

COMMENT OPEN



Adipocyte and Cell Biology

What defines a cell type? Perspectives from adipocyte biology

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The question “What is a cell type?” has been central to biology for over a century, but recent advances in molecular biology, particularly single-cell and single-nuclei RNA sequencing techniques, have complicated this definition. As Amber Dance recently highlighted in *Nature* [1], single-cell RNA sequencing (scRNA-seq) provides unprecedented resolution in examining individual cell transcriptomes, uncovering significant heterogeneity within populations once thought to be homogeneous. Despite the power of RNA-based cell atlases, some scientists argue that defining cell types purely by gene expression is reductive [2]. The debate now centers on whether cells should be classified based on morphology, function, molecular signatures, or if entirely new frameworks are needed [3].

Historically, cell types were defined based on morphology observed under a microscope, which led to breakthroughs like Ramón y Cajal’s neuroanatomical discoveries [4]. In recent decades, molecular markers, such as glial fibrillary acid protein (GFAP) for astrocytes, have refined classification methods, made visible through immunohistochemical techniques with antibodies or tagging the *GFAP* gene green fluorescent protein [5]. However, the rise of high-throughput molecular methods like scRNA-seq has added new layers of complexity, uncovering previously unknown cell subtypes, complicating the concept of cell identity. This complexity is particularly evident in adipose tissue biology, where the identification of beige adipocytes has fueled debate over whether they represent distinct cell types or dynamic states transitioning between white and brown adipocytes.

ADIPOSE TISSUE: A DIVERSE CELLULAR LANDSCAPE

Adipose tissue is now recognized as a dynamic, metabolically active endocrine organ, that regulates many aspects of whole-body physiology, including food intake, maintenance of energy levels, insulin sensitivity, body temperature, and immune responses [6]. It actively participates in the pathogenesis of diseases, as acknowledged in the definitions of metabolic syndrome and cardiovascular-kidney-metabolic syndrome [7, 8]. Although some researchers remain cautious about these interpretations [9].

In adipose biology, the foundational definition of an adipocyte is centered on its function as a spherical, lipid-storing cell, where lipids accumulate as a single large droplet filling nearly the entire cytoplasmic space. This structural characteristic enables the adipocyte to perform two key functions: maintaining energy homeostasis by

storing triglycerides as a metabolic reservoir, and buffering other tissues from ectopic lipid deposition, thereby preventing lipotoxicity in non-adipose tissues. The identity and functionality of an adipocyte are shaped by its microenvironment, which consists of a highly complex cellular and structural network. While adipocytes constitute more than 90% of adipose tissue volume, they represent less than 50% of its cellular population, with the remaining cell types including endothelial, smooth muscle, nervous, and various immune cells [10]. Together, these cellular and structural components enable adipose tissue to dynamically respond to metabolic demands and environmental changes, both under physiological conditions (e.g., fasting and feeding cycles) and pathological states (e.g., overnutrition, obesity, type 2 diabetes, infections).

In response to specific environmental stimuli, such as cold exposure, and endogenous cues—such as sympathetic activation, nutrients, and signaling molecules like menthol—a distinct form of adipocyte, the brown adipocyte, can emerge. Brown adipocytes are polygonal in shape, contain multilocular lipid droplets, and are enriched with specialized mitochondria for thermogenesis. These cells uniquely express the uncoupling protein UCP1, which facilitates the dissipation of the proton gradient across the inner mitochondrial membrane, effectively uncoupling respiration from ATP synthesis to produce heat [11]. UCP1 is widely recognized as the primary driver of adaptive, non-shivering thermogenesis. Although alternative thermogenic mechanisms, including UCP1-independent futile cycles like the carnitine cycle, have been proposed in recent years, conclusive evidence supporting their physiological significance remains limited [12].

While white and brown adipocytes are two morphologically and functionally distinct cell types in adipose tissue, each with specialized roles in energy storage and thermogenesis, a third subset exists. This subset includes adipocyte progenitors and white adipocytes capable of “browning” in response to certain stimuli, thereby adopting characteristics of brown adipocytes; these cells are commonly referred to as beige adipocytes [13].

WHITE ADIPOCYTES

Mature white adipocytes originate from progenitor cells within the stromal vascular fraction (SVF) of white adipose tissue (WAT), a compartment that includes not only adipose progenitors but also stem cells and immune cells, such as M2 macrophages and T cells [14].

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A variety of cell surface markers associated with SVF progenitors involved in adipogenesis have been identified, including platelet-derived growth factor receptor alpha (PDGFR α), stem cell antigen-1 (Sca1, in mice), and others like CD13, CD29, CD34, CD44, CD73, CD90, and CD142. However, there remains a lack of agreement on the precise developmental trajectories of these progenitor populations, and it is probable that they represent different stages of adipocyte lineage commitment and differentiation [15] (Supplementary Table 1). scRNA-seq and cell trajectory analysis have deepened our insight into the origins of mature adipocytes. For example, cells expressing dipeptidyl peptidase-4 (DPP4) have been confirmed as genuine multipotent mesenchymal progenitors [10, 16]. In addition, advanced methods like spatial transcriptomics paired with scRNA-seq have provided new details on the spatial distribution of adipose progenitors within adipose tissue [17]. Notably, collagen-rich progenitor cells tend to localize near M2 macrophages, creating specialized adipogenic niches, while spatial mapping followed by hyperinsulinemic-euglycemic clamps has demonstrated that mature adipocyte subpopulations in humans have markedly distinct sensitivities to insulin [17].

BEIGE VS. BROWN ADIPOCYTES: DISTINCT CELL TYPES OR TRANSITIONAL STATES?

Thermogenic beige and brown adipose tissues play crucial roles beyond energy expenditure; they enhance glucose metabolism, reduce fibrosis, and provide anti-inflammatory and anti-tumor effects that collectively offer systemic health benefits [18, 19]. In terms of development, embryonic brown adipocytes are derived prenatally from specific precursors that express somite markers, including engrailed 1, myogenic factor 5 (Myf5), paired-box proteins 3 and 7, and mesenchyme homeobox 1 [20]. More recent findings indicate that vascular smooth muscle cells, characterized by the TRPV1 temperature-sensitive cation channel, can also give rise to brown adipocytes when exposed to cold [21].

Beige adipocytes, however, emerge from Myf5-negative adipose progenitors and differentiate from precursors marked by PDGFR α , Sca1 (in mice), smooth muscle actin, and CD81 [20]. Unlike brown adipocytes, beige cells initiate a thermogenic program only in response to cold or β_3 -adrenergic signaling [22]. Once these stimuli are removed, beige cells revert to a phenotype resembling white adipose tissue through a process of mitophagy-mediated mitochondrial removal, restoring white fat characteristics [23]. Despite distinct molecular signatures, beige adipocytes also express markers typical of white fat, such as leptin, suggesting they may serve as a hybrid cell type, combining properties of both energy-storing white fat and energy-dissipating brown fat. This unique combination has led to speculation that beige adipocytes might not represent a completely separate cell type, but rather an intermediate state between white and brown adipocytes.

Both brown and beige adipose tissues exhibit a high degree of cellular diversity. scRNA-seq and 3D tissue profiling have identified low- and high-thermogenic brown adipocyte subpopulations, with the latter characterized by elevated levels of UCP1 and adiponectin [24]. These two groups are dynamic and interchangeable: cold exposure promotes the conversion of low-thermogenic brown adipocytes to a highly thermogenic state, while thermoneutrality (30 °C) reverses this shift [24]. Beige fat also exhibits cellular diversity. In a mouse model that lacks all three β -adrenergic receptors, a specific subpopulation of MyoD⁺ beige adipocytes has been shown to engage in thermogenesis and exhibit high glycolytic activity, indicating that these cells may be capable of increasing energy expenditure independently of β_3 -adrenergic signaling [25]. In addition, while certain adipocyte populations promote thermogenesis and the differentiation of brown and beige fat, others actively inhibit these processes. Recent studies using single-nucleus RNA sequencing (snRNA-seq) have identified CYP2E1⁺ ALDH1A1⁺ cells in the interscapular

brown adipose tissue (BAT) of mice that reduce thermogenesis under warm conditions by secreting acetate. This metabolite binds to G-protein-coupled receptor 43 (GPR43), leading to a suppression of UCP1 activity and mitochondrial respiration [26]. However, a critical gap still exists in our understanding of the molecular pathways that define and regulate these distinct adipocyte populations, as well as their precise roles in adipose biology and metabolic disorders.

CHARACTERIZATION OF FACTORS INFLUENCING ADIPOCYTE PHENOTYPE

The phenotypic diversity of adipocytes is shaped by a complex interplay of hormonal, environmental, and molecular factors that govern their metabolic roles and functionality, with implications for metabolic health and therapeutic strategies. Although a comprehensive review of adipocyte characterization is beyond the scope of this paper and is available elsewhere [6], we briefly highlight key drivers of adipocyte phenotypic flexibility, particularly hormonal and sympathetic nervous system (SNS) signals, which are crucial under conditions of metabolic stress or environmental challenges. For example, cold exposure activates the SNS, resulting in norepinephrine release that targets β_3 -adrenergic receptors on adipocytes. This activation initiates a signaling cascade involving cyclic AMP and protein kinase A, leading to increased transcription of UCP1 and enhanced lipid breakdown. In addition, reactive oxygen species generated during this process play a critical role in activating UCP1, facilitating heat production and thermogenic adaptation [27].

Dietary composition and nutrient availability also have profound impacts on adipocyte phenotype. Caloric restriction promotes the recruitment of beige adipocytes and enhances mitochondrial function, potentially through nutrient-sensing pathways such as AMPK and SIRT1, which adjust energy output during reduced caloric intake [28]. Thermoneutrality-induced BAT whitening, in contrast, is predominantly fueled by newly synthesized fatty acids accumulating within storage and membrane lipids and not by the accretion of dietary fatty acids [29]. This study introduces the concept of BAT involution as an active process driven by the lipogenic transcription factor carbohydrate response element binding protein (ChREBP). High-fat diets, in contrast, can promote inflammation within WAT, diminishing beige adipocyte recruitment and impairing thermogenic capacity [30]. This pro-inflammatory state suppresses mitochondrial biogenesis and skews adipocytes toward a storage phenotype, reducing metabolic flexibility.

Additionally, immune cells within adipose tissue also influence adipocyte phenotype through complex interactions. Pro-inflammatory macrophages within WAT secrete cytokines such as TNF- α and IL-6, which inhibit browning processes and promote insulin resistance, favoring lipid storage [31]. Anti-inflammatory cytokines, like IL-4 and IL-13, conversely support the beige adipocyte phenotype by shifting macrophage polarization towards an M2 anti-inflammatory state, facilitating thermogenesis and mitochondrial activity [14]. These interactions indicate that the immune microenvironment can actively remodel adipocyte function, influencing the tissue's metabolic profile and energy balance.

FUNCTIONAL PLASTICITY AND ADIPOCYTE TRANSDIFFERENTIATION

A "cell type" is traditionally defined by its distinct anatomy and physiology, yet certain cell types possess the ability to undergo physiologically reversible changes, a process known as cellular transdifferentiation. Both white and brown adipose cell types perform vital roles and under specific conditions—such as chronic cold exposure—white adipocytes can transdifferentiate into brown-like adipocytes to enhance thermogenesis, a process critical for survival [11]. Conversely, during chronic hypercaloric

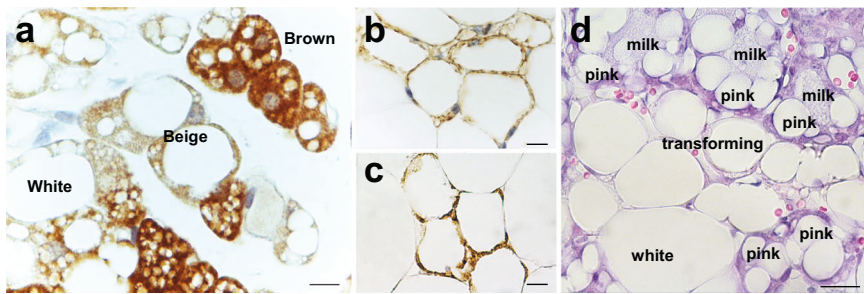


Fig. 1 **Adipocyte transdifferentiation under different conditions.** **a** Perirenal adipose tissue in a cold-exposed mouse. UCP1 immunostaining reveals unilocular, UCP1-negative adipocytes adjacent to multilocular, UCP1-positive adipocytes, with several intermediate forms showing weak UCP1 staining (beige adipocytes). Adapted from Smorlesi et al., *Obesity Rev. Suppl.* 2: 83–96, 2012, with permission. Scale bar: 10 μ m. **b** Subcutaneous white adipose tissue from a mouse exposed to cold (4 °C) for two hours. UCP1 immunostaining shows numerous small lipid droplets at the periphery of each cell, where mitochondria express UCP1 (paucilocular, UCP1-positive adipocytes). Scale bar: 10 μ m. **c** Perirenal adipose tissue from the autopsy of a 53-year-old man living in Siberia. UCP1 immunostaining shows similarities with cold-exposed adipocytes in panel (b). Adapted from Efremova et al., *J. Physiol. Biochem.* 76: 185–192, 2020, with permission. Scale bar: 35 μ m. **d** Mammary gland of an 18-day pregnant mouse. The presence of white adipocytes and early-forming milk-producing glands composed of epithelial cells with large lipid droplets (pink adipocytes) is visible, with intermediate forms (transforming) also noted (Cinti, unpublished results). Hematoxylin and eosin staining. Scale bar: 10 μ m.

states, brown adipocytes can convert back into white adipocytes to store surplus energy [11].

This plasticity is supported by studies like those of Rosenwald et al. [32], which provide robust evidence for adipocyte transdifferentiation. During transdifferentiation, adipocytes can adopt intermediate forms both in morphology and function (Fig. 1a). Beige adipocytes, for instance, may represent transitional stages in this process rather than distinct cell types. The thermogenic capability of these transforming white adipocytes becomes apparent with the early activation of UCP1, particularly in paucilocular UCP1⁺ adipocytes. These cells maintain a morphology closer to white adipocytes but express UCP1 in “transforming” mitochondria, enabling a mild thermogenic response (Fig. 1b, c).

While recent studies have confirmed the *Myf5* origin of brown adipocytes, perirenal adipose tissue exhibits a distinctive brown-to-white transition [33]. During prenatal stages, perirenal fat shows a high expression of *Myf5*, but this expression significantly decreases as the tissue matures, becoming almost undetectable in adulthood, at which point it is predominantly composed of white adipocytes. These findings support the idea that markers such as *Myf5* may reflect a cell’s phenotype at a specific developmental stage or functional state, rather than defining a static cell type.

Another striking example of adipocyte plasticity, that seems to confirm previous findings, occurs in female mice during pregnancy and lactation, where white adipocytes in the breast convert into milk-producing epithelial cells and then revert back to white adipocytes after lactation. Notably, the early stages of differentiation in these milk-producing cells closely resemble the anatomical appearance of white adipocytes. Given the pinkish hue of subcutaneous adipose tissue during pregnancy and lactation—likely due to the presence of milk (white) and blood (red) in the lactating breast—we coined the term “pink adipocyte” to describe this transitional cell type (Fig. 1d). Evidence from cell lineage tracing, explant studies, ultrastructural analysis, and immunohistochemical techniques supports this interpretation [11, 34, 35].

Multilocular beige adipocytes share anatomical similarities with *in vitro* differentiated preadipocytes, prompting the provocative hypothesis that beige adipocytes could represent a dedifferentiated state of white adipocytes. This idea posits an intermediate phase in which a cell reverts to a more stem-like, progenitor phenotype, a concept well-documented in systems like hematopoiesis and lymphocyte development. For example, B lymphocytes can dedifferentiate into uncommitted progenitors before differentiating into T lymphocytes with distinct functional roles [36]. However, in the case of adipocyte plasticity, there is limited evidence to suggest a true dedifferentiation step occurs during

the reversible transitions between white, beige, and pink adipocytes (e.g., WAT-to-BAT or WAT-to-Pink). Interestingly, studies have shown that mature human adipocytes can dedifferentiate *in vitro*, acquiring properties resembling bone marrow-derived stem cells and expressing genes associated with stem cell potential and reprogramming. These dedifferentiated adipocytes can further differentiate into multiple cell lineages [37].

Taken together, these findings suggest that white, brown, and beige adipocytes, along with the pink adipocytes, should not be viewed as fixed cell types but as dynamic entities capable of reversible transitions depending on physiological demands.

CONCLUSIONS

The advent of single-cell technologies and other molecular profiling techniques has revolutionized our understanding of adipocyte diversity. These technologies have revealed not only molecular distinctions between beige and brown adipocytes but also the existence of subpopulations within beige adipose tissue. This molecular heterogeneity challenges the notion of beige adipocytes as a single-cell type and instead suggests they represent a continuum of cellular states [38].

In conclusion, the ongoing debate about whether beige adipocytes are distinct cell types or transitional states reflects broader challenges in defining cellular identity in the post-genomic era. In addition to scRNA-seq and snRNA-seq, cell trajectory analysis and spatial transcriptomics have revealed the limitations of traditional classification systems, showing that adipocytes, like many other cell types, exhibit remarkable plasticity. Instead of being static members of a single type, cells may embody multiple identities depending on the biological context and pathways they engage at any given time. This evolving view of cellular identity is particularly relevant in the study of obesity and metabolic diseases, where a better understanding of beige and brown adipocytes could offer novel therapeutic opportunities. However, the interconvertibility of these cells emphasizes the need for more flexible and dynamic frameworks for classifying cell types—frameworks that recognize the fluid and dynamic nature of cellular states in health and disease.

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AUTHOR CONTRIBUTIONS

EN and SC conceptualized, wrote, edited, and revised the manuscript. SC prepared the histological images. EN elaborated their combination with advice from SC.

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ADDITIONAL INFORMATION

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