Review

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The brown fat secretome: metabolic functions beyond thermogenesis

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Brown fat is highly active in fuel oxidation and dissipates chemical energy through uncoupling protein (UCP)1-mediated heat production. Activation of brown fat leads to increased energy expenditure, reduced adiposity, and lower plasma glucose and lipid levels, thus contributing to better homeostasis. Uncoupled respiration and thermogenesis have been considered to be responsible for the metabolic benefits of brown adipose tissue. Recent studies have demonstrated that brown adipocytes also secrete factors that act locally and systemically to influence fuel and energy metabolism. This review discusses the evidence supporting a thermogenesis-independent role of brown fat, particularly through its release of secreted factors, and their implications in physiology and therapeutic development.

Introduction

Brown adipose tissue (BAT) defends against hypothermia in small mammals and newborn infants through thermogenesis. Mature brown adipocytes contain abundant mitochondria and express high levels of UCP1, which dissipates the proton gradient across the mitochondrial inner membrane to produce heat [1]. BAT thermogenesis is stimulated by cold exposure through activation of the sympathetic nervous system (SNS), which triggers local catecholamine release and thyroid hormone production [1–3]. The marked increase in glucose and lipid uptake and oxidation is accompanied by an induction of genes involved in mitochondrial biogenesis, fatty acid β oxidation, and uncoupled respiration [4,5]. Not surprisingly, BAT thermogenesis also contributes to whole body energy balance. Thus, genetic ablation of brown fat renders mice sensitive to cold and prone to the development of obesity [6], whereas activation of BAT thermogenesis has been linked to increased energy expenditure, reduced adiposity, and lower plasma lipids [7–9].

In humans, brown fat is present in newborn infants and is thought to be absent in adults. Recent studies using positron emission tomography (PET) demonstrated that metabolically active brown fat is present in some adults [10–13]. Human brown fat appears to contain both classical and brown-like adipocytes; cells that have both distinct molecular signatures and developmental origins [14–17]. The latter was also called beige, brite, or inducible brown adipocytes (referred to beige hereafter). In rodents, cold acclimation and the β3-selective adrenergic agonist CL316,243 promote the formation of beige adipocytes within white adipose tissue (WAT), particularly the inguinal fat depot [18,19]. WAT browning is also induced by the insulin-sensitizing agent rosiglitazone and a growing list of secreted factors [20]. The developmental origin and molecular control of brown and beige fat formation have been discussed in detail in several recent reviews [20–22].

Does brown fat contribute to systemic metabolism via thermogenesis-independent mechanisms?

Mitochondrial uncoupling has been recognized as a central aspect of brown fat biology. Genetic deletion of UCP1 completely abolished uncoupled respiration and thermogenesis in BAT and rendered the null mice cold sensitive [23]. Similarly, diphtheria-toxin-mediated ablation of brown fat also severely impaired cold-induced thermogenesis and defense against hypothermia [6,24]. Mice lacking brown fat were more prone to high-fat-diet-induced obesity and its associated metabolic disorders, including insulin resistance and hyperlipidemia. Surprisingly, UCP1 deficiency had a modest effect on diet-induced obesity in mice when housed at ambient room temperature [23,25,26]. These paradoxical observations strongly suggest that brown fat contributes to whole body energy homeostasis through additional mechanisms beyond UCP1-mediated thermogenesis.

Secreted factors are important regulators of fuel metabolism and energy balance, as illustrated by the classic endocrine hormones, such as insulin and glucagon. Furthermore, adipose tissue hormones, such as leptin and adiponectin, gut-derived fibroblast growth factors, skeletal myokines, and immune-cell-derived factors are emerging to coordinate diverse aspects of metabolic physiology. While WAT has been recognized as an endocrine organ [27,28], much less is known about the extent to which BAT engages other tissues through its release of protein and non-protein factors [29]. Recent studies demonstrated that BAT transplantation profoundly improves metabolic parameters in mouse models of obesity and diabetes [30–33]. Subcutaneous transplantation of embryonic BAT corrected type 1 diabetes in mice treated with streptozotocin; possibly due to increased serum levels of insulin-like growth factor (IGF)-1 and potential activation of the insulin receptor [31]. Similarly, BAT transplantation improved metabolic parameters in diet-induced obese mice; such a beneficial effect required the expression and release of interleukin (IL)-6 from the BAT used for transplantation [33]. Interestingly, transplantation of BAT also conferred

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resistance to high-fat diet-induced obesity through enhanced sympathetic activity, although the nature of factors that increase sympathetic activity in the recipient mice remains unknown [30]. Together, these observations support the emerging concept that the brown fat secretome provides a physiologically significant link between BAT and systemic metabolism.

The brown fat secretome: autocrine, paracrine, and endocrine functions

WAT is known to release important endocrine factors such as leptin and adiponectin [27,28]. The repertoire of secreted proteins released by brown and beige fat and their physiological functions have not been fully defined. Previous studies have demonstrated that brown fat also synthesizes diverse signaling molecules that alter metabolic physiology via autocrine, paracrine, and endocrine mechanisms. Biologically active molecules, such as thyroid hormone, lipid metabolites, and lactate, may act locally to modulate brown fat development and thermogenesis, whereas secreted factors may enter circulation to exert metabolic effects on other tissues. Recent secretome profiling analysis revealed a distinct set of brown fat-enriched secreted factors [34]. While the existence of brown-fat-specific secreted protein) appears unlikely, a growing list of extracellular factors exhibits enriched expression in brown fat and is inducible in response to thermogenic activation. In this section, we summarize several protein and non-protein factors produced by BAT and discuss their potential role in metabolic signaling and homeostasis.

Neuregulin (Nrg)4

Nrg4 was recently identified as a brown-fat-enriched secreted factor in a recent analysis of secretomes across mouse tissues and during brown adipocyte differentiation [34]. Nrg4 expression is strongly induced during brown adipogenesis and further increased by adrenergic receptor activation in brown adipocytes [34,35]. Acute cold exposure stimulates Nrg4 expression in BAT, whereas cold acclimation elevates Nrg4 mRNA levels in both BAT and inguinal WAT (Figure 1). Nrg4 belongs to the epidermal growth factor (EGF) family of extracellular ligands that bind to and activate the receptor tyrosine kinases ErbB3 and ErbB4 [36–38]. Nrg4 is synthesized as a single-span transmembrane protein that contains an extracellular EGF-like domain responsible for receptor binding. A proteolytic site exists between the EGF-like domain and the transmembrane fragment, allowing Nrg4 to be shed from the plasma membrane by one or more matrix metalloproteinases. Using a binding assay, Nrg4 was found to bind to the liver, among a panel of mouse tissues.

It is somewhat unexpected that Nrg4 is largely dispensable for brown fat development and function [34]. In fact, mice lacking Nrg4 are comparable with wild type control littermates in defense against hypothermia caused by cold exposure. These findings suggest that, despite its abundant expression in brown fat, Nrg4 is not required for

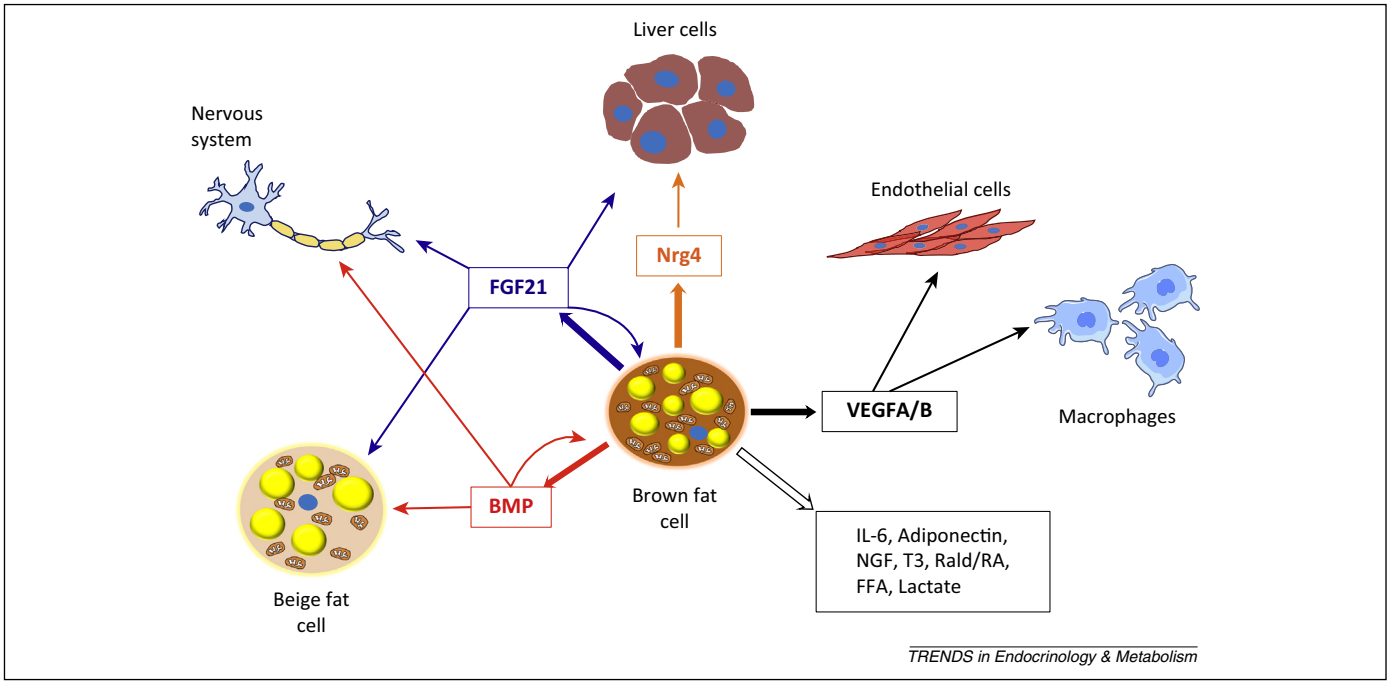

Figure 1. Secreted factors released by brown fat. BAT is a source of protein and non-protein signaling factors that influence diverse metabolic processes. While brown fat is not the exclusive source of these extracellular signaling factors, many of them exhibit enriched and/or inducible expression in BAT upon thermogenic stimulation. Nrg4 is an EGF-like endocrine factor that is enriched in brown fat. Nrg4 binds to ErbB receptors in the liver and preserves metabolic homeostasis in obesity through attenuating hepatic lipogenesis. FGF21 is induced in brown fat by cold exposure and exerts pleiotropic effects on hepatic metabolism, white fat browning, sympathetic outflow, and BAT thermogenesis. BMP promotes brown and beige fat formation and also acts on the central nervous system to regulate thermogenesis. VEGFA and VEGFB are expressed at high levels in brown fat and regulate angiogenesis, thermogenesis, and macrophage function. T3, Rald, and RA exert effects locally to promote thermogenesis. Additional secreted factors include IL-6, Adiponectin, and metabolites released upon thermogenic activation, such as FFA and lactate. Abbreviations: BAT, brown adipose tissue; BMP: bone morphogenetic protein, EGF, epidermal growth factor; ErbB, epidermal growth factor receptor; FFA, free fatty acid; FGF, fibroblast growth factor; IL, interleukin; NGF, nerve growth factor; Nrg, neuregulin; RA, retinoic acid; Rald, retinaldehyde; VEGF, vascular endothelial growth factor.