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INVITED REVIEW

Fat tissues, the brite and the dark sides

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Abstract Fat tissue is well known for its capacity to store energy and its detrimental role in obesity and metaflammation. However, humans possess different types of fat that have different functions in physiology and metabolic diseases. Apart from white adipose tissue (WAT), the body's main energy storage, there is also brown adipose tissue (BAT) that dissipates energy as a defense against cold and maintains energy balance for the whole body. BAT is present not only in newborns but also in adult humans and its mass correlates with leanness. Moreover, "brown-like" adipocytes have been detected in human WAT. These "brown-in-white" (brite) or beige cells can be induced by cold and a broad spectrum of pharmacological substances and, therefore, they are also known as "inducible brown adipocytes." Activation of brown and/or brite adipocytes reduces metabolic diseases, at least in murine models of obesity. Thus, brown/brite adipocytes represent the "brite" side of fat and are potential targets for novel therapeutic approaches for treatment of obesity and obesity-associated diseases.

Keywords Metabolism · Obesity · Brown adipose tissue · Brite/beige adipocytes · Energy expenditure

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Introduction

Obesity and overweight have been conclusively shown to increase the risk of type 2 diabetes, hypertension, hypercholesterolemia, cardiovascular disease, and certain types of cancer [27]. Obesity not only affects people in developed countries but also people in developing countries who intake large amounts of calorie-dense food. The World Health Organization (WHO) reported in 2014 that 39 % of adults worldwide were overweight and 13 % were obese. Overweight and obesity are urgent health issues: the numbers have doubled since 1990 and—according to the WHO—more people die of obesity and its consequences than of undernutrition and famine.

An important pathophysiological basis of obesity and obesity-associated disorders is the increase in adipocyte size due to the uptake/storage of excess energy in the form of lipids, which causes cellular stress and an inflammatory response that spreads throughout the whole body (metaflammation) [19].

In addition to the "bad" white fat that represents, for many people, the "dark side" of fat tissue, there is also a bright side: brown fat takes up glucose and lipids and burns energy to generate heat. Moreover, cold exposure and different pharmacological stimuli bring out "brown-like" cells in white fat depots. These cells function similar as brown adipocytes and are also termed brite or beige cells.

Types of fat

White fat

White adipose tissue (WAT) is the major adipose organ in adults and is the main storage site of energy in the form of triacylglycerols. Whenever fuel is required, fatty acids are released from WAT by lipolysis. This process is initiated by

norepinephrine which binds to the beta-adrenergic receptors on white adipocytes leading to the generation of cAMP. The second messenger cAMP activates protein kinase A and, in turn, stimulates the hormone-sensitive lipase releasing free fatty acids from triacylglycerol in the lipid droplets. WAT composes as much as 20 % of the body weight of healthy adult humans. Although it is widely distributed throughout the whole body, separate/specific depots can be distinguished: visceral white adipose tissue (vWAT) mainly surrounds internal organs, whereas superficial or inguinal white adipose tissue (igWAT) is located beneath the skin.

Morphologically, a white adipocyte is a unilocular cell and contains a single large lipid droplet that pushes the nucleus close to the plasma membrane. Mitochondria are located mainly in the thicker portion of the cytoplasmic rim near the nucleus. Beyond simple fat storage, WAT is also a secretory and endocrine organ that secretes hormones (including leptin, adiponectin, angiotensinogen, tumor necrosis factor α (TNFα), interleukin 6 (IL-6), metallothionein, resistin, and etc.) and has an important role in metabolic homeostasis, inflammatory processes, and vascular homeostasis [46]. Although no specific markers for WAT have been identified, several genes including fatty-acid binding protein 4 (FABP4 or aP2), peroxisome proliferator-activated receptor γ (PPARγ), and CCAAT/enhancer-binding protein α (C/EBPα) have been found to have an important role and/or are highly expressed in WAT.

Development of WAT is initiated in the mesoderm during the embryonic period [12]. Murine igWAT develops between embryonic days 14 and 18, whereas vWAT develops postnatally [54]. White adipocytes have been thought to originate from precursors that lack myogenic factor 5 (Myf5) [5, 7, 48], until Guertin's group discovered different origins of white adipocytes from different WAT depots: white adipocytes from posterior subcutaneous, mesenteric, and perigonadal visceral depots are all Myf5-negative, whereas those from anterior subcutaneous and retroperitoneal visceral depots are nearly all Myf5-positive [39].

The transcriptional regulation of WAT adipogenesis involves the activation of several transcriptional factors including PPARγ and C/EBPs [36]. PPARγ is a master regulator of all kinds/colors of adipose tissue and is indispensable for WAT development [2, 37]. C/EBPα maintains expression of PPARγ and, together with PPARγ, regulates gene transcription to promote adipocyte differentiation. Consequently, C/EBPα deficiency in mice inhibits WAT development [23].

Brown fat

Brown adipose tissue (BAT) is a special type of adipose organ found in almost all mammals including mice, rats, rabbits, sheep, bears, and humans [44]. Pigs are one exception: they lack BAT and are completely dependent on shivering thermogenesis to keep warm [47]. Activated BAT burns lipids and glucose, contributing to energy dissipation and thus results in heat production, a process known as non-shivering thermogenesis (NST). NST is critically dependent on uncoupling protein 1 (UCP1), a brown adipocyte-specific protein. UCP1 uncouples the respiratory chain of oxidative phosphorylation within mitochondria, shifts energy from the mitochondrial electron chain away from ATP production, and releases the superfluent energy as heat. BAT has been thought to exist only in hibernating mammals and newborns, until functional BAT was discovered in adult humans in 2009 [6, 38, 50, 51]. Regarding its location, unlike WAT, its distribution is limited mainly in the supraclavicular, neck, and perirenal regions of human body [28, 45]. In comparison to lipid-loaded, mature white adipocytes, brown adipocytes are smaller and contain multilocular smaller lipid droplets and many UCP1 positive mitochondria, which vary in size and shape and are a major reason for the color of BAT. Apart from *UCP1*, several markers for brown adipocytes have been described including, peroxisome-proliferator-activated receptor γ-coactivator 1α (*PGC-1α*), cell death-inducing DNA fragmentation factor alpha-like effector A (*Cidea*), *Zic1*, *Lhx8*, *Eva1*, and *Epsti1* [11].

BAT develops earlier than WAT during embryogenesis (as early as day 9.5) [3, 22, 55]. Brown adipocytes arise from central dermomyotome during embryonic development, and they share their origin with skeletal muscle cells, dermal cells, and a subpopulation of white adipocytes [1, 22, 40, 41]. Although Myf5 was initially reported as a specific marker for precursors that give rise to brown adipocytes and muscle cells [41], recent studies in mice showed that Myf5-positive precursors also give rise to white adipocytes in anterior/dorsal depots indicating that Myf5 is rather a marker for cell position [39].

During BAT development, some positive regulators have been identified so far, including protein PR domain containing 16 (PRDM16), PPARα, bone morphogenetic protein 7 (BMP7) and Orexin. Although PRDM16 was shown to be dispensable for brown adipocyte development [4], it is required for maintaining BAT function during aging. PRDM16 forms complexes with other regulatory factors including PPARγ, PGC-1α/β, euchromatic histone-lysine *N*-methyltransferase 1 (EHMT1), C-terminal-binding proteins (CtBPs), and early B cell factor-2 (EBF2) [20, 21, 30, 34, 41, 42]. PPARα was demonstrated to bind to a PPAR-responsive element in the distal PGC-1α gene promoter, thereby, inducing expression of PGC-1α [17]. BMP7 and Orexin have been shown to promote brown adipocyte development via induction of PGC-1α, UCP1, PPARγ, and C/EBPs [49] as well as through p38 mitogen-activated protein kinase

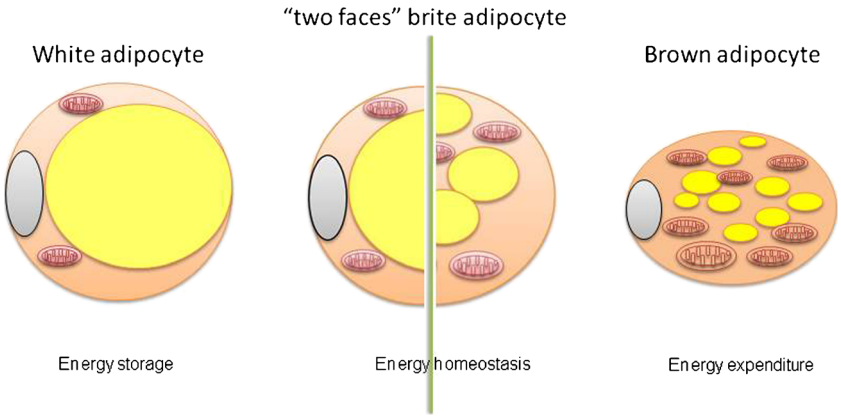

Fig. 1 White, brite, brown adipocytes and the two faces of brite adipocytes

(MAPK) and bone morphogenetic protein receptor-1α (BMPR1A)-dependent Smad 1/5 signaling [43].

Brite fat

Brite/beige fat, which is also known as inducible brown adipose tissue, functions as an extra or reserve brown adipose tissue that can be induced by cold exposure to dissipate energy [15, 32]. Brite adipocytes are dispersed among the white adipocytes and are morphologically similar to a classical brown adipocyte (Fig. 1) containing multilocular, but variable-in-size, lipid droplets and plenty of UCP1-positive mitochondria [57, 58]. Brite cells also express brown fat-specific genes, including *UCP1*, *Cidea*, *PGC-1α*, *PRDM16*, and CCAAT/enhancer-binding protein β (*C/EBPβ*). In mice, Zic1 and Hoxc9 have been identified as the most specific markers for classical BAT and brite fat, respectively [53]. In addition, several other potential brite-selective markers including *Cd137*, *Tbx1*, *Tmem26*, *Cited1*, and *Shox2* have been suggested [11].

There is no consensus concerning the mechanism of "browning" and the embryonic origin of brite adipocytes. There is evidence that brite adipocytes arise from pre-existing white adipocytes [13, 52]. On the other hand, there is also evidence that they arise by de novo adipogenesis from precursors [54]. Moreover, it was postulated that brite cells are masked as white adipocytes and might "de-mask" upon cold exposure or pharmacological stimulation [29]. Interestingly, another study showed about 10 % of brite adipocytes in igWAT arise from smooth muscle [24]. Thus, brite adipocytes might be more heterogenous than other adipocytes.

PRDM16 and PPARα/γ play critical roles in brite cell development. Their positive regulatory effect has been shown to be related to an induction in PGC-1α expression [16, 56] and a stable interaction of PRDM16 and PPARγ, which might be promoted by a Sirtuin 1 (SIRT1)-dependent deacetylation of PPARγ [33]. In addition, the cyclic GMP (cGMP) pathway has been shown to induce brite adipocyte development as well [14, 15, 25].

Prospect and challenges

Since white fat is often viewed as "bad" or as the "dark side" of adipose tissue, one might be inclined to overcome or ease obesity via inhibition of adipose tissue expansion [10, 26]. It sounds like a reasonable therapeutic approach, since many regulatory factors have been identified that regulate differentiation of precursor cells to mature adipocytes. However, evidence from several animal models [8, 26, 35] show that blocking adipocyte development is unhealthy. If lipids are not stored by adipose tissue, they "spill over" and are stored ectopically. Ectopic storage of excess lipids in the liver and muscle is detrimental for these tissues and will worsen the metabolic dysfunction [10]. Moreover, adipose tissue functions as a secretory organ and secretes hormones like leptin and adiponectin that play important roles in appetite regulation and cardiovascular health, respectively [9, 18]. For these reasons, it is clear that other ways to fight obesity are needed.

An alternative might be to further the "brite side" of fat by increasing the number of brown and/or of brite cells. According to the evidence of numerous animal models [4, 11, 14, 15, 25, 31–33, 53], several regulatory factors of brown and brite fat development might be used for such an approach. However, there is a lack of human studies on this subject. A major reason for this is the lack of easy accessible biomarkers for brown and brite fat in humans. It is also not known whether there might be unwanted side effects of a long-term enhancement of thermogenesis. Thus, more human studies are needed to unravel the role of human brown and brite fat in physiology and disease.

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