Thermogenesis

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Thermogenesis is an energy demanding process by which endotherms produce heat to maintain their body temperature in response to cold exposure. Mitochondria in the brown and beige adipocytes play a key role in thermogenesis, as the site for uncoupling protein 1 (UCP1), which allows for the diffusion of protons through the mitochondrial inner membrane to produce heat.

brown adipose tissue thermogenesis mitochondria lipids

1. Introduction

Body temperature regulation is a selective advantage that has allowed endotherms to thrive in diverse climates. Heat production can occur through shivering and nonshivering thermogenesis; nonshivering thermogenesis primarily occurs in the brown and beige adipocytes [1]. One of the major mechanisms of heat production in these thermogenic adipocytes is through uncoupling protein 1 (UCP1), which facilitates the diffusion of protons into the inner mitochondria without coupling the proton mobility to ATP synthase. The potential energy of the proton gradient is converted to heat as the protons diffuse into the inner mitochondria [2]. Other mechanisms of thermogenesis include futile cycles of calcium, phosphocreatine, and free fatty acids [3].

Due to the dissipation of the proton gradient and futile cycles, thermogenesis is energy demanding and has been an area of intense study for body weight control and metabolic health [4]. The maintenance of elevated energy consumption requires the uptake of glucose, amino acids, and lipids as energy substrates. Numerous lipids have been shown to have increased uptake into brown and beige adipocytes with cold exposure including free fatty acids, acylcarnitines, and lipoprotein complexes [5]. Beyond their direct role in fueling thermogenesis, lipids are important for their capacity as signaling molecules, components of membranes, and as posttranslational modifications [6]. These dynamic roles for lipids highlight their molecular complexity and the shift in lipid abundance as a measure of stored energy availability.

At the heart of thermogenic regulation and lipid processing is the mitochondrion, which is the site of the UCP1 function and lipid catabolism through β-oxidation. Mitochondria are highly abundant in brown and beige adipocytes and take on distinct morphology and inter-organelle interactions upon cold stimulation [7].

2. Mitochondrial Lipid Signaling and Adaptive Thermogenesis

Thermogenesis in brown and beige adipocytes is dependent on mitochondrial lipid processing. These lipids can be produced directly in brown and beige adipocytes or can come from peripheral sources including white adipocytes or the liver. Lipids generated in the brown and beige adipocytes that alter mitochondrial function include CLs, 12,13-diHOMEs, and plasmalogens. Peripherally produced lipids and lipid complexes enter the circulation and are taken up by thermogenic adipocytes including acylcarnitines and triglyceride-rich lipoproteins [8][9]. Other lipids have numerous sources including FFAs and the lipid-derived metabolite ketones. FFAs primarily come from white adipose tissue lipolysis but can also come from brown and beige adipocytes. Many lipids have several roles, such as cardiolipins that provide structural support to mitochondrial membranes, stabilize UCP1, and signal to the nucleus for transcriptional regulation [10]. Similarly, ketones are an important fuel substrate but also regulate beige adipocyte differentiation. The ability of lipids to play numerous roles highlights the dynamic nature of these molecules and emphasizes the need to reassess our limited view of lipids as single purpose molecules.

We have limited the scope of this review to focus on lipids that are produced by or impact mitochondria in the brown and beige adipocytes. There are several lipids that impact thermogenesis that were left out due to this narrow designation including sphingolipids, dolichols, diacylglycerols, prostaglandins, and 12-hydroxyeicosapentaenoic acid (12-HEPE) [11][12][13]. Some of these lipids function through mechanisms that impact mitochondria only in a secondary manner such as 12-HEPE, which activates G-protein coupled receptors to increase glucose uptake in brown adipocytes [13]. Other lipids potentially have a role in mitochondrial regulation, such as sphingolipids and ceramides, but the exact mechanism of this action is yet to be understood. Recent work demonstrated that a UCP1-cre mediated knockout of serine palmitoyltransferase subunit 2, an enzyme important in ceramide synthesis, led to increased mitochondrial density, while knockout of an enzyme in ceramide degradation led to reduced mitochondrial density [14]. Further exploration into the mechanisms by which ceramides are driving these mitochondrial differences is needed. Another subset of these lipids impacts the conversion of white adipocytes to beige adipocytes such as prostaglandin H2, but the direct regulation of mitochondria function and thermogenesis is unexplored [6]. The importance of prostaglandins in thermoregulation warrants further investigation, but their known regulation of body temperature for fevers is intriguing.

Physiological factors such as sex or age influence the lipid composition of brown adipocytes. The lipidomic analysis of BAT from female or male mice revealed sex-specific differences in phospholipid acyl chains, with more incorporation of stearic and arachidonic acid in females, and palmitic and linoleic acid in males [15]. Increased desaturation of mitochondrial phospholipids impacts membrane dynamics and may underly the dimorphism in the mitochondrial size and shape observed between male and female BAT in rats [16]. Aging also alters BAT lipid metabolism. In the BAT of aged mice, decreased production of lipoic acid leads to suppression of catabolic pathways including fatty acid oxidation [17]. It was also seen that as mice age, their capacity to regulate body temperature during cold exposure is limited because of reduced acylcarnitine production in the liver. When acylcarnitines were administered to aged mice during cold exposure, BAT thermogenesis improved [9]. How lipid-based signaling in BAT is impacted by sex and age requires further study.

More work is needed to understand lipids that impact mitochondria in beige adipocytes. This is difficult because the emergence of beige adipocytes in subcutaneous adipose tissue is heterogeneous and occurs in pockets

surrounding vasculature [18]. Moreover, the advent of single cell and single nuclei RNA sequencing, as well as the refinement of cold stress conditions, have demonstrated that there are numerous subtypes of beige adipocyte that have differences in glycolytic capacity and cellular origin [19][20][21][22]. These studies have also revealed lipid signaling between beige adipocytes and resident macrophages that regulates the thermogenic response [20][23]. The advent of single cell metabolomics coupled with cell sorting will enable the exploration of the lipid composition of individual subtypes of beige adipocytes [24].

At the cellular level, several emerging technologies have led to higher lipid visualization and quantitation. Mass-spectrometry-based lipidomics has unearthed previously unidentified lipids including signaling molecules such as fatty acid esters of hydroxy fatty acids (FAHFAs), which regulate insulin sensitivity [25][26]. Chemical probes including photoswitches have the capacity to functionally characterize lipids and the proteins they interact with, while photocleavable groups can facilitate the temporal range of lipid activity [27]. Labels including fluorescent tags such as Bodipy and GFP as well as luminescent tags on acyl-chains provide imaging potential to determine cellular localization and lipid uptake [28][29][30]. Further tools are needed to increase the capacity to track lipid mobility and uptake in vivo to determine novel inter-organ communication pathways. Currently, quantitative assessment of lipid mobility is through radioactive or heavy isotope labeling. Radioactivity is sensitive and can be used to assess lipid uptake from the circulation and quantitatively assess oxidation but can be difficult to use in vivo. Heavy isotope labeling is cost prohibitive in vivo and the expertise for the quantitative calculation of pathway input is limited to several labs around the world [31][32]. Both technologies are limited in their ability to assess inter-organ signaling pathways. As these tools are developed and applied in tandem, they will expand our depth of understanding for the importance of lipid metabolism in thermogenic adipose tissue.

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