

The origin and definition of brite versus white and classical brown adipocytes

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White adipose tissue stores energy while brown adipose tissue contributes to body temperature maintenance through non-shivering thermogenesis. In addition, brite (brown-in-white) adipocytes resembling classical brown adipocytes within predominantly white adipose tissue can be found in response to cold adaptation or other stimuli. Even though our understanding of brite adipocyte formation has increased substantially in the last few years, it is still unclear how brite and classical brown adipocytes are formed *in vivo*. In this review, we outline and discuss the current understanding of brite adipocyte nomenclature, developmental origin and possible mechanisms of their recruitment. We reason that future work in the field will bridge *in vivo* tracing studies and primary cell characterization with molecular mechanistic data from *in vitro* approaches to devise new means to increase energy expenditure.

Introduction

Two major types of adipose tissue exist in mammals, named brown and white fat based on their macroscopic appearance. These two types are mainly composed of and functionally defined by their most important cell type, brown or white adipocytes, respectively. White adipocytes are roundish cells of large diameter that consist of one massive lipid droplet and a thin rim which contains the cytoplasm and the nucleus. White adipocytes primarily act as storage cells for neutral triacylglycerols, storing excess calories for use in times of scarcity. They contribute to whole body insulation and have endocrine functions including the secretion of adipokines such as leptin, resistin, and adiponectin.

Brown adipocytes are usually of smaller diameter than white adipocytes and are composed of several small lipid droplets. Their cytoplasm contains a high amount of mitochondria that are functionalized by uncoupling protein 1 (UCP1). This protein mediates non-shivering thermogenesis, which is the main physiological function of brown adipose tissue. Brown adipocytes generate heat via a futile cycle of proton transport across the inner mitochondrial membrane. Accordingly, they contribute to

the maintenance of body temperature homeostasis during both chronic and long-term cold exposure.

Human Relevance

The accumulating evidence for the presence of functional brown adipose tissue not only in newborn but also in adult humans^{1–5}—or in a major subset of the population—led to a revival of ideas about the therapeutic potential of activated brown adipocytes.^{6,7} It was estimated that even small amounts of active brown adipose tissue could lead to a significant increase in basal energy expenditure thus promoting weight loss.⁸ The resulting weight-lowering effect would not only be of aesthetic interest, but could also decrease the risk for certain co-morbidities of obesity such as type 2 diabetes and cardiovascular complications.^{9,10}

First studies indicate that the oxidative metabolism of human brown adipose tissue can indeed contribute significantly to total energy expenditure.^{11–13} Conversely, a negative correlation of the occurrence of detectable brown adipose tissue and the body mass index (BMI) was reported.³ Activation of brown adipose tissue could only be observed in lean but not obese patients.¹⁴ The past years have revealed a plethora of novel factors that can induce brown adipocyte formation or activation in animal models more specifically (not reviewed here). Clinical studies will show if one or a combination of these can lead to an efficacious weight reduction in humans.

Brown Adipocyte Nomenclature

Laboratory mice as the most widely used model for metabolic research contain a rather homogeneous depot of brown adipose tissue in the interscapular area and smaller ones in its vicinity.^{15,16} These depots are most often referred to as classical brown fat and are present throughout life. In addition, several predominantly white adipose tissues of mice can contain cells with the characteristics of brown adipocytes.^{17,18} These cells were named brite (brown-in-white), beige, inducible, or recruitable brown or brown adipocyte-like cells.^{19–23} We will subsequently use the term brite, which we consider to be a definition of the localization and the characteristics of a brown adipocyte. A brite adipocyte thus is a cell with the multilocular morphology and functional properties (including UCP1 expression) of brown adipocytes found in predominantly white adipose tissue depots with the definition being independent of the developmental origin. While most

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researchers use the various mentioned terms as synonyms for brite adipocytes, some point out differences in their definitions and even the meaning of the term “brite adipocyte” is under debate. Following the original publication that introduced this name, it has recently been used to describe cells that are indistinguishable from white adipocytes on the morphological level, but which can be converted into UCP1-expressing cells with the characteristics of brown adipocytes upon β -adrenergic stimulation.¹⁶ The ambiguity of terminology also reflects the current debates in the field of brown and white adipocyte biology, as it is unclear how brite adipocytes are formed and what the origin of these cells is.

Classical Brown versus Brite Adipocytes

Apart from the localization in either predominantly brown or white adipose tissue, other traits have been reported that differentiate classical brown and brite adipocytes in mice, including genetic variability in their occurrence, developmental origin, cell size, and elevated expression of certain transcripts.^{16,24-27} Transcriptome data of adipocytes differentiated *in vitro* from primary precursor cells or from immortalized cell lines led the basis for many of the characterizations of brite adipocytes published to date. The problem associated with these *in vitro* studies is the artificial induction of brown and white adipocyte formation that might not resemble the physiological situation. *In vivo* studies comparing the transcriptome of whole tissues containing brown (classical or brite) and white adipocytes revealed substantial differences between classical brown and brite-enriched depots. However, as whole tissues were employed in these studies, it remains to be shown whether these results can be attributed to intrinsic differences in adipocytes. Using some of these characteristics, the brown adipose tissue in adult humans was classified as more closely resembling brite adipocytes, while the brown fat tissue of newborn humans was considered to be more similar to classical brown adipose tissue in the mouse.^{27,28}

As mentioned above, a major part of the scientific community nowadays refers to three types of adipocytes—brown, brite, and white.^{27,29-31} From our point of view, and based on our recent results, classical brown and brite adipocytes could still be considered as brown adipocytes and not independent cell types (Fig. 1). First of all and most importantly, until today there is no evidence suggesting that the functions of brown and brite adipocytes might be any different from each other. Second, classical brown and brite adipocytes *in vivo* are remarkably alike both with regard to molecular and morphological markers.

We recently published the first gene expression data of FACS-sorted primary adipocytes comparing classical brown and brite adipocytes.³² The mRNA levels of both general adipocyte markers as well as typical brown markers were virtually identical in both populations. Regarding the transcriptional markers to distinguish classical brown from brite adipocytes reported in the above mentioned *in vitro* studies or whole tissue transcriptome analyses,^{16,27,28,33} we could only confirm one of the proposed brite-typical transcripts. We thus fully agree that there are measurable differences between classical brown and brite adipocytes in the most commonly studied depots. However, just as skeletal

myocytes exist in different fiber types with differing transcript levels of certain typical genes^{34,35} but are still the same cell type, at present we would not consider brite adipocytes sufficiently different from classical brown adipocytes to regard them as a cell type of their own. This could also apply to human brown fat as recent studies detected both brite-like as well as classical brown-like adipocyte properties in various human fat depots.^{29,31}

Brite Adipocyte Formation

Inguinal adipose tissue constitutes the biggest and thus physiologically most important fat depot capable of recruiting brite adipocytes upon chronic cold exposure of mice.¹⁶ We could recently show that mature adipocytes in this depot have the potential to interconvert between cells with the typical characteristics of white and brown adipocytes.³² This means that the ratio of lipid-storing to lipid-burning cells can be adjusted within an existing adipose depot depending on the environmental temperature without the need for *de novo* cell differentiation from precursors. Although this mechanism was proposed decades ago,³⁶ we provided the first direct experimental validation using lineage tracing in adult mice. Our findings support the idea of pharmacologically targeting white adipocytes to increase the number of brown adipocytes. The future will show if this approach—as a single therapy or in conjunction with other measures—will result in efficacious therapies for weight loss and help to counteract metabolic disorders.

Given the diametrically opposed function of brown and white adipocytes, this interconversion could be considered a transdifferentiation process, which is the biologically rare conversion of one differentiated somatic cell type into another one without returning to an undifferentiated state³⁷ (Fig. 1).

Based on a detailed analysis of the transcriptomes of primary adipocytes and stromal-vascular fractions from different adipose tissue depots with or without cold stimulation,³² we identified a set of genes most highly transcribed in white adipocytes. However, we could not detect a single transcript uniquely expressed in white adipocytes that shows a similar specificity as Ucp1 in brown adipocytes, suggesting that such a unique marker for white adipocytes may not exist. Therefore, the definition of a white (in contrast to a brown) adipocyte might always depend on the presence/absence or the expression levels of multiple marker genes. Hence, genetic approaches targeting only white adipocytes *in vivo* will be only feasible with more sophisticated mouse strains that employ combinations of markers to drive expression of a transgene.

Determinants of Brite Adipocyte Formation

Let's return to the above-mentioned ambiguity in terminology and the resulting problems associated with the lack of knowledge on brite adipocyte origin. One major question that remains unresolved is whether every “apparently white” adipocyte could be turned into a brown adipocyte or if there might be a finite pool of adipocytes that can undergo this transdifferentiation. We concluded our recent study with an experiment determining what

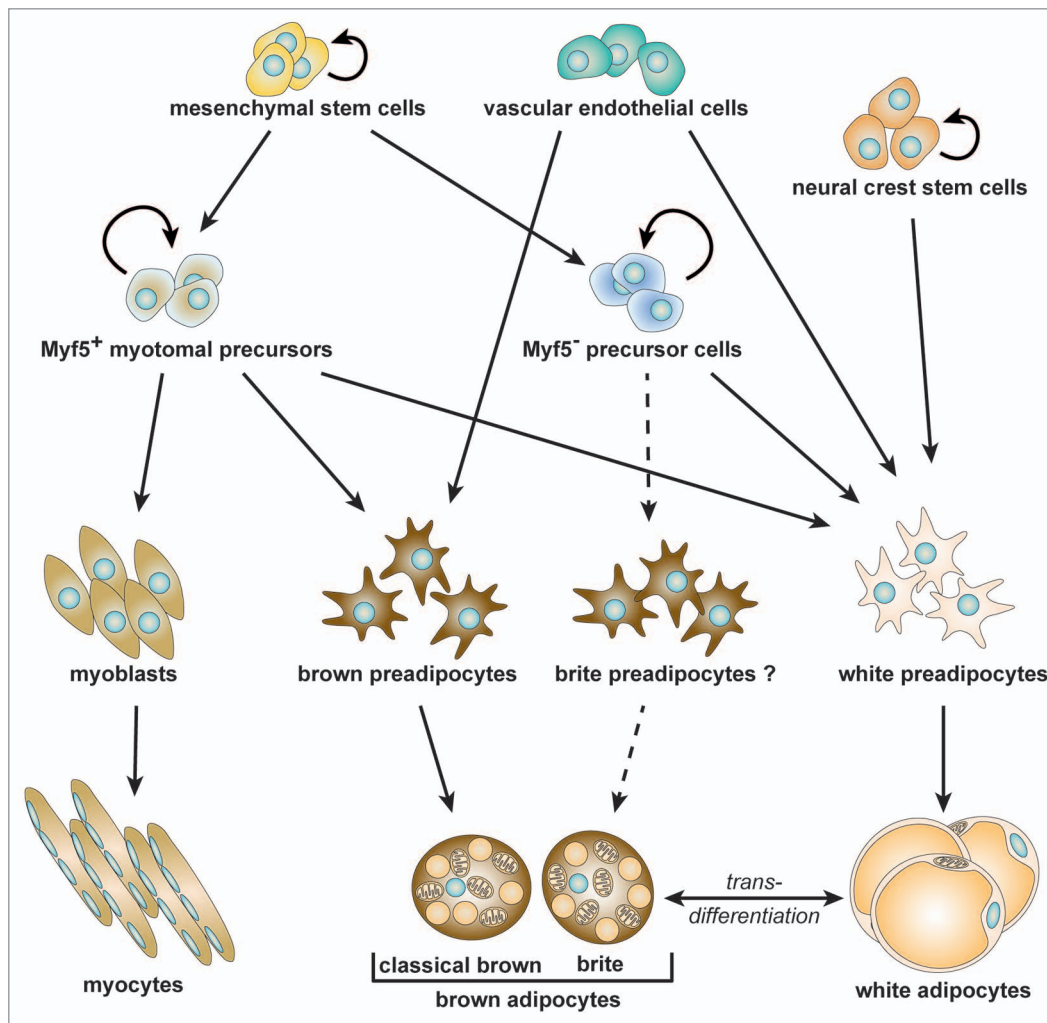


Figure 1. Developmental lineages of adipocytes. Schematic representation of the current knowledge about the possible developmental origins of murine adipocytes, including skeletal myocytes for comparison. At the level of preadipocytes (or myoblasts), the cells are considered committed to a specific differentiation. However, due to the lack of definite molecular markers, it should be noted that precursor cells and preadipocytes can be at least partly overlapping populations. Solid arrows represent conclusions from *in vivo* lineage tracing studies, dotted lines represent conclusions inferred from *ex vivo* or *in vitro* studies.

percentage of cells that became brite adipocytes during a first one-week cold stimulation turn into UCP1-positive brite adipocytes during a later second cold stimulation. We detected that about half of the new brite adipocytes were derived from former brite adipocytes labeled during the first cold stimulation that underwent “whitening” in the intermediate warm phase. The origin of the newly formed brite adipocytes could include other white adipocytes or cells from the stromal–vascular fraction. Brite adipocytes constitute approximately 10% of total adipocytes in the cold-stimulated inguinal depot under our experimental conditions. Thus, the observed 50% overlap is more than what could be expected from a completely stochastic selection of cells that undergo transdifferentiation. Intriguingly, most brite adipocytes localize to the same patches within the depot after the first and second cold stimulation, indicating that there are local differences in a white adipocyte’s capacity to brite. This could

be due to different white adipocyte populations or due to a different microenvironment (Fig. 2).

If the microenvironment is the determining factor for an adipocyte’s potential to transdifferentiate, several parameters such as density of vascularization, the types of stromal-vascular cells in the adipocyte’s vicinity, the composition of the extracellular matrix, and the local innervation need to be considered. Several circulating factors have been shown to influence the formation of brite adipocytes;^{23,38–40} however, white adipose tissue depots react very differently to the same cues from the bloodstream,^{16,18} suggesting the neuronal stimuli are the more crucial determinants. The number of brite adipocytes was shown to correlate with noradrenergic nerve fibers and mice lacking β_3 -adrenergic receptors are not capable of brite adipocyte formation during cold stimulation indicating that indeed the microenvironment is a major contributor to brown and brite adipocyte formation.^{41,42}

Lineages

When studying intrinsic differences within cells of a particular population, a commonly used approach is to determine the developmental origin of these cells and their precursors. It is based on the assumption that their lineage defines their fate, i.e., the potential cell type(s) and thus functions one particular cell can acquire. Especially the apparently simple discrimination by the Myf5⁺ lineage giving rise to classical brown but not brite and white adipocytes fuelled this way of thinking.²⁵ If brite adipocytes appear as apparently white adipocytes that can be stimulated quickly to a brown-like phenotype, whereas the “normal white” cannot, the developmental origin might actually be the distinguishing feature.³³

However, recent reports have proven adipocyte development to be more complex than anticipated and that the Myf5 lineage is not exclusive to classical brown in contrast to other adipocytes^{43,44} (Fig. 1). In spite of a number of tracing studies using different markers, the pre-adipocyte is still not a defined cell and no developmental path delineating brown, white or possibly brite adipocytes from each other has been established. Given the multiple cell types (including mesenchymal stem cells, vascular epithelial cells, neural crest cells, and hematopoietic stem cells) that were shown to contribute at least parts of the white and possibly brown adipocyte populations during normal murine life,⁴⁵⁻⁴⁸ we might have to accept that we deal with convergent development to mature cells virtually indistinguishable in spite of different origins. Thus, as long as we lack any trait differentiating adipocytes capable of white to brown transdifferentiation from those cells that are not capable of undergoing this process, the question whether a single or multiple subtypes of apparently white adipocytes exist will have to remain unanswered.

Future Approaches

How could we approach these open questions? Prolonged cold stimulation beyond the commonly employed 7 day stimulation could give additional insights

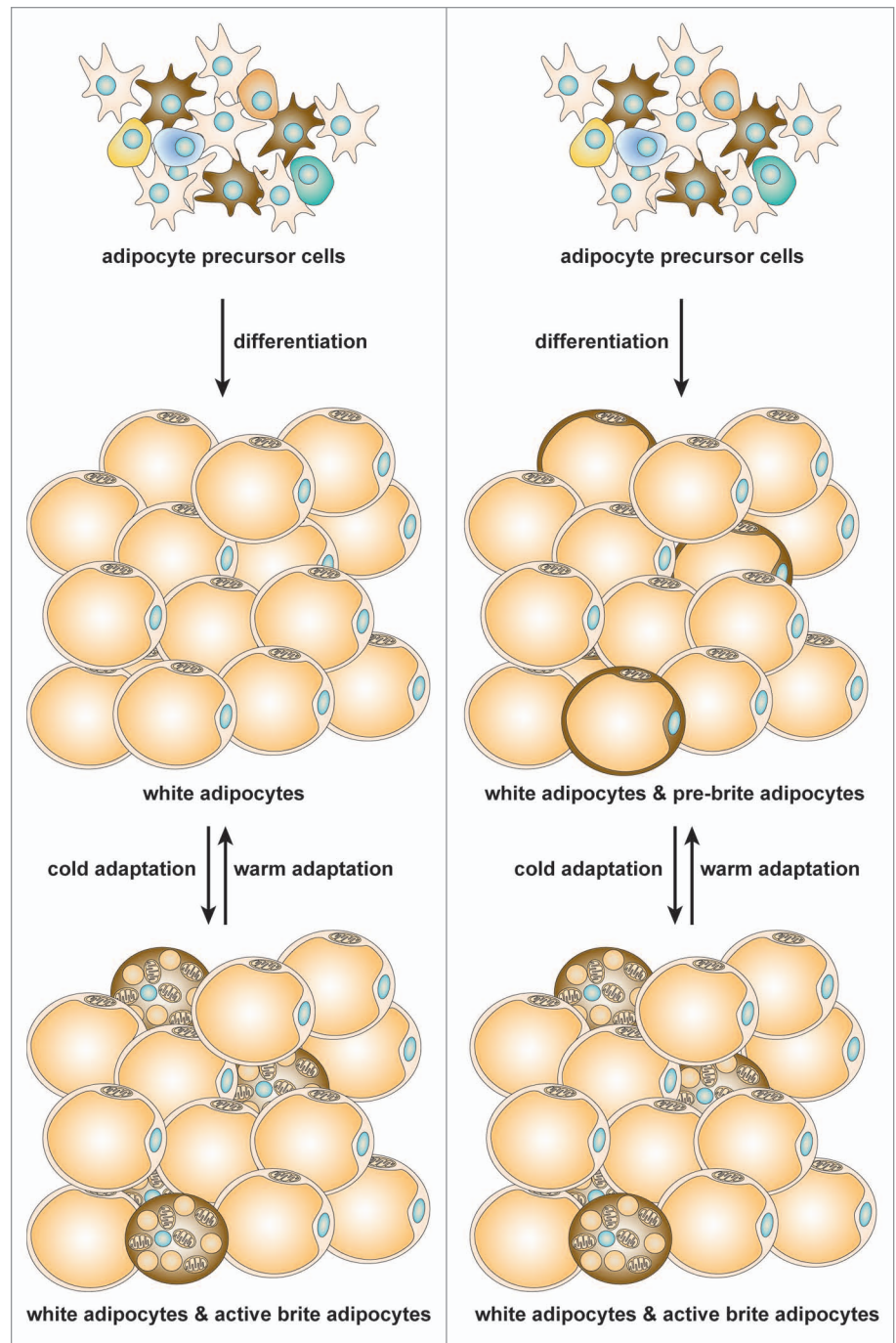


Figure 2. Brite adipocyte formation from white adipocytes. Two potential models of how mature apparently white adipocytes can be transformed into brite adipocytes are depicted. A potential contribution of any precursor cells to brite adipocyte recruitment is not taken into account here. Left: Adipocyte precursors within a white adipose tissue depot develop into a homogenous population of mature white adipocytes. Upon cold adaptation, a subset of these transdifferentiates into thermogenic brite adipocytes. The subset could be determined by their vicinity to blood vessels and thus circulating factors, adrenergic nerve endings or special extracellular matrix components. Right: Different subsets of the adipocyte precursor population within a white adipose tissue depot develop into an apparently homogeneous but intrinsically heterogeneous population of cells with mature white adipocyte characteristics. One subset of these cells holds the potential to transform into thermogenic brite adipocytes upon cold adaptation, while the others remain white adipocytes.

into the question whether only a subset of apparently white adipocytes is capable of turning into brite adipocytes. If the transdifferentiation potential is limited to a finite number of cells, the remaining adipocytes should retain their white phenotype independent of the length of the stimulus. Additional research is also needed regarding the different potential of white adipose tissue depots to form brite adipocytes, for example the epididymal depot remaining purely white fat in comparison to inguinal adipose tissue capable of transdifferentiation. We need to understand which differences are crucial for the different behavior of these tissues upon cold stimulation to induce transdifferentiation efficiently. Neuronal interactions but also contributions from stromal-vascular cells will probably be the major focus of attention. Finally, the ongoing development of novel techniques for characterization and manipulation of primary cells in vivo or ex vivo will be essential. Our presented novel mouse strains

combined with live adipocyte FACS allow for a more selective analysis of the cell types of interest and circumvention of several biases of cell culture work. Transgenic mouse strains allowing specific modifications only in white or brite adipocytes would be a major technical advance, although challenging due to the lack of exclusive markers.

The additional insights should allow us to put the existing and rapidly increasing wealth of molecular information mainly derived from cell culture data into the bigger perspective of in vivo organ function. We are convinced that only a combination of these experimental approaches will allow us to address the challenging task of increasing energy expenditure in adult humans in a safe and efficacious manner.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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