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COMMENTARY

What activates thermogenesis when lipid droplet lipolysis is absent in brown adipocytes?

Hyunsu Shin[a], Hang Shi[b], Bingzhong Xue [b], and Liqing Yu [a]

[a]Center for Molecular and Translational Medicine, Institute for Biomedical Sciences, Georgia State University, Atlanta, GA, USA; [b]Department of Biology, Georgia State University, Atlanta, GA, USA

ABSTRACT

Cold exposure activates the sympathetic nervous system. It is generally thought that this sympathetic activation induces heat production by stimulating lipolysis of cytosolic lipid droplets (LDs) in brown adipocytes. However, this concept was not examined in vivo due to lack of appropriate animal models. Recently, we and others have demonstrated that LD lipolysis in brown adipocytes is not required for cold-induced nonshivering thermogenesis. Our studies uncovered an essential role of white adipose tissue (WAT) lipolysis in fueling thermogenesis during fasting. In addition, we showed that lipolysis deficiency in brown adipose tissue (BAT) induces WAT browning. This commentary further discusses the significance of our findings and how whole body may be heated up without BAT lipolysis.

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Introduction

The recent re-discovery of brown adipose tissue (BAT) in human adults has generated enormous interest in mechanisms for non-shivering thermogenesis (NST) because BAT and NST may be targeted to prevent obesity and its metabolic sequelae [1–3]. NST heavily depends on uncoupling protein 1 (UCP1) that dissipates metabolic energy in mitochondria to produce heat. Although the detailed molecular itinerary for NST remains largely unknown, it is generally accepted that cold exposure induces secretion of norepinephrine from the sympathetic nerves innervating BAT to activate protein kinase A (PKA) through the β3 adrenergic receptor signaling, which stimulates lipolysis of fat stored in cytosolic lipid droplets (LDs) of brown adipocytes releasing free fatty acids (FFAs) to ignite mitochondrial UCP1 for heat production [4]. With the discovery of many key molecules in intracellular lipolysis in the last decade or so [5], scientists have begun to experimentally examine this norm of NST *in vivo* in genetically altered animals. Several observations appeared to be consistent with the proposed role of cytosolic LD lipolysis in NST. For example, mice lacking Adipose Triglyceride Lipase (ATGL) globally or in whole adipose tissue, a key enzyme that cleaves the first acyl chain of a triglyceride (TG) molecule in LDs, showed reduced UCP1 expression in BAT and were cold intolerant [6,7]. Up-regulation of Hormone Sensitive Lipase (HSL) via ablation of SERTA domain containing 2 (TRIP-Br2), or lipolysis de-repression via deletion of a lipolytic suppressor called G0/G1 switch protein 2 (G0S2) [8], was associated with activation of the thermogenic program [9,10]. In addition, men or rats treated with nicotinic acid (niacin), an inhibitor of intracellular lipolysis, displayed impaired BAT thermogenesis during cold exposure [11–13]. However, our recent findings in mice lacking a lipolytic activator named Comparative Gene Identification-58 (CGI-58) in BAT, together with those from BAT-specific ATGL knockout mice, challenged this norm of NST and demonstrated a dispensable role of BAT LD lipolysis in NST [14,15].

Thermogenic capacity without BAT LD lipolysis

In the aforementioned studies using adipose or whole-body ATGL knockout mice, or men or rats treated with niacin, the subjects were not provided with food during cold exposure. Food is an important fuel source. It induces thermogenesis by stimulating the sympathetic nervous system [16], and activating the β-adrenergic receptor signaling [17]. We found that mice deficient in the isoproterenol-stimulated lipolysis due to lack of CGI-

CONTACT Bingzhong Xue bxue@gsu.edu; Liqing Yu lyu68@gsu.edu 157 Decatur St., SE, Atlanta, GA 30303, USA.
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58 in both BAT and white adipose tissue (WAT) were not cold sensitive when food was provided during cold exposure [14]. They were cold sensitive and developed hypothermia only during fasting. Similar results were obtained by Dr. Rudolf Zechner's group using the whole adipose ATGL knockout mice [15]. Importantly, BAT-specific CGI-58 or ATGL knockout mice did not display cold intolerance regardless of food availability, and these animals versus their controls even maintained a higher body temperature when food was provided during cod exposure [14,15]. When the whole-body thermogenic capacity of BAT-specific CGI-58 knockout mice was assessed using the β3 adrenergic receptor agonist CL-316,243 under the thermoneutral zone, only a minor reduction was observed, which was likely caused by reduced release of total FFAs after CL-316-243 injection due to a decrease in the total WAT weight in these animals [14]. Indeed, when normalized by fat mass, the thermogenic capacity was indistinguishable between knockouts and controls (data not shown). In line with this, the differentiated brown adipocytes isolated from BAT-specific CGI-58 knockout mice did not show any changes in oxygen consumption rates in response to the sympathetic (isoproterenol) stimulation [14]. On the other hand, the thermogenic capacity of mice lacking CGI-58 in both BAT and WAT was dramatically reduced under the same condition [14]. These findings collectively demonstrated a novel paradigm in NST, *i.e.*, WAT LD lipolysis is essential for fueling NST during cold exposure and fasting while BAT LD lipolysis is not.

Many studies have shown that brown fat is depleted of LDs in mice upon acute and long-term cold exposure [18–21]. It should be pointed out that our data do not exclude the possibility that brown fat lipolysis may still play a role in activating and fueling UCP1 in normal animals upon cold exposure, and thus its stimulation may still increase thermogenesis and energy expenditure, at least for a short duration.

WAT thermogenesis

During cold exposure, WAT not only provides substrates for thermogenesis, but also produces heat by browning, *i.e.*, recruiting thermogenic brown-like or brown-in-white multilocular LD-containing beige or brite adipocytes that may or may not express UCP1 protein [22-29]. Loss or denervation of BAT in mice also enhanced WAT browning [30]. Selective denervation of the sympathetic nerves innervating the interscapular BAT stimulated beige cell recruitment in WAT in hamsters [31]. These studies suggest an important role of BAT function and innervation in governing beige cell recruitment in WAT. Interestingly, although lipolysis-deficient brown adipocytes isolated from BAT-specific CGI-58 knockout mice had normal oxygen consumption rates (indicative of thermogenic capacity), the mice displayed augmented WAT browning when housed at the room temperature (a mild cold condition), during cold exposure, or after treatment with the β3 adrenergic receptor agonist CL-316,243 [14]. They had increased sympathetic innervation in both BAT and WAT. In addition, WAT browning in these animals was largely dependent on its sympathetic innervation. Perhaps, lipolysis deficiency induced by CGI-58 ablation in brown adipocytes has reprogrammed cells' metabolism, resulting in changes in its metabolome, secretome, and/or signal transduction. These changes, though yet to be determined, may collectively have reset the sympathetic outflow into adipose tissues to a higher level through signaling to the Central Nervous System. The increased sympathetic innervation in adipose tissues, together with the relatively normal UCP1 expression in BAT and the enhanced browning in WAT, may explain why BAT-specific CGI-58 knockout versus control mice had higher body temperatures during cold exposure [14]. It has been reported that FFAs liberated from WAT can be sensed by WAT sensory nerves [32]. It may be interesting to test whether the reduced release of FFAs from cytosolic LDs in brown adipocytes can be sensed by local sensory nerves in BAT. Nonetheless, future studies are required to molecularly define how BAT-specific CGI-58 knockout mice increase their sympathetic innervation in both BAT and WAT, and whether this increase is correlated with adipose sympathetic activity. Importantly, we need to establish whether the increased sympathetic innervation/activity in WAT and/or BAT is essential for BAT-specific CGI-58 knockout mice to maintain the capacity of whole-body NST.

Thermogenic fuels in the absence of BAT LD lipolysis

Our finding that WAT, but not BAT, lipolysis is essential for thermogenesis during fasting highlights a critical role of circulating FFAs in fueling BAT. Cold exposure increases BAT uptake of FFAs from the blood circulation [33,34]. These FFAs are likely derived from WAT lipolysis during fasting, or from chylomicron hydrolysis by Lipoprotein Lipase (LPL) after a meal [21,34], which may explain why mice with lipolysis deficiency in both BAT and WAT were cold sensitive only when food was not available [14,15]. Mice with lipolysis deficiency in BAT alone had relatively normal WAT lipolysis, and they expressed increased levels of LPL and the fatty acid transporter CD36, which may underlie why they were not cold sensitive regardless of food availability [14]. In humans and rats, it was estimated that utilization of triglycerides stored in cytosolic LDs of brown adipocytes

plays a predominant role in acute cold-induced thermogenesis [35,36]. It was unlikely that FFAs taken up by lipolysis-deficient (*i.e.*, CGI-58 or ATGL knockout) brown adipocytes during cold exposure and fasting were utilized by mitochondria after esterification to triglycerides in cytosol because cytosolic triglyceride hydrolysis was defective in these cells. A recent study showed that FFAs liberated from WAT lipolysis promoted acylcarnitine production in the liver by activating hepatic nuclear factor 4α and serving as the substrates for acylcarnitine synthesis, and these acylcarnitines can enter the blood circulation and fuel BAT thermogenesis [37]. It is currently unknown if this pathway played any role in helping maintain the thermogenic capacity of BAT-specific CGI-58 or ATGL knockout mice. Administration of carnitine itself was shown to significantly restore body temperature and BAT morphology in mice with juvenile visceral steatosis [38]. A creatine-driven substrate cycle was recently shown to enhance energy expenditure and thermogenesis in beige and brown adipocytes [27]. It is not known whether our mice with adipose lipolysis deficiency increased utilization of carnitine and/or the creatine-driven substrate cycle for heat generation.

Glucose can also be utilized for BAT thermogenesis, at least during acute cold exposure. Relative to an FFA molecule, glucose is not rich in energy. However, increases in glucose flux rates through glycolysis may generate abundant energy [39]. Cold exposure rapidly and significantly increases glucose uptake in BAT in rodents [34]. Mice lacking mTORC2 in whole fat tissue develop hypothermia and cold intolerance, and show impaired cold-induced glucose uptake and glycolysis in BAT, which can be restored by BAT overexpression of Hexokinase II or a constitutively active Akt2 [20]. In humans, glucose can also serve as a substrate for BAT thermogenesis [40]. Despite the positive correlation of glucose utilization and BAT thermogenesis, it remains unclear how BAT UCP1 is activated under this condition. One possibility is that glucose is quickly converted to FFAs and these newly formed FFAs then directly activate UCP1.

For beige adipocytes, UCP1-independent mechanisms may exist for glucose thermogenesis. It was recently reported that transgenic expression of PRDM16 on the UCP1-null background increased glucose utilization and heat production in beige adipocytes via ATP-dependent $Ca2^{+}$ cycling by sarco/endoplasmic reticulum $Ca2^{+}$-ATPase 2b and ryanodine receptor 2 [41]. We observed that mice with LD lipolysis deficiency in BAT only had increased glucose uptake in both BAT and inguinal subcutaneous WAT. They were resistant to glucose-induced increases in blood glucose levels and displayed increased body temperature after a bolus of glucose administration during acute cold exposure [14], implying the increased amount of glucose being utilized for thermogenesis in these animals. It is currently unknown whether this glucose-induced increase in body temperature resulted from BAT, WAT, or both.

What is the role of the sympathetic innervation in BAT?

In BAT, it is generally thought that a major function of the sympathetic innervation is to stimulate cytosolic LD lipolysis through the β3-adrenergic signaling, mobilizing FFAs for activation of UCP1-dependent NST during cold exposure [4,42]. However, BAT-specific CGI-58 or ATGL knockout mice are not cold sensitive [14,15], arguing against an essential role of this pathway in cold-induced NST. A 220-basepair enhancer element, located approximately 2.4 kilobases upstream of the mouse and rat UCP-1 genes, is believed to be responsible for β-adrenergically stimulated UCP1 transcription through cAMP/PKA signaling [43]. However, hamsters with selective denervation of the sympathetic nerves innervating the interscapular BAT are not cold sensitive, suggesting a dispensable role of BAT sympathetic innervation in sustaining whole-body thermogenesis [31]. Despite this, it was observed that brown fat lipolysis deficiency induced by CGI-58 ablation, selective denervation of the sympathetic nerves innervating the interscapular BAT in hamsters, and denervation of the interscapular BAT in mice all induced WAT browning [14,30,31]. These observations argued for an important role of brown fat lipolysis and sympathetic innervation in regulating compensatory WAT thermogenesis. The role of sympathetic nerves in sustaining BAT growth was well recognized [4]. Cold exposure significantly increases BAT proliferation, which can be mimicked by treating animals with norepinephrine [44]. In addition, norepinephrine stimulates BAT precursor cell proliferation and promotes brown adipocyte differentiation and maturation [44]; whereas surgical BAT denervation suppresses BAT progenitor cell proliferation [45]. We observed that BAT-specific inactivation of CGI-58 increased sympathetic innervation and cell proliferation in BAT [14]. ATGL-deficient BAT also had augmented cell proliferation, though its level of sympathetic innervation was not determined [15]. Perhaps, BAT sympathetic innervation is more crucial for governing BAT cell proliferation and regulating whole-body thermogenesis than mobilizing local FFAs to activate and fuel UCP1.

Perspectives

In summary, the two pieces of animal studies support a novel concept that LD lipolysis in brown adipocytes is

not required for cold-induced NST [14, 15]. Adaptations include at least the following: 1) increased sympathetic innervation in BAT and WAT, 2) increased BAT cell proliferation, 3) increased WAT browning, and 4) increased utilization of circulating substrates from diet and WAT lipolysis. To fight against the cold for survival during evolution, mammals may have developed multiple adaptive mechanisms to regulate body temperatures via NST. These mechanisms may, at least, include BAT thermogenesis, WAT thermogenesis, adipose lipolysis, flexibilities in use of various types of thermogenic substrates and in selection of different substrate sources (stored versus exogenous ones), changes in food intake, and adjustments of basal metabolic rates in all tissues. The plasticity of thermogenic programs may explain why BAT LD lipolysis and sympathetic innervation are not essential for maintaining whole-body thermogenic capacity. Without any one or more of these adaptive thermogenic mechanisms, animals may have no problems to survive for at least a short duration of cold exposure as long as appropriate acclimation procedures are employed.

As in other studies, our findings answered a few questions, but raised more. For example, what is the signal that stimulates the sympathetic innervation in BAT and WAT in BAT-specific CGI-58 knockout mice? How does BAT lipolysis deficiency alter local and global lipid homeostasis? Does BAT lipolysis deficiency induce a unique pattern of "Batokines"? How does this unique set of batokines, if identified, communicate with other organs/cell types to influence whole-body metabolism and pathophysiology? Do any specific batokines in our animal model promote WAT browning? Why do BAT-specific ATGL knockout mice show no signs of enhanced WAT browning? Compared to ATGL, does CGI-58 deletion induce a unique cellular response generating specific neural and humoral signals to activate WAT browning? What is the origin of beige adipocytes in BAT-specific CGI-58 knockout mice? Does WAT lipolysis affect WAT browning? Future studies are required to address these outstanding questions. We could employ systems biology approaches and team up with scientists in other disciplines, such as neuroscience, to further explore molecular details and neural circuits of our observations. In addition, the whole adipose CGI-58 or ATGL knockout mice do not directly test the function of WAT lipolysis. We could re-introduce CGI-58 or ATGL back to UCP1-positive brown/beige adipocytes using UCP1 promoter in the whole adipose CGI-58 or ATGL knockout mice and then specifically examine the role of WAT lipolysis in thermoregulation and metabolic health.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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ORCID

Bingzhong Xue http://orcid.org/0000-0002-7857-1343
Liqing Yu http://orcid.org/0000-0002-5186-9182

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