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REVIEW ARTICLE

The thermogenic circuit: Regulators of thermogenic competency and differentiation

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Abstract In mammals, a thermogenic mechanism exists that increases heat production and consumes energy. Recent work has shed light on the cellular and physiological mechanisms that control this thermogenic circuit. Thermogenically active adipocytes, namely brown and closely related beige adipocytes, differentiate from progenitor cells that commit to the thermogenic lineage but can arise from different cellular origins. Thermogenic differentiation shares some features with general adipogenesis, highlighting the critical role that common transcription factors may play in progenitors with divergent fates. However, thermogenic differentiation is also discrete from the common adipogenic program and, excitingly, cells with distinct origins possess thermogenic competency that allows them to differentiate into thermogenically active mature adipocytes. An understanding of this thermogenic differentiation program and the factors that can activate it has led to the development of assays that are able to measure thermogenic activity both indirectly and directly. By combining these assays with appropriate cell models, novel therapeutic approaches to combat obesity and its related metabolic disorders by enhancing the thermogenic circuit can be developed.

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Background/significance

Obesity and metabolic syndrome has reached worldwide pandemic. According to the U.S. Center for Disease Control and Prevention, two-thirds of the US population is overweight or obese. More than one-third of US adults and approximately 17% of US children are obese. Worldwide, more than 1 billion adults (15% of the world population) are overweight and over 300 million people rank as truly obese. Obesity and insulin resistance are two hallmark features for a larger collection of metabolic syndromes. Indeed, in addition to the 20 million people with type 2 diabetes, it is estimated that over 40 million people in the U.S. have metabolic syndrome, and it is this collection of abnormalities which generates risk for many of our most common medical disorders, including type 2 diabetes, dyslipidemia, non-alcoholic fatty liver, cardiovascular disease, renal failure, and even some cancers.[1–4] The development of prevention and treatment strategies for obesity and its comorbidities is of the utmost importance for the healthcare and research communities. One appealing approach that has garnered considerable interest over the last several years is the investigation of the therapeutic potential of brown adipose tissue (BAT).

BAT plays a pivotal role in thermogenesis, which is the process by which energy is released in the form of heat to maintain body temperature. In mice and humans, this process can be mediated by the function of uncoupling protein 1 (UCP1), which is expressed in the mitochondria of brown and brown-like (also known as beige or brite) adipocytes. Brown adipocytes are mostly located in the interscapular region in rodents and constitutively express UCP1 while beige adipocytes can be induced in white adipose tissue upon cold or β-adrenergic stimulations.[5] In adult humans, UCP1-positive adipocytes are found in the neck, supraclavicular and spinal cord regions.[6–9]

Simplifying the mechanism of UCP1 mediated thermogenesis

UCP1 is a proton leak channel in the inner mitochondrial membrane that uncouples the proton motive force generated by the electron transport chain (ETC) from ATP generation. UCP1 allows protons that are actively transported across the semi-permeable membrane by the ETC to pass back down their concentration gradient and bypass the V-ATPase, releasing energy as heat rather than to activate phosphorylation of ADP. One characteristic that distinguishes brown from beige adipocytes is that UCP1 expression is highly inducible by activators of thermogenic activity in beige adipocytes, while UCP1 is constitutively expressed at high levels in classical brown adipocytes.[10–14]

The molecular mechanism is easy to understand with the simple metaphor of a car engine (Fig. 1). During normal function, your car engine uses gasoline as an energy source to move the wheels forward, like cells use glucose and fatty acids as energy sources for their mitochondria to produce ATP. When the gas pedal is depressed and fuel is injected into the engine cylinder, an explosion is triggered that combusts the gasoline and produces carbon dioxide and water. This gas is contained in the cylinder, producing energy to push up the engine piston and propel the car forward and the cycle is then repeated. In cells, the electron transport chain uses fuel like glucose and fatty acids to pump protons into the inner mitochondrial membrane generating a proton motive force. During normal oxidative phosphorylation, the energy in these substrates would be used to "push" the ATPase enzyme that generates ATP akin to the way the gasoline combustion pushes the engine piston.[15] The function of UCP1 can be thought of as having the same effect as a small hole drilled into the side of the engine cylinder in your car. Instead of pushing up the piston and doing work for your car, all of the gas and energy from combustion escapes through the hole without pushing the piston. In cells, thermogenesis occurs because the protons that might provide energy for the ATPase are simply released by UCP1 back into the mitochondrial matrix, like gas escaping an engine cylinder. It's easy to imagine sitting in your driveway, pressing the gas pedal and revving your car's engine, but going nowhere as you generate no force to push the engine pistons and move your car forward. Though you wouldn't go anywhere as you revved your engine and burned fuel, you would generate plenty of heat, the same way brown and beige fat are able to burn fuel and generate significant heat at the expense of ATP production using UCP1 mediated proton leak.

Activating a thermogenic mechanism

By activating the UCP1 mediated thermogenic mechanism, BAT has been shown to regulate fatty acid metabolism and glucose homeostasis.[16–18] Given its influential role in the regulation of nutrient metabolism, it is not surprising that BAT mass/activity is inversely correlated to body mass index and percent body fat in humans.[19,20] Increasing the size and activation of brown and beige adipose tissue has the potential to alleviate the clinical sequelae of the metabolic syndrome making recent clinical efforts to demonstrate the feasibility of using cold regiments to activate BAT in humans an exciting frontier.[21–24]

Therefore, brown and beige fat are the body's main tissues capable of activating a thermogenic circuit consisting of adipocytes that metabolize substrates in order to generate a proton motive force in mitochondria that is subsequently uncoupled from ATP production to generate heat. The steps of thermogenic differentiation can be coopted by distinct progenitor cell types that produce mature cells with thermogenic capacity. Though they can share certain aspects of a common adipogenic and thermogenic differentiation program, cells at discrete stages of differentiation express surface proteins and transcriptional networks that are unique signatures of their specific cellular lineage. The factors that promote the thermogenic circuit at each of its stages are of great therapeutic interest in the field of obesity and diabetes and several comprehensive reviews have thoroughly listed these browning agents.[14,25] In this review, in addition to updating the list of browning agents, we will define the stages of cell differentiation and the inductive networks required to complete full differentiation and activation of the thermogenic circuit.