CDCA) administration increases BAT activity and whole body energy metabolism in adult human [73]. Both glucagon-like peptide 1 receptor (GLP-1R) [74, 75] and its agonist liraglutide [76] increase thermogenesis in BAT and induce browning within WAT.

3.6 Non-coding RNAs

There are two classes of non-coding RNAs that play vital role in brown/beige development and activation: microRNA and long non-coding RNA (lncRNAs). MiR-196a is recently introduced as the first miRNA to regulate brown adipogenesis in vitro and in vivo [77]. However, it should be pointed out that miR-196a is also associated with an oncogenic phenotype in various malignancies [78–81], which might limit its potential therapeutic value. MiR-26 family also increases brown adipogenesis and thermogenic program [82]. Moreover, miR-133a and miR-133b [83, 84] and miR-106b-93 cluster [85] inhibit brown adipogenesis and mitochondrial activity. In addition, it was demonstrated that miR-155 inhibits brown adipogenesis in vitro and cold induced thermogenesis in mice [86]. Compared with microRNA, less is known about lncRNAs, however, several groups have recently found BAT-specific lncRNAs and verified the function of them. Blnc1 was the first lncRNA identified to induce brown and beige fat thermogenesis by forming ribonucleoprotein complex with transcription factor EBF2 [87]. In addition, lnc-BATE1 is confirmed as another lncRNAs regulator of BAT development and the important role in BAT identity and thermogenic ability [88]. Thus, future studies are needed to identify specific microRNA or long non-coding RNA (lnRNA) for gene therapy based obesity treatment.

4 Concluding remarks

As a thermogenic organ, BAT plays predominant role in energy homeostasis. To treat obesity with BAT, two

potential therapeutic approaches could be anticipated: increasing mass of BAT and increasing activity of BAT. For the increase of BAT mass, BAT transplantation or BAT cell therapy has been considered.

Interestingly, BAT transplantation could reverse streptozotocin (STZ) induced type 1 diabetes without exogenous insulin treatment in mice [89]. Furthermore, we and other group showed that BAT transplantation improves glucose homeostasis, reduces body weight and reverses hepatic steatosis [28, 29, 90]. However, such approach is not applicable for clinical field. The key challenge is to generate large volume of human-derived brown fat progenitor cells for cell therapy. Therefore, it is critical to identify the key genes and/or pathways that are involved in brown adipogenesis and beige formation for the development of human brown adipocytes. To this end, Tseng and her colleagues extensively characterized brown adipocyte progenitor cells from adult human neck, and found that the gene signatures of these cells share similarity with that of mouse classical BAT [91, 92]. Identifying molecule(s) that could mimic cold environment to increase BAT activity would be an alternative therapeutic option for obesity treatment. Indeed, functional thermogenic screening is an attractive option for discovery of small molecule modulators of BAT activity. As mentioned above, many factors such as cold exposure, FGF21, BMP7 have effect on BAT activity and stimulate the recruitment of beige fat cells. Increasing evidences show that beige fat is also extremely promising way to combat obesity. Further discovery for new factors that activate brown and/or beige fat will open new avenue for developing anti-obesity drugs. We believe that BAT is a fascinating target organ for obesity treatment and BAT activation with drug will be available in the near future.

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