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Systematic Review

Thermogenic Differentiation of Human Adipocyte Precursors in Culture: A Systematic Review

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Abstract

Thermogenic adipocytes present a promising therapeutic strategy for metabolic diseases. While murine models have provided valuable insights into thermogenic adipose tissue, their relevance to human physiology is constrained by species-specific differences in tissue distribution and thermogenic capacity. In vitro human models offer a more controlled platform to study adipocyte differentiation, addressing challenges such as limited access to deep fat depots and individual variability. This systematic review summarizes the current literature on human in vitro models for thermogenic adipocyte induction, encompassing 117 studies involving primary human adipocyte progenitors differentiated into thermogenic adipocytes in 2D cultures. Most studies relied on classical adipogenic inducers, including isomethylbutylxanthine, dexamethasone, and insulin, with additional use of triiodothyronine, rosiglitazone, or indomethacin. A few studies incorporated adrenergic stimulation or exposure to lower temperatures to simulate cold exposure. Notably, some studies demonstrated successful differentiation under serum-free, chemically defined conditions, highlighting their potential for reproducibility and translational relevance. A key limitation remains the predominant reliance on gene expression as the primary outcome, with few studies assessing mitochondrial respiration or broader metabolic functions. Moving forward, the development and adoption of standardized, functionally validated protocols will be critical to fully realize the potential of human in vitro thermogenic adipocyte models in metabolic research.

Keywords: adipocyte differentiation; cell culture; thermogenic adipocyte

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1. Introduction

Obesity is a chronic and multifactorial disease defined by the excessive accumulation of body fat; it significantly increases the risk of type 2 diabetes, cardiovascular disease, certain cancers, and overall mortality [1]. Currently available treatment strategies for obesity primarily aim to reduce energy intake [2], with relatively limited emphasis on enhancing energy expenditure. Lifestyle interventions—particularly hypocaloric diets, macronutrient modulation, and intermittent fasting—remain the foundation of clinical management, producing initial weight loss through sustained caloric restriction [2]. Pharmacotherapies such as glucagon-like peptide 1 receptor agonists reinforce the intake-focused paradigm by reducing appetite and slowing gastric emptying, with no proven direct effects on energy

expenditure [3]. Bariatric surgery, the most effective long-term treatment for severe obesity, also acts chiefly by restricting intake, although some procedures may modestly influence energy expenditure and substrate utilization [2].

The prevailing focus on intake restriction underscores a critical gap in current therapies and highlights the need for strategies that effectively and safely enhance energy output in parallel with intake modulation. While physical activity contributes to increased energy output, its impact on weight loss is typically modest [4]. An alternative or synergistic approach involves stimulating nonshivering thermogenesis in thermogenic adipose tissue, which comprises brown and beige adipocytes [5]. Brown adipocytes are typically located in dedicated depots, such as the deep neck and supraclavicular regions, and are present from infancy through adulthood [5]. In contrast, beige adipocytes emerge within white adipose tissue in response to specific stimuli, including cold exposure and β-adrenergic activation [5]. Both cell types contribute to increased energy expenditure and have emerged as potential therapeutic targets for obesity and metabolic disorders. However, the extent, inducibility, and metabolic relevance of beige adipocytes in adult humans remain areas of active investigation.

In this scenario and considering the substantial challenges associated with investigating human thermogenic adipocytes in vivo—such as limited accessibility of deep fat depots, variability in thermogenic capacity across individuals, and the influence of environmental and physiological factors [6]—human cellular models have emerged as valuable platforms for both mechanistic studies and translational research, enabling controlled investigation of the molecular pathways underlying beige adipocyte differentiation and function. Therefore, we conducted a systematic review to critically evaluate and synthesize the existing literature on human in vitro models for thermogenic adipocyte induction.

2. Materials and Methods

2.1. Statement and Registration

This systematic review followed the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) [7] and was registered on PROSPERO (CRD420251019278). The PRISMA checklist is presented in Table S1.

2.2. Search Strategy

The literature search strategy was developed using the PICOS acronym, in which P (population) was defined as 'human adipocyte precursors,' I (intervention) as 'exposure to differentiation medium to induce the differentiation of thermogenic adipocytes,' C (comparator) as 'comparison group with a control group (non-differentiated adipocyte precursors, adipocyte precursors induced to differentiate into white adipocyte, or precursors from different adipose depots),' O (outcome) as 'molecular markers of thermogenic adipocytes (mRNA, protein), mitochondrial content, or functional measures of oxygen consumption,' and S (study type) as 'cell culture-based studies assessing the differentiation of adipocyte precursors into thermogenic adipocytes.'

We searched PubMed, Web of Science, Scopus, and Google Scholar from inception to 26 March 2025, without language restriction, using the search strategy detailed in Table S2. The reference lists of included articles were also manually searched. References were managed using a reference management system [8].

2.3. Eligibility Criteria, Study Selection, and Data Extraction

The studies were selected in a two-phase process. In the first phase, two reviewers (G.L.A.S.P. and E.C.G.) independently screened the retrieved studies by assessing their titles and abstracts to select eligible studies. On the second phase, the same reviewers

independently assessed the full-text version of eligible studies and applied the inclusion criteria. Disagreements between the reviewers in the first two phases were resolved through discussion with a third reviewer (A.A.A.).

Studies describing protocols to induce the differentiation of precursors into thermogenic adipocytes in primary cell models and assessing molecular markers or functional measures of the thermogenic adipocyte were included. While immortalized cell lines are widely used for mechanistic studies due to their ease of use, reproducibility, and scalability, their adipogenic potential—and likely their thermogenic capacity—may differ substantially from that of primary human cells [9]. To minimize confounding factors and enhance translational relevance, we therefore restricted our review to studies employing primary human adipocyte precursors.

Abstracts, reviews, editorials, book chapters, and studies that discussed mouse cells or cell lines or in which the composition of the differentiation medium was not described were excluded. When the composition of the medium used to induce the thermogenic phenotype was described in a citation, the citation was searched to retrieve the information. The following information were collected from the included studies: author, year of the publication, type of adipocyte precursor used, growth medium, cell confluency at adipocyte differentiation induction, composition of the medium used to induce differentiation into thermogenic adipocytes, and outcomes related to the thermogenic phenotype, including mRNA and protein expression of thermogenic markers, mitochondrial content, and oxygen consumption rate.

2.4. Quality Appraisal

The risk of bias was assessed independently by two reviewers (G.L.A.S.P. and E.C.G.) using the United States National Toxicology Program's Office of Health Assessment and Translation (NTP/OHAT) risk of bias rating tool [10], and disagreements were resolved by discussion with a third reviewer (A.A.A.). Risk of bias was classified as definitely low (++), probably low (+), probably high (-), definitely high (--), and not applicable (NA).

2.5. Qualitative Analysis

We summarized data by describing the adipocyte differentiation protocols and results concerning characterization of the thermogenic adipocyte in a table format (structured summary method).

3. Results

3.1. Study Selection

A total of 6426 studies were identified in the searched databases. After duplicate removal, 2634 articles were screened and 270 were selected for full-text analysis. A total of 117 studies [11–127] were included (Figure 1), and their characteristics are described in Table S3. The excluded studies and reasons for their exclusion are presented in Table S4.

3.2. Characteristics of the Protocols to Induce Differentiation of Adipocyte Precursors into Thermogenic Adipocytes

The protocols described in the included studies to induce differentiation of primary adipocyte precursors into thermogenic adipocytes varied with respect to the specific precursor used, cell confluency at adipogenic induction, induction medium, and duration of induction (Table S3). Most studies (n = 70/116) used cells from the stromal vascular fraction of adipose tissue obtained from different tissue depots, including subcutaneous white adipose tissue (abdominal, thigh, neck, supraclavicular, breast, subacromial, chin, knee, flank, hip), visceral white adipose tissue (omental, peri-carotid, pericardial, mediastinal, perirenal, periadrenal), deep neck adipose tissue, prevertebral adipose tissue, or fetal

brown adipose tissue. A total of 35 studies reported that FGF was used during precursor expansion, before adipocyte differentiation induction (Table 1).

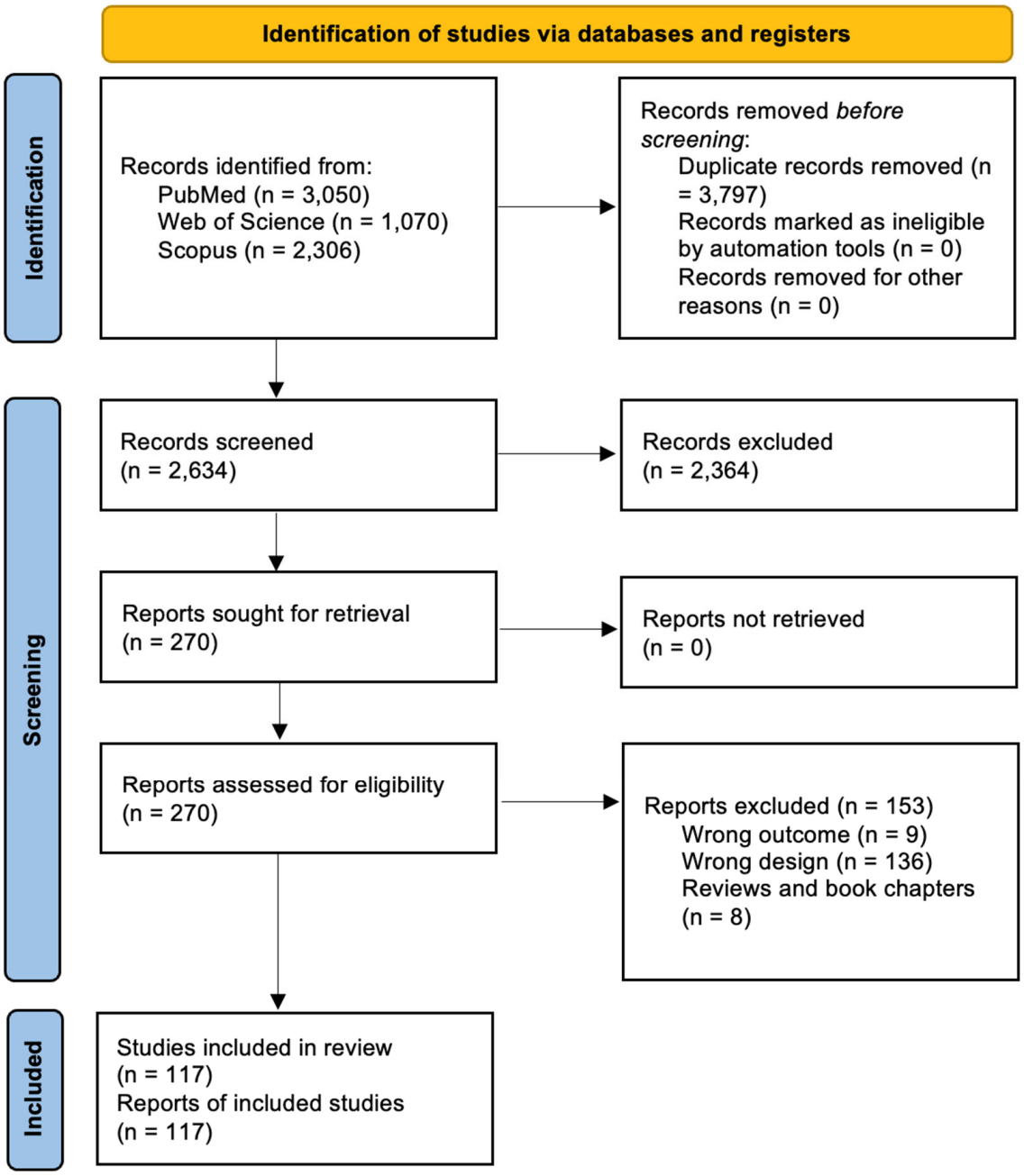

Figure 1. Flow diagram of the study selection process.

Table 1. Precursor origin and characteristics of thermogenic adipocyte differentiation conditions described in the included studies.

Characteristics [1]	No of Studies (%)
Precursor origin	
SVF	70/117 (59.8)
Abdominal SC AT	25 (35.7)
SC WAT	21 (30)
Deep neck AT	8 (11.4)
Subcutanous neck AT	7 (10)

Table 1. *Cont.*

Characteristics [1]	No of Studies (%)
Supraclavicular AT	6 (8.6)
Embryonic/fetal AT	5 7.1)
Omental WAT	4 (5.7)
Breast AT	4 (5.7)
Perirenal AT	4 (5.7)
Pericardial AT	3 (4.3)
Periadrenal AT	1 (1.4)
Mediastinal AT	1 (1.4)
Mixture of AT depots	1 (1.4)
Other (chin, thigh, knee, and subacromial AT)	4 (5.7)
WAT (depot NR)	1 (1.4)
NR	3 (4.3)
ADSC	16 (13.7)
MADSC	11 (9.4)
Stromal cells	8 (6.8)
BM	6 (75)
Umbilical cord	1 (12.5)
WAT SC	1 (12.5)
Preadipocytes	6 (5.1)
MSCs	5 (4.3)
Other [2]	9 (7.7)
Confluency at induction	
<100%	14 (12.8)
At confluency	48 (41)
After confluency	
2 days	26 (22.2)
1 day	1 (0.9)
NR	28 (23.9)
FGF for proliferative phase (before induction)	35 (29.9)
Medium for induction	
DMEM	41 (35)
Serum free	1 (2.4)
FBS	32 (78)
Other type of serum (NCS, FCS)	8 (19.5)
DMEM-F12	42 (35.9)
Serum free	21 (50)
FBS	16 (38.1)
Other type of serum (human, FCS)	5 (11.9)
DMEM-F12-Ham's	20 (17.1)
Serum free	15 (75)
FBS	4 (20)
Other (FCS)	1 (5)
MEMα	4 (3.4)
Serum free	0 (0)
FBS	4 (100)
Commercial medium	2 (1.2)
NR	5 (4.3)
Other [3]	4 (3.4)
Differentiation period	
<7 days	5 (4.3)
7–14 days	67 (57.3)
>14 days	38 (32.5)
Other ranges	6 (5.1)
NR	2 (1.7)

Table 1. *Cont.*

Characteristics [1]	No of Studies (%)
Differentiation stages	
One	35 (29.9)
Two	65 (55.6)
Three or more	17 (14.5)

[1] As some studies reported more than one outcome/measure, the total percentage exceeds 100%. [2] Adipocytes from ceiling culture, microvascular fragments, dermal fibroblasts, progenitor from adipose tissue explants, sprouting cells from cultured AT, endothelial/capillary network cells. [3] IMDM, DMEM/DMEM-F12, DMEM-F10, DMEM-F10-Ham's. ADSCs: Adipose-derived stem cells; AT: adipose tissue; DMEM: Dulbecco's Modified Eagle's Medium; DMEM-F12: Dulbecco's Modified Eagle's Medium/Nutrient F-12; FBS: fetal bovine serum; FCS: fetal calf serum; FGF: fibroblast growth factor; IMDM: Iscove's modified Dulbecco's medium; MADSCs: multipotent adipose-derived stem cells; MEM: Minimum Essential Medium; MSC: mesenchymal stem cells; NCS: neonatal calf serum; NR: not reported; SC: subcutaneous; WAT: white adipose tissue.

In most studies (n = 48/117), precursor cells were induced to differentiate into thermogenic adipocytes at 100% confluency. Fewer studies induced cells one (n = 1/117) to two days (n = 26/117) after confluency or at 70 to 95% confluency (n = 15/117). A total of 28 studies did not report confluency at adipogenic induction. Most studies (n = 112/117) reported the cell culture medium used to induce adipogenic differentiation, and the most frequently used were DMEM/F12 (n = 42/112), DMEM (n = 41/112), and DMEM/F12/Ham's (n = 20/112). Most studies (n = 74/112) supplemented induction medium with serum, whereas in 38/112 studies, adipogenic differentiation was carried out in serum-free medium. The most frequently used serum was fetal bovine serum (38/74), with concentrations ranging from 2 to 20% (volume/volume). Adipocyte differentiation duration ranged from three to 32 days, with most studies conducting differentiation for 7–14 days. Moreover, in most studies (65/117) differentiation was conducted in two stages, comprising the addition of different substances to cell culture medium in each (Table 1).

All studies induced adipocyte differentiation using IBMX and dexamethasone, at concentrations ranging from 0.03 to 1 mM and 0.1 to 100 μM, respectively. Most studies (114/117) used insulin at concentrations ranging from 1 to 1000 nM, triiodothyronine (T3, 90/117) at concentrations ranging from 0.2 to 1000 nM, and rosiglitazone (89/117) at concentrations ranging from 0.1 to 10 μM. Few studies used indomethacin (30/117) at concentrations ranging from 2 to 100 μM. Other browning agents, such as bone morphogenetic proteins, fibroblast growth factors, irisin, and its precursor FNDC5 were used in a minority of the studies. In addition, transferrin, biotin, and pantothenate were added to the differentiation induction medium by less than half of the studies. Additionally, thermogenic induction was implemented by acute (<12 h) or chronic (>12 h) adrenergic stimulation in a subset of studies, whereas a smaller proportion employed exposure to lower temperatures for variable durations to upregulate thermogenic markers (Table 2).

Table 2. Characteristics of induction medium to promote thermogenic adipocyte differentiation in the included studies.

Characteristics	No of Studies (%)
IBMX—no (%)	117 (100)
No IBMX—no (%)	9 (7.7)
IMBX at induction—no (%)	82 (70.1)
Concentration	0.1–1 mM
Duration	2–14 days
IMBX during whole differentiation—no (%)	26 (22.2)
Concentration	0.03–0.5 mM
Duration	4–32 days

Table 2. *Cont.*

Characteristics	No of Studies (%)
Dexamethasone—no (%)	117 (100)
At induction	71 (60.7)
Concentration	0.1–25 μM
Duration	2–14 days
During whole differentiation	46 (39.3)
Concentration	0.1–100 μM
Duration	7–32 days
Insulin—no (%)	114 (97.4)
At induction—no (%)	16 (14.0)
Concentration	1–1000 nM
Duration	1–14 days
During whole differentiation—no (%)	98 (86.0)
Concentration	1–1000 nM
Duration	7–32 days
T3—no (%)	90 (76.9)
At induction—no (%)	13 (14.4)
Concentration	0.2–250 nM
Duration	3–10 days
During whole differentiation—no (%)	73 (81.1)
Concentration	0.2–1000 nM
Duration	6–32 days
After induction—no (%)	4 (4.4)
Concentration	0.2–1 nM
Duration	6–10 days
Other browning agents—no (%)	18 (15.3)
BMP4 or 7—no (%)	12 (66.7)
FGF—no (%)	4 (22.2)
Irisin—no (%)	1 (5.5)
FNDC5—no (%)	1 (5.5)
Rosiglitazone—no (%)	89 (76.1)
At induction—no (%)	25 (28.1)
Concentration	0.2–5 μM
Duration	3–14 days
During whole differentiation—no (%)	41 (46.1)
Concentration	0.1–10 μM
Duration	3–32 days
At different time points—no (%)	23 (25.8)
Concentration	0.1–1 μM
Indomethacin—no (%)	30 (25.6)
Concentration	2–200 μM
At induction—no (%)	18 (60)
During whole differentiation—no (%)	12 (40)
Transferin—no (%)	51 (43.6)
Concentration	6.25–10 μg/mL
At induction—no (%)	10 (19.6)
During whole differentiation—no (%)	40 (78.4)
After induction—no (%)	1 (2)
Biotin—no (%)	37 (31.6)
Concentration	3.3–330 μM
At induction—no (%)	4 (10.8)
During whole differentiation—no (%)	33 (89.2)
Pantothenate—no (%)	34 (29.1)
Concentration	17–20 μM
At induction—no (%)	4 (11.8)
During whole differentiation—no (%)	30 (88.2)

Table 2. *Cont.*

Characteristics	No of Studies (%)
Adrenergic stimulation	
NE—no (%)	12 (10.3)
Concentration	1–10 μM
Acute (<12 h)—no (%)	10 (83.3)
Chronic (>12 h)—no (%)	2 (16.7)
Forskolin—no (%)	12 (10.3)
Concentration	1–50 μM
Acute (<12 h)—no (%)	6 (50)
Chronic (>12 h)—no (%)	6 (50)
CL 316,243—no (%)	9 (7.7)
Concentration	1–10 μM
Acute (<12 h)—no (%)	3 (33.3)
Chronic (>12 h)—no (%)	6 (66.7)
Isoproterenol	6 (5.1)
Concentration	0.1–100 μM
Acute (<12 h)—no (%)	4 (66.7)
Chronic (>12 h)—no (%)	1 16.7)
NR	1 (16.7)
cAMP—no (%)	4 (3.4)
Concentration	0.5–1 mM
Acute (<12 h)—no (%)	4 (100)
Chronic (>12 h)—no (%)	1 (25)
Cold exposure—no (%)	6 (5.1)
Temperature range	16–32 °C
Acute (<12 h)	5 (83.3)
Chronic (>12 h)	1 (16.7)

As some studies reported more than one outcome/measure, the total percentage exceeds 100%. BMP: bone morphogenetic protein; cAMP: cyclic adenosine monophosphate; IBMX: isomethylbuthylxanthine; FGF: fibroblast growth factor; FNDC5: fibronectin type III domain-containing protein 5; NR: not reported; T3: triiodothyronine.

3.3. Characteristics of Thermogenic Adipocytes in the Included Studies

The thermogenic phenotype was characterized by RNA (mRNA or miRNA, 104/117) and protein (70/117) of thermogenic markers, mitochondrial bioenergetics (48/117), or mitochondrial content (20/117). The thermogenic markers (RNA and protein) assessed in the included studies are presented in Figure 2, Tables 3 and S5.

Table 3. Characterization of thermogenic adipocyte in the included studies.

Characteristics	No of Studies (%)
Outcomes	
RNA expression (thermogenic markers)—no (%)	104/117 (88.9)
qPCR—no (%)	102/104 (98.1)
Transcriptome—no (%)	3/104 (2.9)
Protein expression (thermogenic markers)—no (%)	70/117 (59.8)
Mitochondrial bioenergetics—no (%)	48/117 (41)
Mitochondrial content—no (%)	21/117 (17.9)
Comparison	108/117 (92.3)
Thermogenic vs. white adipocytes—no (%)	43/108 (39.8)
↑ thermogenic markers (RNA)	35/38 (92.1)
↑ thermogenic markers (protein)	25/28 (89.3)
↑ mitochondrial activity	10/12 (83.3)
↑ mitochondrial content	7/8 (87.5)

Table 3. *Cont.*

Characteristics	No of Studies (%)
Stimulated vs. non-stimulated with adrenergic agonists/FSK/cAMP—no (%)	28/108 (25.9)
↑ thermogenic markers (RNA)	21/28 (75)
↑ thermogenic markers (protein)	8/9 (88.9)
↑ mitochondrial activity	14/17 (82.4)
↑ mitochondrial content	2/2 (100)
Thermogenic adipocytes vs. undifferentiated cells—no (%)	25/108
↑ thermogenic markers (RNA)	19/21 (90.5)
↑ thermogenic markers (protein)	12/14 (85.7)
↑ mitochondrial activity	1/1 (100)
↑ mitochondrial content	4/4 (100)
Thermogenic adipocytes differentiated from precursors from different AT depots—no (%)	19/117 (16.2)
Deep cervical vs. superficial cervical and other subcutaneous AT depots—no (%)	6/19 (31.6)
↑ thermogenic markers (RNA)	4/4 (100)
↑ thermogenic markers (protein)	1/1 (100)
↑ mitochondrial activity	2/2 (100
↑ mitochondrial content	-
Supraclavicular vs. other subcutaneous AT depots—no (%)	4/19 (21.1)
↑ thermogenic markers (RNA)	3/3 (100)
↑ thermogenic markers (protein)	2/2 (100
↑ mitochondrial activity	-
↑ mitochondrial content	-
Periadrenal/perirenal vs. other subcutaneous AT depots—no (%)	3/19 (15.8)
↑ thermogenic markers (RNA)	2/3 (66.7)
↑ thermogenic markers (protein)	1/1 (100)
↑ mitochondrial activity	1/1 (100)
↑ mitochondrial content	-
Fetal/embryonic vs. adult AT depots—no (%)	3/19 (15.8)
↑ thermogenic markers (RNA)	3/3 (100)
↑ thermogenic markers (protein)	2/2 (100)
↑ mitochondrial activity	1/1 (100)
↑ mitochondrial content	2/2 (100)
Cells not treated with glitazones—no (%)	9/107 (8.4)
↑ thermogenic markers (RNA)	6/7 (85.7)
↑ thermogenic markers (protein)	4/4 (100)
↑ mitochondrial activity	2/2 (100)
↑ mitochondrial content	2/2 (100)
Adipocytes exposed to lower vs. higher temperature—no (%)	6/107 (5.6)
↑ thermogenic markers (RNA)	2/4 (50)
↑ thermogenic markers (protein)	3/3 (100)
↑ mitochondrial activity	-
↑ mitochondrial content	-

As some studies reported more than one outcome/measure, the total percentage exceeds 100%. RNA: ribonucleic acid; qPCR: quantitative real-time polymerase chain reaction; AT: adipose tissue.

Most studies (108 of 117) compared adipocyte precursors induced to differentiate thermogenic adipocytes with various control conditions, including undifferentiated precursors (25 of 108), precursors differentiated into white adipocytes (43 of 108), mature adipocytes not stimulated with adrenergic agents, forskolin or cAMP (28 of 108), precursors from

distinct adipose depots (19 of 108), those differentiated in the absence of glitazones (9 of 108), or cells differentiated at lower versus higher temperatures (6 of 108). Among studies comparing the thermogenic potential of precursors derived from different anatomical depots, heterogeneous methodologies precluded a definitive synthesis. Nonetheless, a consistent trend was observed: twelve out of twelve studies reported greater thermogenic capacity in precursors from adult adipose tissue located in the deep neck, supraclavicular, perirenal, or periadrenal regions compared with those from superficial subcutaneous or visceral depots. Additionally, three out of four studies comparing developmental origins found that precursors from fetal tissues exhibited higher thermogenic potential than those derived from adult adipose tissue.

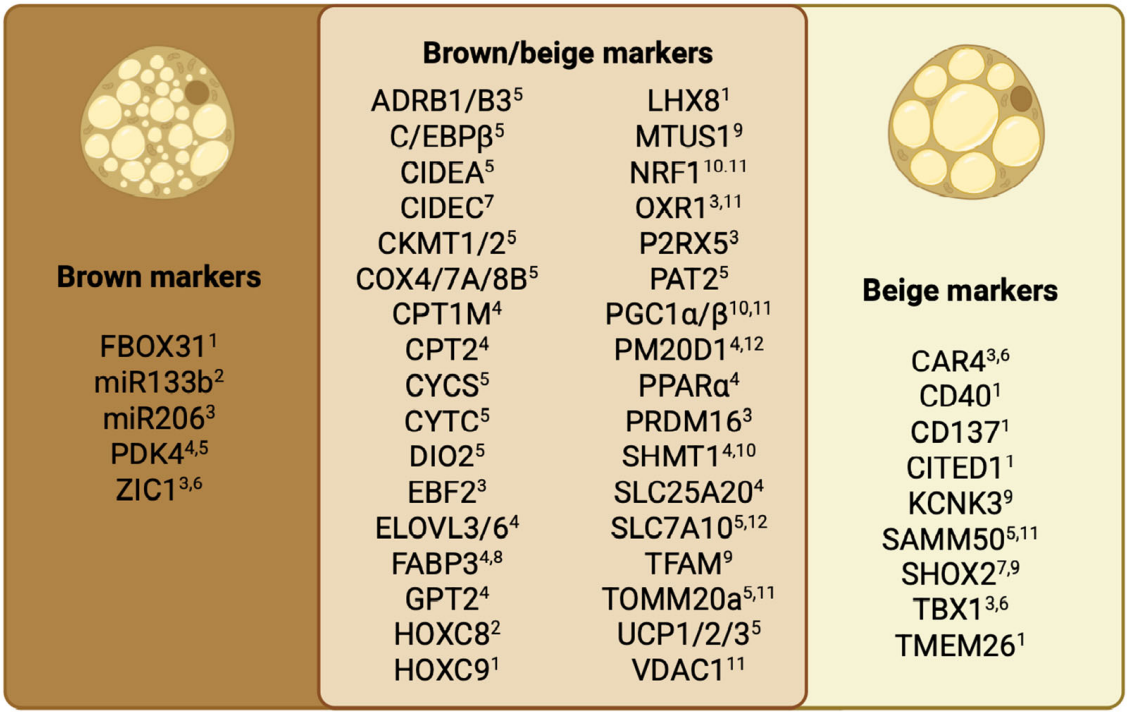

Figure 2. Diagram of brown, beige, and overall thermogenesis (overlapping brown/beige) RNA and protein markers assessed in the included studies. The markers are categorized as (1) having their function not defined despite being highly expressed in the indicated cells, or involved in (2) negative regulation of adipocyte type differentiation, (3) positive regulation of adipocyte type differentiation, (4) lipid metabolism, (5) thermogenesis, (6) cell function, (7) negative regulation of lipolysis, (8) lipid transport, (9) negative regulation of thermogenesis, (10) mitochondrial biogenesis, (11) mitochondrial function, (12) amino acid metabolism. Created with Biorender.com'.

In most cases, the intended thermogenic phenotype was confirmed, based on mRNA and protein expression of thermogenic markers, mitochondrial content, and mitochondrial activity. Only a minority of studies assessed mitochondrial activity and content directly. Notably, among the 38 studies investigating thermogenic adipocyte differentiation under serum-free conditions, the majority reported successful differentiation, as evidenced by the induction of thermogenic mRNA expression (35 of 36 studies), protein-level confirmation (25 of 26), increased mitochondrial content (8 of 9), and enhanced mitochondrial bioenergetic function (17 of 18).

3.4. Risk of Bias in Individual Studies

The risk of bias was assessed using the US NTP/OHAT Risk of Bias Rating Tool for Human and Animal Studies, and the results are summarized in Table S6. All included studies were classified as having a low risk of bias.

4. Discussion

Thermogenic adipose tissue, encompassing classical brown and inducible beige fat, has emerged as a compelling target for the treatment of obesity and associated metabolic disease [128]. Recent studies in rodents have highlighted the potential of activating or expanding thermogenic adipocytes to counteract excess adiposity and improve metabolic outcomes such as insulin sensitivity and glucose tolerance [128]. In this scenario, therapeutic strategies aimed at harnessing the metabolic capacity of thermogenic fat through pharmacological, environmental, or nutritional means are gaining traction as viable interventions in the fight against metabolic disease.

Despite notable physiological and molecular parallels between rodent and human adipose tissues, key species-specific differences in depot distribution, gene expression, and thermogenic regulation limit the direct translational applicability of rodent findings to human biology. In rodents, classical BAT is abundant and organized in discrete depots, while beige adipocytes are readily recruited within multiple WAT depots. In contrast, genuine BAT is primarily present during fetal and neonatal stages in humans, and thermogenic fat in adults is more restricted, residing mainly in the supraclavicular and thoracic regions. These depots exhibit molecular signatures more akin to murine beige adipocytes than classical BAT [129].

Although human and mouse thermogenic adipocytes share comparable UCP1-dependent mitochondrial function, the upstream regulatory mechanisms differ significantly. In mice, β_3-adrenergic receptors are abundantly expressed and play a central role in activating thermogenesis and lipolysis. In humans, however, thermogenic adipocytes respond to both β_2- [130] and β_3 [39]-adrenergic stimulation, but with less pronounced effects, reflecting differences in receptor expression patterns and downstream signaling. Additionally, retinoic acid receptor signaling robustly induces UCP1 expression in murine adipocytes but fails to do so in their human counterparts [120], underscoring further divergence in transcriptional regulation of thermogenesis.

Although the study of human thermogenic adipocytes is critical for advancing translational strategies, in vivo investigation remains challenging due to the relative scarcity of thermogenic adipose tissue and its dispersed anatomical localization compared to white adipose depots. Therefore, the development of human cell models remains crucial for advancing our understanding of thermogenic adipose biology and its therapeutic potential. Given the importance of these models, we conducted a comprehensive literature review of studies investigating the differentiation of primary adipocyte precursors into thermogenic adipocytes in 2D culture systems, irrespective of the specific research question, to evaluate the differentiation protocols and the criteria used to define the thermogenic phenotype.

We identified 117 studies fulfilling our inclusion criteria, the majority (114/117) published after 2009, following the discovery that adult humans possess thermogenic adipose tissue and that its presence is positively correlated with metabolic health [131–133]. This surge in research aligns with growing recognition that human cell models, particularly those derived from primary tissues or pluripotent stem cells, offer a more physiologically relevant platform for elucidating the regulatory mechanisms of human thermogenic adipocytes and for screening pharmacological agents with translational potential.

Almost all studies induced adipocyte differentiation by exposing precursors to the classic adipogenic cocktail comprising the phosphodiesterase inhibitor isomethylbutylxanthine (IBMX), the synthetic glucocorticoid dexamethasone, and insulin [134], albeit with varying concentrations and exposure duration. IBMX leads to increased intracellular levels of cAMP and activation of protein kinase and C/EBP-δ. By activating glucocorticoid receptor, dexamethasone induces the expression of C/EBP-β. The latter, in concert with C/EBP-δ,

induces the expression of C/EBPα and PPARγ. Insulin, in turn, induces transcription factors such as SREBP-1C to stimulate adipogenesis and lipogenesis [135].

A significant proportion of studies (76.9%) added triiodothyronine to the induction medium, at varying concentrations and exposure duration. Thyroid hormone is well-known to regulate the expression of many adipocyte-specific genes involved in acquisition of adipocytic phenotype, including those involved lipogenesis and lipolysis [136]. Moreover, thyroid hormone is a pivotal regulator of brown and beige adipocyte development and thermogenic function, by inducing key transcriptional programs that drive the differentiation of thermogenic adipocytes, notably through upregulation of UCP1 and PGC-1α, which are essential for mitochondrial biogenesis, oxidative metabolism, mitochondrial uncoupling, and heat generation [137,138]. Thyroid hormone also increases β-adrenergic receptor expression in adipocytes, thereby potentiating sympathetic activation of thermogenesis [139].

Surprisingly, few studies have systematically examined how the absence, presence, or varying concentrations of T3 influence the acquisition of a thermogenic phenotype in adipocyte precursors during differentiation. Herbers et al. (2022) [28] evaluated five adipogenic differentiation protocols in human adipocyte progenitors derived from the stromal vascular fraction (SVF) of abdominal subcutaneous white adipose tissue (WAT). One protocol included 2 nM T3 during the seven-day induction phase of adipogenesis, but not during the maintenance phase. Although this condition did not enhance the mRNA or protein expression of thermogenic markers relative to other protocols, it significantly increased basal respiration, maximal respiration, and proton leak [28]. In contrast, Wang et al. (2018) optimized differentiation conditions for human thermogenic adipocytes derived from fetal BAT SVF and reported that 1 nM T3 during a four-day induction period significantly upregulated thermogenic gene expression [79]. Similarly, Lee et al. (2012) [121] investigated the effects of varying T3 concentrations in the induction medium of adipose-derived stem cells from infants. They observed a dose-dependent increase in thermogenic gene expression from 10 to 250 nM T3, whereas lower concentrations (0.4 and 2 nM) had no such effect [121]. Collectively, these findings suggest that there is no universally optimal T3 concentration for thermogenic adipocyte induction. The efficacy of T3 may depend on the specific progenitor population, differentiation protocol, and the presence of additional components in the medium, which varied across these studies.

Rosiglitazone was included in the adipogenic differentiation medium of most included studies (76.1%), whereas indomethacin was used in a smaller proportion of studies (25.6%). Both chemicals are well-known for their adipogenic activity by directly activating peroxisome-proliferator activated receptor gamma2 (PPARγ2) [140]. Indomethacin, additionally, promotes adipogenesis by upregulating C/EBPβ and PPARγ2 [141]. Consistent with their action to activate PPARγ2, the inclusion of either rosiglitazone or indomethacin in the differentiation medium induces the expression of thermogenic markers in human primary adipocytes to a comparable extent [142]. However, the degree to which these effects reflect physiological thermogenic differentiation remains unclear.

Notably, only a minority of the included studies employed other agents known to induce the development of thermogenic adipocytes, such as bone morphogenetic proteins, fibroblast growth factors, irisin, and its precursor FNDC5 [109,116]. These molecules activate more complex signaling pathways and often require specific progenitor types, precisely timed intervention, and additional factors to drive thermogenic programs in adipocytes. As such, they are typically used to enhance the thermogenic phenotype rather than to initiate adipogenesis. In contrast, the routine inclusion of rosiglitazone and indomethacin in differentiation media likely reflects both their dual ability to support adipogenesis and

the thermogenic phenotype in culture, in addition to their practical advantages such as lower cost and greater chemical stability compared with recombinant proteins.

Several studies also included biotin (31.6%), pantothenate (29.1%), and the iron-binding protein transferrin (43.6%) in the adipogenic differentiation medium. While biotin, pantothenate, and iron are known to influence overall adipogenesis and mitochondrial function, their specific roles in regulating thermogenic differentiation remain underexplored. Most studies have focused on their general metabolic functions, and direct mechanistic insights into their contribution to thermogenic programming are limited. Nevertheless, given the essential roles of these micronutrients in cellular metabolism, it is plausible that they also support thermogenic adipocyte development and function.

Biotin (vitamin B5) has long been recognized for its role in promoting lipid synthesis during adipogenesis by regulating acetyl-CoA carboxylase activity [143]. More recently, biotin was shown to enhance thermogenic gene expression in human primary brown adipocytes derived from the stromal vascular fraction of fetal brown adipose tissue [79]. Pantothenate (vitamin B7) similarly upregulates thermogenic markers in this model [79]. Notably, pantothenate exhibits concentration-dependent effects: at lower doses, it increases thermogenic gene expression, proton leak-associated mitochondrial respiration, and expression of genes related to the futile creatine cycle; however, higher concentrations reverse these effects and suppress glycolysis [144]. Collectively, these findings highlight the importance of biotin and pantothenate in promoting the acquisition of thermogenic characteristics during adipocyte differentiation in culture.

Transferrin is a glycoprotein with pleiotropic functions, most notably facilitating iron transport and cellular iron uptake. Iron, in turn, is essential for numerous physiological processes, particularly mitochondrial function [145]. In murine 3T3-L1 preadipocytes, iron deficiency—either through transferrin gene silencing or pharmacological chelation with deferoxamine—has been shown to impair adipogenesis [146]. Notably, brown adipogenesis appears to require greater iron availability than white adipogenesis, coinciding with increased expression of transferrin receptor 1 (TfR1) during brown, but not white, adipocyte differentiation [147]. Silencing of TfR1 disrupted the acquisition of thermogenic features in brown adipocytes, suggesting a direct link between iron uptake and thermogenic programming. Similar results were reported by Qiu et al. (2020), who further identified TfR1 as a functional marker of thermogenic adipocytes and demonstrated its essential role in maintaining mitochondrial function both in vitro and in vivo [52]. These findings suggest that transferrin may act synergistically with other components of the differentiation medium to support the induction of thermogenic phenotypes in cultured adipocytes.

Adrenergic stimulation is a well-established approach, both in vivo and in vitro, for recruiting and activating beige and brown adipocytes to induce thermogenesis. Cold exposure, the primary physiological trigger for thermogenic activation, stimulates the sympathetic nervous system to release norepinephrine, which binds to β-adrenergic receptors on brown and beige adipocytes. This signaling cascade enhances the expression of thermogenic genes and promotes lipolysis, liberating fatty acids that serve as allosteric activators of UCP1 [148]. Despite this well-characterized mechanism, only a small subset of the included studies employed pharmacological adrenergic stimulation—either short-term or prolonged—to promote thermogenic differentiation. Similarly, few studies used mild hypothermic conditions to induce thermogenic phenotypes in culture. Interestingly, previous research has shown that adipogenic precursors derived from white, but not brown, adipose tissue exhibit cold-induced thermogenic gene expression through mechanisms that appear to be independent of β-adrenergic signaling [78,149].

Adipocyte differentiation media are commonly supplemented with serum, typically fetal bovine serum (FBS), due to its content of growth factors, hormones, and nutrients

that support adipogenesis [150]. Consistently, most of the studies included in this review employed serum during differentiation. However, a notable subset of studies achieved thermogenic adipocyte differentiation under serum-free conditions, as indicated by the expression of mRNA or protein thermogenesis-related markers, mitochondrial content, or mitochondrial bioenergetics. These findings suggest that chemically defined media, when supplemented with appropriate factors, can effectively support both adipogenic and thermogenic programming in primary human adipocyte precursors. The ability to induce thermogenic phenotypes in the absence of serum offers significant advantages, including improved reproducibility, reduced batch variability, and more precise control over experimental conditions. This supports the growing interest in serum-free systems for mechanistic and translational studies of human thermogenic adipocytes.

We found that thermogenic adipocytes were successfully obtained, as indicated by the expression of specific molecular markers in most studies, by the induction of precursors such as cells from the stromal vascular fraction, mesenchymal cells, and preadipocytes, despite the variations with respect to cell confluency at induction, the specific cell culture medium used, the total duration of differentiation, or the fact that differentiated was conducted in one or two or more states. Very few studies used other precursors, including adipocytes from ceiling culture, microvascular fragments, dermal fibroblasts, or progenitor cells from adipose tissue explants. This implies that precursors obtained from adipose tissue, bone marrow, or umbilical cord can be driven to express thermogenic markers when induced to differentiate with the proper ingredients.

Moreover, despite the scarcity of studies directly comparing the thermogenic potential precursors from different sources differentiated into adipocytes, the studies assessing precursors from deep neck, supraclavicular, perirenal, or periadrenal adipose tissue consistently indicated that they exhibited higher thermogenic capacity—evidenced by higher expression of thermogenesis-related markers, mitochondrial content, and mitochondrial bioenergetics—than those obtained from superficial subcutaneous or visceral depots. These findings align with imaging and histological studies identifying thermogenically active adipose regions in adult humans, particularly in the cervical and thoracic areas [131–133].

The most frequently reported outcomes used to assess thermogenic adipocyte differentiation in the included studies were the expression of canonical thermogenic markers at the mRNA and protein levels, along with markers distinguishing beige from brown adipocyte phenotypes. While these molecular signatures offer valuable insights into the differentiation state of adipocytes, they provide only a partial view of thermogenic identity. Notably, relatively few studies assessed mitochondrial content or function—parameters more directly linked to thermogenic capacity.

Only a minority of studies included in this review assessed mitochondrial respiration to functionally characterize thermogenic adipocytes, most commonly using extracellular flux analysis (Seahorse XF technology) to measure the oxygen consumption rate (OCR) as a proxy for mitochondrial activity. This methodology offers a valuable real-time assessment of cellular bioenergetics, allowing for the evaluation of basal respiration, proton leak, ATP-linked respiration, and maximal respiratory capacity [151,152]. In the context of thermogenic adipocytes, these parameters can provide functional validation of uncoupled respiration and UCP1 activity, which are not captured by gene or protein expression alone [153]. However, Seahorse assays also have limitations, including variability introduced by differences in cell seeding density, differentiation efficiency, and sensitivity to experimental conditions [154]. Moreover, OCR measurements must be interpreted with caution, as they do not directly quantify heat production and may reflect both UCP1-dependent and -independent pathways.

Given that thermogenic activity is fundamentally driven by mitochondrial uncoupling and oxidative metabolism, functional assays of mitochondrial bioenergentics are essential for distinguishing truly thermogenic adipocytes from those merely expressing associated markers [155]. Given the need for multi-level validation of thermogenic activity, future studies should integrate gene expression, protein abundance, and functional bioenergetic assays to more comprehensively characterize thermogenic potential and enhance the translational relevance of in vitro models.

Moreover, the physiological relevance of thermogenic adipocytes extends beyond their role in heat production. These cells are increasingly recognized for their endocrine and metabolic functions, including the secretion of lipid and protein mediators that influence systemic energy balance [128,155], as well as their capacity to act as metabolic sinks for glucose, fatty acids, and amino acids—functions that contribute to improved glucose tolerance and lipid clearance [128]. Therefore, a comprehensive in vitro characterization should go beyond classical thermogenic endpoints to include assessments of mitochondrial function, substrate utilization, and secretory activity. This broader perspective may yield more physiologically relevant models and enhance the translational potential of thermogenic adipocyte research.

It should be noted that the heterogeneity in precursor cell sources, differentiation protocols, and phenotypic characterization of thermogenic adipocyte across studies limits both direct comparisons and the synthesis of results in meta-analyses. This variability highlights the urgent need for greater standardization in protocols for differentiating and validating human thermogenic adipocytes. Despite the promising therapeutic potential of thermogenic adipocytes for obesity and its associated metabolic disorders, significant challenges remain in translating in vitro findings into clinical applications. Human cell-based models, while invaluable for mechanistic insights, lack the complex endocrine, neural, immune, and vascular signals present in vivo that are essential for thermogenic regulation [128]. Moreover, differentiation efficiency, functional maturation, and phenotypic stability of beige and brown adipocytes vary substantially depending on the cell source and protocol, which can compromise reproducibility and translational relevance [99,156].

To advance the translational relevance of human thermogenic adipocyte research, future studies should prioritize protocol standardization and comprehensive functional validation. First, clearly defining and reporting the anatomical origin, donor characteristics (e.g., age, sex, BMI), and passage number of precursor cells is essential to improve reproducibility and interpretability across studies. Second, harmonizing differentiation protocols—including media composition, duration of differentiation induction and maintenance, and exposure to key inducers such as PPARγ agonists, thyroid hormone, or cAMP induction/analogs—would enable more meaningful comparisons. Third, adopting a multi-tiered validation framework is critical: beyond mRNA and protein expression of thermogenic markers, studies should routinely incorporate functional assays such as mitochondrial respiration measurements. Moreover, adopting existing reporting standards with adaptations, such as those proposed by the Science in Risk Assessment and Policy [157] or the Organization for Economic Co-operation and Development guidance for in vitro methods [158], would further strengthen methodological transparency and data quality. Collectively, these steps would improve consistency, comparability, and translational potential across the field. Finally, given their superior ability to replicate the native adipose tissue environment, three-dimensional (3D) models should be more widely adopted as a standard approach for studying thermogenic human adipocytes. Integrating 3D and organoid systems into thermogenic research would significantly enhance the physiological relevance of in vitro studies by more accurately recapitulating critical features such as ex-

tracellular matrix composition, spatial architecture, and cell–cell interactions that influence both adipogenesis and thermogenic function.

5. Conclusions

This review underscores the feasibility of differentiating thermogenic adipocytes from primary human precursors using a range of two-dimensional culture protocols. While most studies employed classical adipogenic inducers alongside frequent use of triiodothyronine, rosiglitazone, or indomethacin, relatively few incorporated more complex thermogenic stimuli such as BMPs, FGFs, or irisin. Some of the included studies demonstrated thermogenic adipocyte differentiation under serum-free, chemically defined conditions, supporting their relevance for reproducible and translational applications. However, a major limitation remains the predominant reliance on gene expression as the primary outcome, with comparatively few studies evaluating mitochondrial respiration or broader aspects of metabolic function. Going forward, the development and adoption of standardized, functionally validated protocols will be critical to fully realize the potential of human in vitro thermogenic adipocyte models in metabolic research and therapeutic innovation.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/cells14231907/s1, Table S1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist; Table S2: Search strategies with appropriated keywords and MeSH terms; Table S3: Characteristics of the included studies (n = 117); Table S4: Brown, beige, and overall thermogenic (overlapping brown/beige) RNA and protein markers assessed in the included studies to characterize the thermogenic adipocyte phenotype [5,20,30,33,48,60,116,121,159–185]; Table S5: Excluded articles and reasons for exclusion (n = 153) [36,142,144,156,184,186–333]; Table S6: Risk of bias assessed in the included "in vitro" studies (n = XX) by NTP/OHAT Risk of Bias Rating Tool for Human and Animal Studies. Risk of bias was categorized as (++) when definitely low risk of bias; (+) probably Low risk of bias; (-) Probably High risk of bias, (--) definitely high risk of bias, and "NA" not applicable.

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Abbreviations

The following abbreviations are used in this manuscript:

AMP	Adenosine monophosphate
BAT	Brown adipose tissue
C/EBP-β	C/EBPβ: CCAAT enhancer binding protein delta

C/EBP-α	C/EBPβ: CCAAT enhancer binding protein alpha
C/EBP-δ	C/EBPβ: CCAAT enhancer binding protein beta
DMEM	Dulbecco's Modified Eagle's Medium
F12	Nutrient F-12
FBS	Fetal bovine serum
FNDC5	fibronectin type III domain-containing protein 5
IBMX	Isobutylmethylxanthine
PGC-1α	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PICOS	Population, intervention, control, outcome, study type
PPARγ	Peroxisome proliferator-activated receptor
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analysis
PROSPERO	International Prospective Register of Systematic Reviews
SREBP-1C	Sterol regulatory element-binding protein 1c
SVF	Stromal vascular fraction
T3	Triiodothyronine
TfR1	transferrin receptor 1
UCP1	Uncoupling protein 1
US NTP/OHAT	National Toxicology Program's Office of Health Assessment and Translation
WAT	White adipose tissue

References

1. Blüher, M. Obesity: Global epidemiology and pathogenesis. *Nat. Rev. Endocrinol.* **2019**, *15*, 288–298. [CrossRef]
2. Katya, P.; Mark, E. Review on obesity management: Diet, exercise and pharmacotherapy. *BMJ Public Health* **2024**, *2*, e000246. [CrossRef]
3. Zheng, Z.; Zong, Y.; Ma, Y.; Tian, Y.; Pang, Y.; Zhang, C.; Gao, J. Glucagon-like peptide-1 receptor: Mechanisms and advances in therapy. *Signal Transduct. Target. Ther.* **2024**, *9*, 234. [CrossRef] [PubMed]
4. Pontzer, H.; Durazo-Arvizu, R.; Dugas, L.R.; Plange-Rhule, J.; Bovet, P.; Forrester, T.E.; Lambert, E.V.; Cooper, R.S.; Schoeller, D.A.; Luke, A. Constrained Total Energy Expenditure and Metabolic Adaptation to Physical Activity in Adult Humans. *Curr. Biol.* **2016**, *26*, 410–417. [CrossRef] [PubMed]
5. Cohen, P.; Kajimura, S. The cellular and functional complexity of thermogenic fat. *Nat. Rev. Mol. Cell Biol.* **2021**, *22*, 393–409. [CrossRef] [PubMed]
6. Cypess, A.M.; Cannon, B.; Nedergaard, J.; Kazak, L.; Chang, D.C.; Krakoff, J.; Tseng, Y.-H.; Schéele, C.; Boucher, J.; Petrovic, N.; et al. Emerging debates and resolutions in brown adipose tissue research. *Cell Metab.* **2025**, *37*, 12–33. [CrossRef]
7. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* **2021**, *372*, n71. [CrossRef]
8. Ouzzani, M.; Hammady, H.; Fedorowicz, Z.; Elmagarmid, A. Rayyan—A web and mobile app for systematic reviews. *Syst. Rev.* **2016**, *5*, 210. [CrossRef]
9. Kulebyakin, K.; Tyurin-Kuzmin, P.; Efimenko, A.; Voloshin, N.; Kartoshkin, A.; Karagyaur, M.; Grigorieva, O.; Novoseletskaya, E.; Sysoeva, V.; Makarevich, P.; et al. Decreased Insulin Sensitivity in Telomerase-Immortalized Mesenchymal Stem Cells Affects Efficacy and Outcome of Adipogenic Differentiation in vitro. *Front. Cell Dev. Biol.* **2021**, *9*, 662078. [CrossRef]
10. Rooney, A.A.; Boyles, A.L.; Wolfe, M.S.; Bucher, J.R.; Thayer, K.A. Systematic review and evidence integration for literature-based environmental health science assessments. *Environ. Health Perspect.* **2014**, *122*, 711–718. [CrossRef]
11. Batrow, P.L.; Roux, C.H.; Gautier, N.; Martin, L.; Sibille, B.; Guillou, H.; Postic, C.; Langin, D.; Mothe-Satney, I.; Amri, E.Z. Regulation of UCP1 expression by PPARα and pemafibrate in human beige adipocytes. *Life Sci.* **2025**, *363*, 123406. [CrossRef]
12. Desai, A.; Loureiro, Z.Y.; DeSouza, T.; Yang, Q.; Solivan-Rivera, J.; Corvera, S. cAMP driven UCP1 induction in human adipocytes requires ATGL-catalyzed lipolysis. *Mol. Metab.* **2024**, *90*, 102051. [CrossRef]
13. Díez-Sainz, E.; Milagro, F.I.; Aranaz, P.; Riezu-Boj, J.I.; Batrow, P.L.; Contu, L.; Gautier, N.; Amri, E.Z.; Mothe-Satney, I.; Lorente-Cebrián, S. Human miR-1 Stimulates Metabolic and Thermogenic-Related Genes in Adipocytes. *Int. J. Mol. Sci.* **2024**, *26*, 276. [CrossRef]
14. Wu, H.; Adebesin, A.M.; Falck, J.R.; Xu, X.; Chen, J.; Masi, T.J.; Stephenson, S.M.; Zhao, L. Effects of 17,18-EEQ analog (TZ-1) on brown adipogenesis and browning of human adipose-derived stromal cells. *Biochem. Biophys. Res. Commun.* **2024**, *734*, 150660. [CrossRef]

15. Colson, C.; Batrow, P.L.; Dieckmann, S.; Contu, L.; Roux, C.H.; Balas, L.; Vigor, C.; Fourmaux, B.; Gautier, N.; Rochet, N.; et al. Effects of Fatty Acid Metabolites on Adipocytes Britening: Role of Thromboxane A2. *Cells* **2023**, *12*, 446. [CrossRef]
16. Giroud, M.; Kotschi, S.; Kwon, Y.; Le Thuc, O.; Hoffmann, A.; Gil-Lozano, M.; Karbiener, M.; Higareda-Almaraz, J.C.; Khani, S.; Tews, D.; et al. The obesity-linked human lncRNA AATBC stimulates mitochondrial function in adipocytes. *EMBO Rep.* **2023**, *24*, e57600. [CrossRef]
17. Palani, N.P.; Horvath, C.; Timshel, P.N.; Folkertsma, P.; Grønning, A.G.B.; Henriksen, T.I.; Peijs, L.; Jensen, V.H.; Sun, W.; Jespersen, N.Z.; et al. Adipogenic and SWAT cells separate from a common progenitor in human brown and white adipose depots. *Nat. Metab.* **2023**, *5*, 996–1013. [CrossRef]
18. Shon, D.H.; Park, S.J.; Yoon, S.J.; Ryu, Y.H.; Ko, Y. Identification of Browning in Human Adipocytes by Partial Least Squares Regression (PLSR), Infrared Spectral Biomarkers, and Partial Least Squares Discriminant Analysis (PLS-DA) Using FTIR Spectroscopy. *Photonics* **2023**, *10*, 2. [CrossRef]
19. Suchacki, K.J.; Ramage, L.E.; Kwok, T.C.; Kelman, A.; McNeill, B.T.; Rodney, S.; Keegan, M.; Gray, C.; MacNaught, G.; Patel, D.; et al. The serotonin transporter sustains human brown adipose tissue thermogenesis. *Nat. Metab.* **2023**, *5*, 1319–1336. [CrossRef] [PubMed]
20. Vámos, A.; Arianti, R.; Vinnai, B.; Alrifai, R.; Shaw, A.; Póliska, S.; Guba, A.; Csősz, É.; Csomós, I.; Mocsár, G.; et al. Human abdominal subcutaneous-derived active beige adipocytes carrying FTO rs1421085 obesity-risk alleles exert lower thermogenic capacity. *Front. Cell Dev. Biol.* **2023**, *11*, 1155673. [CrossRef]
21. Vinnai, B.; Arianti, R.; Győry, F.; Bacso, Z.; Fésüs, L.; Kristóf, E. Extracellular thiamine concentration influences thermogenic competency of differentiating neck area-derived human adipocytes. *Front. Nutr.* **2023**, *10*, 1207394. [CrossRef]
22. Wu, R.; Park, J.; Qian, Y.; Shi, Z.; Hu, R.; Yuan, Y.; Xiong, S.; Wang, Z.; Yan, G.; Ong, S.G.; et al. Genetically prolonged beige fat in male mice confers long-lasting metabolic health. *Nat. Commun.* **2023**, *14*, 2731. [CrossRef]
23. Di Maio, G.; Alessio, N.; Peluso, G.; Perrotta, S.; Monda, M.; Di Bernardo, G. Molecular and Physiological Effects of Browning Agents on White Adipocytes from Bone Marrow Mesenchymal Stromal Cells. *Int. J. Mol. Sci.* **2022**, *23*, 12151. [CrossRef]
24. Farrar, J.S.; Martin, R.K. Isolation of the Stromal Vascular Fraction from Adipose Tissue and Subsequent Differentiation into White or Beige Adipocytes. In *Non-Alcoholic Steatohepatitis*; Sarkar, D., Ed.; Methods in Molecular Biology; Humana: New York, NY, USA, 2022; Volume 2455, pp. 103–115. [CrossRef]
25. Fu, T.; Li, C.; Sun, Z.; Yan, B.; Wu, Y.; Huang, Z.; Yin, X. Integrin αV Mediates the Effects of Irisin on Human Mature Adipocytes. *Obes. Facts* **2022**, *15*, 442–450. [CrossRef] [PubMed]
26. Guillemet, D.; Belles, C.; Gomes, A.; Azalbert, V.; André, M.; Faresse, N.; Burcelin, R.; Lagarde, J.M.; Lacasa, D.; Kéophiphath, M. Screening for anti-adipogenic, pro-lipolytic and thermogenic plant extracts by models associating intestinal epithelial cells with human adipose cells. *Eur. J. Nutr.* **2022**, *61*, 2201–2215. [CrossRef]
27. He, Y.; Liang, Z.; Wang, J.; Tang, H.; Li, J.; Cai, J.; Liao, Y. Ceiling culture of human mature white adipocytes with a browning agent: A novel approach to induce transdifferentiation into beige adipocytes. *Front. Bioeng. Biotechnol.* **2022**, *10*, 905194. [CrossRef] [PubMed]
28. Herbers, E.; Patrikoski, M.; Wagner, A.; Jokinen, R.; Hassinen, A.; Heinonen, S.; Miettinen, S.; Peltoniemi, H.; Pirinen, E.; Pietiläinen, K.H. Preventing White Adipocyte Browning during Differentiation in Vitro: The Effect of Differentiation Protocols on Metabolic and Mitochondrial Phenotypes. *Stem Cells Int.* **2022**, 3308194. [CrossRef]
29. Lin, C.; He, X.; Chen, X.; Liu, L.; Guan, H.; Xiao, H.; Li, Y. MiR-1275 Inhibits Human Omental Adipose-Derived Stem Cells Differentiation Toward the Beige Phenotype via PRDM16. *Stem Cells Dev.* **2022**, *31*, 799–809. [CrossRef]
30. Nagy, L.; Rauch, B.; Szerafin, T.; Uray, K.; Tóth, A.; Bai, P. Nicotinamide-riboside shifts the differentiation of human primary white adipocytes to beige adipocytes impacting substrate preference and uncoupling respiration through SIRT1 activation and mitochondria-derived reactive species production. *Front. Cell Dev. Biol.* **2022**, *10*, 979330. [CrossRef] [PubMed]
31. Ngono Ayissi, K.; Gorwood, J.; Le Pelletier, L.; Bourgeois, C.; Beaupère, C.; Auclair, M.; Foresti, R.; Motterlini, R.; Atlan, M.; Barrail-Tran, A.; et al. Inhibition of Adipose Tissue Beiging by HIV Integrase Inhibitors, Dolutegravir and Bictegravir, Is Associated with Adipocyte Hypertrophy, Hypoxia, Elevated Fibrosis, and Insulin Resistance in Simian Adipose Tissue and Human Adipocytes. *Cells* **2022**, *11*, 1841. [CrossRef]
32. Niemann, B.; Haufs-Brusberg, S.; Puetz, L.; Feickert, M.; Jaeckstein, M.Y.; Hoffmann, A.; Zurkovic, J.; Heine, M.; Trautmann, E.M.; Müller, C.E.; et al. Apoptotic brown adipocytes enhance energy expenditure via extracellular inosine. *Nature* **2022**, *609*, 361–368. [CrossRef]
33. Park, S.J.; Shon, D.H.; Kim, J.H.; Ryu, Y.H.; Ko, Y. SAMM50 Regulates Thermogenesis of Beige Adipocytes Differentiated from Human Adipose-Derived Stem Cells by Balancing Mitochondrial Dynamics. *Int. J. Mol. Sci.* **2022**, *23*, 6764. [CrossRef]
34. Park, S.J.; Shon, D.H.; Ryu, Y.H.; Ko, Y. Extract of Ephedra sinica Stapf Induces Browning of Mouse and Human White Adipocytes. *Foods* **2022**, *11*, 1028. [CrossRef]
35. Porras, M.G.A.; Stojkova, K.; Acosta, F.M.; Rathbone, C.R.; Brey, E.M. Engineering Human Beige Adipose Tissue. *Front. Bioeng. Biotechnol.* **2022**, *10*, 906395. [CrossRef]

36. Takeda, Y.; Dai, P. Capsaicin directly promotes adipocyte browning in the chemical compound-induced brown adipocytes converted from human dermal fibroblasts. *Sci. Rep.* **2022**, *12*, 6612. [CrossRef] [PubMed]
37. Vámos, A.; Shaw, A.; Varga, K.; Csomós, I.; Mocsár, G.; Balajthy, Z.; Lányi, C.; Bacso, Z.; Szatmári-Tóth, M.; Kristóf, E. Mitophagy Mediates the Beige to White Transition of Human Primary Subcutaneous Adipocytes Ex Vivo. *Pharmaceuticals* **2022**, *15*, 363. [CrossRef] [PubMed]
38. Bokhari, M.H.; Halleskog, C.; Åslund, A.; Boulet, N.; Casadesús Rendos, E.; de Jong, J.M.A.; Csikasz, R.; Amri, E.Z.; Shabalina, I.; Bengtsson, T. Isothermal microcalorimetry measures UCP1-mediated thermogenesis in mature brite adipocytes. *Commun. Biol.* **2021**, *4*, 1108. [CrossRef] [PubMed]
39. Cero, C.; Lea, H.J.; Zhu, K.Y.; Shamsi, F.; Tseng, Y.H.; Cypess, A.M. β3-Adrenergic receptors regulate human brown/beige adipocyte lipolysis and thermogenesis. *JCI Insight* **2021**, *6*, e139160. [CrossRef]
40. Di Maio, G.; Alessio, N.; Demirsoy, I.H.; Peluso, G.; Perrotta, S.; Monda, M.; Di Bernardo, G. Evaluation of Browning Agents on the White Adipogenesis of Bone Marrow Mesenchymal Stromal Cells: A Contribution to Fighting Obesity. *Cells* **2021**, *10*, 403. [CrossRef]
41. Jiao, Y.; Liu, L.; Gu, H.; Liang, X.; Meng, X.; Gao, J.; Xu, Y.; Nuermaimaiti, N.; Guan, Y. Ad36 promotes differentiation of hADSCs into brown adipocytes by up-regulating LncRNA ROR. *Life Sci.* **2021**, *265*, 118762. [CrossRef]
42. Nascimento, E.B.M.; Moonen, M.P.B.; Remie, C.M.E.; Gariani, K.; Jörgensen, J.A.; Schaart, G.; Hoeks, J.; Auwerx, J.; van Marken Lichtenbelt, W.D.; Schrauwen, P. Nicotinamide Riboside Enhances In Vitro Beta-adrenergic Brown Adipose Tissue Activity in Humans. *J. Clin. Endocrinol. Metab.* **2021**, *106*, 1437–1447. [CrossRef]
43. Tsagkaraki, E.; Nicoloro, S.M.; DeSouza, T.; Solivan-Rivera, J.; Desai, A.; Lifshitz, L.M.; Shen, Y.; Kelly, M.; Guilherme, A.; Henriques, F.; et al. CRISPR-enhanced human adipocyte browning as cell therapy for metabolic disease. *Nat. Commun.* **2021**, *12*, 6931. [CrossRef]
44. Xia, J.; Zhu, H.; Zhu, S.; Ge, J.; Wang, Z.; Lu, F.; Liao, Y.; Cai, J. Induced Beige Adipocytes Improved Fat Graft Retention by Promoting Adipogenesis and Angiogenesis. *Plast. Reconstr. Surg.* **2021**, *148*, 549–558. [CrossRef] [PubMed]
45. Halbgebauer, D.; Dahlhaus, M.; Wabitsch, M.; Fischer-Posovszky, P.; Tews, D. Browning capabilities of human primary adipose-derived stromal cells compared to SGBS cells. *Sci. Rep.* **2020**, *10*, 9632. [CrossRef] [PubMed]
46. Kroon, T.; Harms, M.; Maurer, S.; Bonnet, L.; Alexandersson, I.; Lindblom, A.; Ahnmark, A.; Nilsson, D.; Gennemark, P.; O'Mahony, G.; et al. PPARγ and PPARα synergize to induce robust browning of white fat in vivo. *Mol. Metab.* **2020**, *36*, 100964. [CrossRef]
47. Li, H.; Shen, L.; Zhang, L.; Yan, B.; Sun, T.; Guo, F.; Yin, X. Reduced Beige Adipogenic Potential in Subcutaneous Adipocytes Derived from Obese Chinese Individuals. *Diabetes Metab. Syndr. Obes.* **2020**, *13*, 2551–2562. [CrossRef]
48. Markan, K.R.; Boland, L.K.; King-McAlpin, A.Q.; Claflin, K.E.; Leaman, M.P.; Kemerling, M.K.; Stonewall, M.M.; Amendt, B.A.; Ankrum, J.A.; Potthoff, M.J. Adipose TBX1 regulates β-adrenergic sensitivity in subcutaneous adipose tissue and thermogenic capacity in vivo. *Mol. Metab.* **2020**, *36*, 100965. [CrossRef] [PubMed]
49. Michurina, S.; Stafeev, I.; Podkuychenko, N.; Sklyanik, I.; Shestakova, E.; Yah'yaev, K.; Yurasov, A.; Ratner, E.; Menshikov, M.; Parfyonova, Y.; et al. Decreased UCP-1 expression in beige adipocytes from adipose-derived stem cells of type 2 diabetes patients associates with mitochondrial ROS accumulation during obesity. *Diabetes Res. Clin. Pract.* **2020**, *169*, 108410. [CrossRef]
50. Moon, H.; Choi, J.W.; Song, B.W.; Kim, I.K.; Lim, S.; Lee, S.; Hwang, K.C.; Kim, S.W. Isoliquiritigenin Enhances the Beige Adipocyte Potential of Adipose-Derived Stem Cells by JNK Inhibition. *Molecules* **2020**, *25*, 5660. [CrossRef]
51. Nascimento, E.B.M.; Konings, M.; Schaart, G.; Groen, A.K.; Lütjohann, D.; van Marken Lichtenbelt, W.D.; Schrauwen, P.; Plat, J. In vitro effects of sitosterol and sitostanol on mitochondrial respiration in human brown adipocytes, myotubes and hepatocytes. *Eur. J. Nutr.* **2020**, *59*, 2039–2045. [CrossRef]
52. Qiu, Y.; Sun, L.; Hu, X.; Zhao, X.; Shi, H.; Liu, Z.; Yin, X. Compromised browning plasticity of primary subcutaneous adipocytes derived from overweight Chinese adults. *Diabetol. Metab. Syndr.* **2020**, *12*, 91. [CrossRef] [PubMed]
53. Saha, P.K.; Hamilton, M.P.; Rajapakshe, K.; Putluri, V.; Felix, J.B.; Masschelin, P.; Cox, A.R.; Bajaj, M.; Putluri, N.; Coarfa, C.; et al. miR-30a targets gene networks that promote browning of human and mouse adipocytes. *Am. J. Physiol. Endocrinol. Metab.* **2020**, *319*, E667–E677. [CrossRef] [PubMed]
54. Singh, A.M.; Zhang, L.; Avery, J.; Yin, A.; Du, Y.; Wang, H.; Li, Z.; Fu, H.; Yin, H.; Dalton, S. Human beige adipocytes for drug discovery and cell therapy in metabolic diseases. *Nat. Commun.* **2020**, *11*, 2758. [CrossRef]
55. Szatmári-Tóth, M.; Shaw, A.; Csomós, I.; Mocsár, G.; Fischer-Posovszky, P.; Wabitsch, M.; Balajthy, Z.; Lányi, C.; Győry, F.; Kristóf, E.; et al. Thermogenic Activation Downregulates High Mitophagy Rate in Human Masked and Mature Beige Adipocytes. *Int. J. Mol. Sci.* **2020**, *21*, 6640. [CrossRef]
56. Tóth, B.B.; Arianti, R.; Shaw, A.; Vámos, A.; Veréb, Z.; Póliska, S.; Győry, F.; Bacso, Z.; Fésüs, L.; Kristóf, E. FTO Intronic SNP Strongly Influences Human Neck Adipocyte Browning Determined by Tissue and PPARγ Specific Regulation: A Transcriptome Analysis. *Cells* **2020**, *9*, 987. [CrossRef]

57. Tran, K.V.; Brown, E.L.; DeSouza, T.; Jespersen, N.Z.; Nandrup-Bus, C.; Yang, Q.; Yang, Z.; Desai, A.; Min, S.Y.; Rojas-Rodriguez, R.; et al. Human thermogenic adipocyte regulation by the long noncoding RNA LINC00473. *Nat. Metab.* **2020**, *2*, 397–412. [CrossRef]
58. Alessio, N.; Squillaro, T.; Monda, V.; Peluso, G.; Monda, M.; Melone, M.A.B.; Galderisi, U.; Di Bernardo, G. Circulating factors present in the sera of naturally skinny people may influence cell commitment and adipocyte differentiation of mesenchymal stromal cells. *World J. Stem Cells* **2019**, *11*, 180–195. [CrossRef] [PubMed]
59. Hedesan, O.C.; Fenzl, A.; Digruber, A.; Spirk, K.; Baumgartner-Parzer, S.; Bilban, M.; Kenner, L.; Vierhapper, M.; Elbe-Bürger, A.; Kiefer, F.W. Parathyroid hormone induces a browning program in human white adipocytes. *Int. J. Obes.* **2019**, *43*, 1319–1324. [CrossRef]
60. Jash, S.; Banerjee, S.; Lee, M.J.; Farmer, S.R.; Puri, V. CIDEA Transcriptionally Regulates UCP1 for Britening and Thermogenesis in Human Fat Cells. *iScience* **2019**, *20*, 73–89. [CrossRef]
61. Jespersen, N.Z.; Feizi, A.; Andersen, E.S.; Heywood, S.; Hattel, H.B.; Daugaard, S.; Peijs, L.; Bagi, P.; Feldt-Rasmussen, B.; Schultz, H.S.; et al. Heterogeneity in the perirenal region of humans suggests presence of dormant brown adipose tissue that contains brown fat precursor cells. *Mol. Metab.* **2019**, *24*, 30–43. [CrossRef]
62. Kim, H.L.; Park, J.; Jung, Y.; Ahn, K.S.; Um, J.Y. Platycodin D, a novel activator of AMP-activated protein kinase, attenuates obesity in db/db mice via regulation of adipogenesis and thermogenesis. *Phytomedicine* **2019**, *52*, 254–263. [CrossRef]
63. Li, H.; Zhang, Y.; Wang, F.; Donelan, W.; Zona, M.C.; Li, S.; Reeves, W.; Ding, Y.; Tang, D.; Yang, L. Effects of irisin on the differentiation and browning of human visceral white adipocytes. *Am. J. Transl. Res.* **2019**, *11*, 7410–7421. [PubMed]
64. Li, Y.; Wang, X.; Wang, F.; You, L.; Xu, P.; Cao, Y.; Chen, L.; Wen, J.; Guo, X.; Cui, X.; et al. Identification of intracellular peptides associated with thermogenesis in human brown adipocytes. *J. Cell. Physiol.* **2019**, *234*, 7104–7114. [CrossRef]
65. Min, S.Y.; Desai, A.; Yang, Z.; Sharma, A.; DeSouza, T.; Genga, R.M.J.; Kucukural, A.; Lifshitz, L.M.; Nielsen, S.; Scheele, C.; et al. Diverse repertoire of human adipocyte subtypes develops from transcriptionally distinct mesenchymal progenitor cells. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 17970–17979. [CrossRef] [PubMed]
66. Nagy, L.; Rauch, B.; Balla, N.; Ujlaki, G.; Kis, G.; Abdul-Rahman, O.; Kristóf, E.; Sipos, A.; Antal, M.; Tóth, A.; et al. Olaparib induces browning of in vitro cultures of human primary white adipocytes. *Biochem. Pharmacol.* **2019**, *167*, 76–85. [CrossRef] [PubMed]
67. Velickovic, K.; Wayne, D.; Leija, H.A.L.; Bloor, I.; Morris, D.E.; Law, J.; Budge, H.; Sacks, H.; Symonds, M.E.; Sottile, V. Caffeine exposure induces browning features in adipose tissue in vitro and in vivo. *Sci. Rep.* **2019**, *9*, 9104. [CrossRef]
68. Raajendiran, A.; Ooi, G.; Bayliss, J.; O'Brien, P.E.; Schittenhelm, R.B.; Clark, A.K.; Taylor, R.A.; Rodeheffer, M.S.; Burton, P.R.; Watt, M.J. Identification of Metabolically Distinct Adipocyte Progenitor Cells in Human Adipose Tissues. *Cell Rep.* **2019**, *27*, 1528–1540.e1527. [CrossRef]
69. West, M.D.; Chang, C.F.; Larocca, D.; Li, J.; Jiang, J.J.; Sim, P.; Labat, I.; Chapman, K.B.; Wong, K.E.; Nicoll, J.; et al. Clonal derivation of white and brown adipocyte progenitor cell lines from human pluripotent stem cells. *Stem Cell Res. Ther.* **2019**, *10*, 7. [CrossRef]
70. Wu, L.; Xia, M.; Duan, Y.; Zhang, L.; Jiang, H.; Hu, X.; Yan, H.; Zhang, Y.; Gu, Y.; Shi, H.; et al. Berberine promotes the recruitment and activation of brown adipose tissue in mice and humans. *Cell Death Dis.* **2019**, *10*, 468. [CrossRef]
71. Ghandour, R.A.; Colson, C.; Giroud, M.; Maurer, S.; Rekima, S.; Ailhaud, G.; Klingenspor, M.; Amri, E.Z.; Pisani, D.F. Impact of dietary ω3 polyunsaturated fatty acid supplementation on brown and brite adipocyte function. *J. Lip. Res.* **2018**, *59*, 452–461. [CrossRef] [PubMed]
72. Haynes, B.A.; Huyck, R.W.; James, A.J.; Carter, M.E.; Gaafar, O.U.; Day, M.; Pinto, A.; Dobrian, A.D. Isolation, Expansion, and Adipogenic Induction of CD34+CD31+ Endothelial Cells from Human Omental and Subcutaneous Adipose Tissue. *J. Vis. Exp.* **2018**, *137*, e57804. [CrossRef]
73. Khanh, V.C.; Zulkifli, A.F.; Tokunaga, C.; Yamashita, T.; Hiramatsu, Y.; Ohneda, O. Aging impairs beige adipocyte differentiation of mesenchymal stem cells via the reduced expression of Sirtuin 1. *Biochem. Biophys. Res. Comm.* **2018**, *500*, 682–690. [CrossRef] [PubMed]
74. Loh, R.K.C.; Formosa, M.F.; Eikelis, N.; Bertovic, D.A.; Anderson, M.J.; Barwood, S.A.; Nanayakkara, S.; Cohen, N.D.; La Gerche, A.; Reutens, A.T.; et al. Pioglitazone reduces cold-induced brown fat glucose uptake despite induction of browning in cultured human adipocytes: A randomised, controlled trial in humans. *Diabetologia* **2018**, *61*, 504–505. [CrossRef]
75. Nascimento, E.B.M.; Sparks, L.M.; Divoux, A.; van Gisbergen, M.W.; Broeders, E.P.M.; Jörgensen, J.A.; Schaart, G.; Bouvy, N.D.; van Marken Lichtenbelt, W.D.; Schrauwen, P. Genetic Markers of Brown Adipose Tissue Identity and In Vitro Brown Adipose Tissue Activity in Humans. *Obesity* **2018**, *26*, 135–140. [CrossRef]
76. Pisani, D.F.; Barquissau, V.; Chambard, J.C.; Beuzelin, D.; Ghandour, R.A.; Giroud, M.; Mairal, A.; Pagnotta, S.; Cinti, S.; Langin, D.; et al. Mitochondrial fission is associated with UCP1 activity in human brite/beige adipocytes. *Mol. Metab.* **2018**, *7*, 35–44. [CrossRef]

77. Rashnonejad, A.; Ercan, G.; Gunduz, C.; Akdemir, A.; Tiftikcioglu, Y.O. Comparative analysis of human UCB and adipose tissue derived mesenchymal stem cells for their differentiation potential into brown and white adipocytes. *Mol. Biol. Rep.* **2018**, *45*, 233–244. [CrossRef] [PubMed]
78. Velickovic, K.; Lugo Leija, H.A.; Bloor, I.; Law, J.; Sacks, H.; Symonds, M.; Sottile, V. Low temperature exposure induces browning of bone marrow stem cell derived adipocytes in vitro. *Sci. Rep.* **2018**, *8*, 4974. [CrossRef]
79. Wang, X.; You, L.; Cui, X.; Li, Y.; Weng, X.; Xu, P.; Zhu, L.; Wen, J.; Pang, L.; Guo, X.; et al. Evaluation and optimization of differentiation conditions for human primary brown adipocytes. *Sci. Rep.* **2018**, *8*, 5304. [CrossRef]
80. Su, S.; Guntur, A.R.; Nguyen, D.C.; Fakory, S.S.; Doucette, C.C.; Leech, C.; Lotana, H.; Kelley, M.; Kohli, J.; Martino, J.; et al. A Renewable Source of Human Beige Adipocytes for Development of Therapies to Treat Metabolic Syndrome. *Cell Rep.* **2018**, *25*, 3215–3228.e3219. [CrossRef] [PubMed]
81. Zhang, C.; Wang, J.J.; He, X.; Wang, C.; Zhang, B.; Xu, J.; Xu, W.; Luo, Y.; Huang, K. Characterization and Beige Adipogenic Potential of Human Embryo White Adipose Tissue-Derived Stem Cells. *Cell. Physiol. Biochem.* **2018**, *51*, 2900–2915. [CrossRef]
82. Berry, D.C.; Jiang, Y.; Arpke, R.W.; Close, E.L.; Uchida, A.; Reading, D.; Berglund, E.D.; Kyba, M.; Graff, J.M. Cellular Aging Contributes to Failure of Cold-Induced Beige Adipocyte Formation in Old Mice and Humans. *Cell Metab.* **2017**, *25*, 166–181. [CrossRef]
83. Cambria, M.T.; Villaggio, G.; Federico, C.; Saccone, S.; Sinatra, F. Bone morphogenic protein BMP7 induces adipocyte differentiation and uncoupling protein UCP1 expression in human bone marrow mesenchymal stem cells. *Rend. Lincei.* **2017**, *28*, 635–641. [CrossRef]
84. Jiang, J.; Emont, M.P.; Jun, H.; Qiao, X.; Liao, J.; Kim, D.I.; Wu, J. Cinnamaldehyde induces fat cell-autonomous thermogenesis and metabolic reprogramming. *Metab.—Clin. Exp.* **2017**, *77*, 58–64. [CrossRef]
85. Kim, H.L.; Jung, Y.; Park, J.; Youn, D.H.; Lim, S.; Lee, B.S.; Jeong, M.Y.; Choe, S.K.; Park, R.; Ahn, K.S.; et al. Farnesol has an anti-obesity effect in high-fat diet-induced obese mice and induces the development of beige adipocytes in human adipose tissue derived-mesenchymal stem cells. *Front. Pharmacol.* **2017**, *8*, 654. [CrossRef] [PubMed]
86. Lizcano, F.; Vargas, D.; Gómez, Á.; Torrado, A. Human ADMC-Derived Adipocyte Thermogenic Capacity Is Regulated by IL-4 Receptor. *Stem Cells Int.* **2017**, 2767916. [CrossRef] [PubMed]
87. Nyman, E.; Bartesaghi, S.; Melin Rydfalk, R.; Eng, S.; Pollard, C.; Gennemark, P.; Peng, X.R.; Cedersund, G. Systems biology reveals uncoupling beyond UCP1 in human white fat-derived beige adipocytes. *NPJ Syst. Biol. Appl.* **2017**, *3*, 29. [CrossRef]
88. Pino, M.F.; Divoux, A.; Simmonds, A.V.; Smith, S.R.; Sparks, L.M. Investigating the effects of Orexin-A on thermogenesis in human deep neck brown adipose tissue. *Int. J. Obes.* **2017**, *41*, 1646–1653. [CrossRef]
89. Rebello, C.J.; Greenway, F.L.; Johnson, W.D.; Ribnicky, D.; Poulev, A.; Stadler, K.; Coulter, A.A. Fucoxanthin and Its Metabolite Fucoxanthinol Do Not Induce Browning in Human Adipocytes. *J. Agric. Food Chem.* **2017**, *65*, 10915–10924. [CrossRef]
90. Yang, J.P.; Anderson, A.E.; McCartney, A.; Ory, X.; Ma, G.; Pappalardo, E.; Bader, J.; Elisseeff, J.H. Metabolically Active Three-Dimensional Brown Adipose Tissue Engineered from White Adipose-Derived Stem Cells. *Tissue Eng. Part A* **2017**, *23*, 253–262. [CrossRef]
91. Abdul-Rahman, O.; Kristóf, E.; Doan-Xuan, Q.M.; Vida, A.; Nagy, L.; Horváth, A.; Simon, J.; Maros, T.; Szentkirályi, I.; Palotás, L.; et al. AMP-Activated Kinase (AMPK) activation by AICAR in human white adipocytes derived from pericardial white adipose tissue stem cells induces a partial beige-like phenotype. *PLoS ONE* **2016**, *11*, e0157644. [CrossRef] [PubMed]
92. Barbagallo, I.; Vanella, L.; Cambria, M.T.; Tibullo, D.; Godos, J.; Guarnaccia, L.; Zappala, A.; Li Volti, G. Silibinin Regulates Lipid Metabolism and Differentiation in Functional Human Adipocytes. *Front. Pharmacol.* **2016**, *6*, 309. [CrossRef]
93. Barquissau, V.; Beuzelin, D.; Pisani, D.F.; Beranger, G.E.; Mairal, A.; Montagner, A.; Roussel, B.; Tavernier, G.; Marques, M.A.; Moro, C.; et al. White-to-brite conversion in human adipocytes promotes metabolic reprogramming towards fatty acid anabolic and catabolic pathways. *Mol. Metab.* **2016**, *5*, 352–365. [CrossRef] [PubMed]
94. Fleckenstein-Elsen, M.; Dinnies, D.; Jelenik, T.; Roden, M.; Romacho, T.; Eckel, J. Eicosapentaenoic acid and arachidonic acid differentially regulate adipogenesis, acquisition of a brite phenotype and mitochondrial function in primary human adipocytes. *Mol. Nut. Food Res.* **2016**, *60*, 2065–2075. [CrossRef]
95. Giroud, M.; Karbiener, M.; Pisani, D.F.; Ghandour, R.A.; Beranger, G.E.; Niemi, T.; Taittonen, M.; Nuutila, P.; Virtanen, K.A.; Langin, D.; et al. Let-7i-5p represses brite adipocyte function in mice and humans. *Sci. Rep.* **2016**, *6*, 28613. [CrossRef] [PubMed]
96. Klepac, K.; Kilić, A.; Gnad, T.; Brown, L.M.; Herrmann, B.; Wilderman, A.; Balkow, A.; Glöde, A.; Simon, K.; Lidell, M.E.; et al. The Gq signalling pathway inhibits brown and beige adipose tissue. *Nat. Commun.* **2016**, *7*, 10895. [CrossRef] [PubMed]
97. Kristóf, E.; Doan-Xuan, Q.M.; Sárvári, A.K.; Klusóczki, Á.; Fischer-Posovszky, P.; Wabitsch, M.; Bacso, Z.; Bai, P.; Balajthy, Z.; Fésüs, L. Clozapine modifies the differentiation program of human adipocytes inducing browning. *Transl. Psychiatry* **2016**, *6*, e963. [CrossRef]
98. Lee, P.; Bova, R.; Schofield, L.; Bryant, W.; Dieckmann, W.; Slattery, A.; Govendir, M.A.; Emmett, L.; Greenfield, J.R. Brown Adipose Tissue Exhibits a Glucose-Responsive Thermogenic Biorhythm in Humans. *Cell Metab.* **2016**, *23*, 602–609. [CrossRef]

99. Min, S.Y.; Kady, J.; Nam, M.; Rojas-Rodriguez, R.; Berkenwald, A.; Kim, J.H.; Noh, H.L.; Kim, J.K.; Cooper, M.P.; Fitzgibbons, T.; et al. Human 'brite/beige' adipocytes develop from capillary networks, and their implantation improves metabolic homeostasis in mice. *Nat. Med.* **2016**, *22*, 312–318. [CrossRef]
100. Vargas, D.; Shimokawa, N.; Kaneko, R.; Rosales, W.; Parra, A.; Castellanos, Á.; Koibuchi, N.; Lizcano, F. Regulation of human subcutaneous adipocyte differentiation by EID1. *J. Mol. Endocrinol.* **2016**, *56*, 113–122. [CrossRef]
101. Wang, Y.L.; Lin, S.P.; Hsieh, P.C.; Hung, S.C. Concomitant beige adipocyte differentiation upon induction of mesenchymal stem cells into brown adipocytes. *Biochem. Biophys. Res. Commun.* **2016**, *478*, 689–695. [CrossRef]
102. Wu, N.N.; Zhang, C.H.; Lee, H.J.; Ma, Y.; Wang, X.; Ma, X.J.; Ma, W.; Zhao, D.; Feng, Y.M. Brown adipogenic potential of brown adipocytes and peri-renal adipocytes from human embryo. *Sci. Rep.* **2016**, *6*, 39193. [CrossRef] [PubMed]
103. Xu, X.; Li, X.; Yan, R.; Jiang, H.; Wang, T.; Fan, L.; Wu, J.; Cao, J.; Li, W. Gene expression profiling of human bone marrow-derived mesenchymal stem cells during adipogenesis. *Folia Histochem. Cytobiol.* **2016**, *54*, 14–24. [CrossRef] [PubMed]
104. Barclay, J.L.; Agada, H.; Jang, C.; Ward, M.; Wetzig, N.; Ho, K.K. Effects of glucocorticoids on human brown adipocytes. *J. Endocrinol.* **2015**, *224*, 139–147. [CrossRef] [PubMed]
105. Gustafson, B.; Hammarstedt, A.; Hedjazifar, S.; Hoffmann, J.M.; Svensson, P.A.; Grimsby, J.; Rondinone, C.; Smith, U. BMP4 and BMP Antagonists Regulate Human White and Beige Adipogenesis. *Diabetes* **2015**, *64*, 1670–1681. [CrossRef]
106. Hartig, S.M.; Bader, D.A.; Abadie, K.V.; Motamed, M.; Hamilton, M.P.; Long, W.W.; York, B.; Mueller, M.; Wagner, M.; Trauner, M.; et al. Ubc9 Impairs Activation of the Brown Fat Energy Metabolism Program in Human White Adipocytes. *Mol. Endocrinol.* **2015**, *29*, 1320–1333. [CrossRef]
107. Kouidhi, M.; Villageois, P.; Mounier, C.M.; Ménigot, C.; Rival, Y.; Piwnica, D.; Aubert, J.; Chignon-Sicard, B.; Dani, C. Characterization of human knee and chin adipose-derived stromal cells. *Stem Cells Int.* **2015**, 592090. [CrossRef]
108. Loft, A.; Forss, I.; Siersbæk, M.S.; Schmidt, S.F.; Larsen, A.S.; Madsen, J.G.; Pisani, D.F.; Nielsen, R.; Aagaard, M.M.; Mathison, A.; et al. Browning of human adipocytes requires KLF11 and reprogramming of PPARγ superenhancers. *Genes Dev.* **2015**, *29*, 7–22. [CrossRef]
109. Okla, M.; Ha, J.H.; Temel, R.E.; Chung, S. BMP7 drives human adipogenic stem cells into metabolically active beige adipocytes. *Lipids* **2015**, *50*, 111–120. [CrossRef]
110. Seiler, S.E.; Xu, D.; Ho, J.P.; Lo, K.A.; Buehrer, B.M.; Ludlow, Y.J.W.; Kovalik, J.P.; Sun, L. Characterization of a primary brown adipocyte culture system derived from human fetal interscapular fat. *Adipocyte* **2015**, *4*, 303–310. [CrossRef]
111. Van Den Beukel, J.C.; Grefhorst, A.; Hoogduijn, M.J.; Steenbergen, J.; Mastroberardino, P.G.; Dor, F.J.M.F.; Themmen, A.P.N. Women have more potential to induce browning of perirenal adipose tissue than men. *Obesity* **2015**, *23*, 1671–1679. [CrossRef]
112. Vargas, D.; Rosales, W.; Lizcano, F. Modifications of Human Subcutaneous ADMSC after PPARγ Activation and Cold Exposition. *Stem Cells Int.* **2015**, *2015*, 196348. [CrossRef]
113. Xue, R.; Lynes, M.D.; Dreyfuss, J.M.; Shamsi, F.; Schulz, T.J.; Zhang, H.; Huang, T.L.; Townsend, K.L.; Li, Y.; Takahashi, H.; et al. Clonal analyses and gene profiling identify genetic biomarkers of the thermogenic potential of human brown and white preadipocytes. *Nat. Med.* **2015**, *21*, 760–768. [CrossRef]
114. Zhu, Y.; Yang, R.; McLenithan, J.; Yu, D.; Wang, H.; Wang, Y.; Singh, D.; Olson, J.; Sztalryd, C.; Zhu, D.; et al. Direct conversion of human myoblasts into brown-like adipocytes by engineered super-active PPARγ. *Obesity* **2015**, *23*, 1014–1021. [CrossRef]
115. Di Franco, A.; Guasti, D.; Mazzanti, B.; Ercolino, T.; Francalanci, M.; Nesi, G.; Bani, D.; Forti, G.; Mannelli, M.; Valeri, A.; et al. Dissecting the origin of inducible brown fat in adult humans through a novel adipose stem cell model from adipose tissue surrounding pheochromocytoma. *J. Clin. Endocrinol. Metab.* **2014**, *99*, E1903–E1912. [CrossRef]
116. Elsen, M.; Raschke, S.; Tennagels, N.; Schwahn, U.; Jelenik, T.; Roden, M.; Romacho, T.; Eckel, J. BMP4 and BMP7 induce the white-to-brown transition of primary human adipose stem cells. *Am. J. Physiol. Cell Physiol.* **2014**, *306*, C431–C440. [CrossRef]
117. Karbiener, M.; Pisani, D.F.; Frontini, A.; Oberreiter, L.M.; Lang, E.; Vegiopoulos, A.; Mössenböck, K.; Bernhardt, G.A.; Mayr, T.; Hildner, F.; et al. MicroRNA-26 family is required for human adipogenesis and drives characteristics of brown adipocytes. *Stem Cells* **2014**, *32*, 1578–1590. [CrossRef]
118. Kern, P.A.; Finlin, B.S.; Zhu, B.; Rasouli, N.; McGehee, R.E., Jr.; Westgate, P.M.; Dupont-Versteegden, E.E. The effects of temperature and seasons on subcutaneous white adipose tissue in humans: Evidence for thermogenic gene induction. *J. Clin. Endocrinol. Metab.* **2014**, *99*, E2772–E2779. [CrossRef] [PubMed]
119. Silva, F.J.; Holt, D.J.; Vargas, V.; Yockman, J.; Boudina, S.; Atkinson, D.; Grainger, D.W.; Revelo, M.P.; Sherman, W.; Bull, D.A.; et al. Metabolically active human brown adipose tissue derived stem cells. *Stem Cells* **2014**, *32*, 572–581. [CrossRef] [PubMed]
120. Murholm, M.; Isidor, M.S.; Basse, A.L.; Winther, S.; Sørensen, C.; Skovgaard-Petersen, J.; Nielsen, M.M.; Hansen, A.S.; Quistorff, B.; Hansen, J.B. Retinoic acid has different effects on UCP1 expression in mouse and human adipocytes. *BMC Cell Biol.* **2013**, *14*, 41. [CrossRef]
121. Lee, J.Y.; Takahashi, N.; Yasubuchi, M.; Kim, Y.I.; Hashizaki, H.; Kim, M.J.; Sakamoto, T.; Goto, T.; Kawada, T. Triiodothyronine induces UCP-1 expression and mitochondrial biogenesis in human adipocytes. *Am. J. Physiol. Cell Physiol.* **2012**, *302*, C463–C472. [CrossRef] [PubMed]

122. Jo, S.J.; Choi, W.W.; Lee, E.S.; Lee, J.Y.; Park, H.S.; Moon, D.W.; Eun, H.C.; Chung, J.H. Temporary increase of PPAR-γ and transient expression of UCP-1 in stromal vascular fraction isolated human adipocyte derived stem cells during adipogenesis. *Lipids* **2011**, *46*, 487–494. [CrossRef]
123. Lee, P.; Swarbrick, M.M.; Zhao, J.T.; Ho, K.K.Y. Inducible brown adipogenesis of supraclavicular fat in adult humans. *Endocrinology* **2011**, *152*, 3597–3602. [CrossRef] [PubMed]
124. Pisani, D.F.; Djedaini, M.; Beranger, G.E.; Elabd, C.; Scheideler, M.; Ailhaud, G.; Amri, E.Z. Differentiation of human adipose-derived stem cells into "brite" (brown-in-white) adipocytes. *Front. Endocrinol.* **2011**, *2*, 87. [CrossRef]
125. Bogacka, I.; Ukropcova, B.; McNeil, M.; Gimble, J.M.; Smith, S.R. Structural and functional consequences of mitochondrial biogenesis in human adipocytes in vitro. *J. Clin. Endocrinol. Metab.* **2005**, *90*, 6650–6656. [CrossRef]
126. Tiraby, C.; Tavernier, G.; Lefort, C.; Larrouy, D.; Bouillaud, F.; Ricquier, D.; Langin, D. Acquirement of brown fat cell features by human white adipocytes. *J. Biol. Chem.* **2003**, *278*, 33370–33376. [CrossRef]
127. Digby, J.E.; Montague, C.T.; Sewter, C.P.; Sanders, L.; Wilkison, W.O.; O'Rahilly, S.; Prins, J.B. Thiazolidinedione exposure increases the expression of uncoupling protein 1 in cultured human preadipocytes. *Diabetes* **1998**, *47*, 138–141. [CrossRef]
128. Kajimura, S.; Spiegelman, B.M.; Seale, P. Brown and Beige Fat: Physiological Roles beyond Heat Generation. *Cell Metab.* **2015**, *22*, 546–559. [CrossRef] [PubMed]
129. Ikeda, K.; Maretich, P.; Kajimura, S. The Common and Distinct Features of Brown and Beige Adipocytes. *Trends Endocrinol. Metab.* **2018**, *29*, 191–200. [CrossRef]
130. Blondin, D.P.; Nielsen, S.; Kuipers, E.N.; Severinsen, M.C.; Jensen, V.H.; Miard, S.; Jespersen, N.Z.; Kooijman, S.; Boon, M.R.; Fortin, M.; et al. Human Brown Adipocyte Thermogenesis Is Driven by β2-AR Stimulation. *Cell Metab.* **2020**, *32*, 287–300.e287. [CrossRef]
131. Cypess, A.M.; Lehman, S.; Williams, G.; Tal, I.; Rodman, D.; Goldfine, A.B.; Kuo, F.C.; Palmer, E.L.; Tseng, Y.H.; Doria, A.; et al. Identification and importance of brown adipose tissue in adult humans. *N. Engl. J. Med.* **2009**, *360*, 1509–1517. [CrossRef] [PubMed]
132. van Marken Lichtenbelt, W.D.; Vanhommerig, J.W.; Smulders, N.M.; Drossaerts, J.M.; Kemerink, G.J.; Bouvy, N.D.; Schrauwen, P.; Teule, G.J. Cold-activated brown adipose tissue in healthy men. *N. Engl. J. Med.* **2009**, *360*, 1500–1508. [CrossRef]
133. Virtanen, K.A.; Lidell, M.E.; Orava, J.; Heglind, M.; Westergren, R.; Niemi, T.; Taittonen, M.; Laine, J.; Savisto, N.J.; Enerbäck, S.; et al. Functional brown adipose tissue in healthy adults. *N. Engl. J. Med.* **2009**, *360*, 1518–1525. [CrossRef] [PubMed]
134. Ntambi, J.M.; Young-Cheul, K. Adipocyte Differentiation and Gene Expression. *J. Nut.* **2000**, *130*, 3122S–3126S. [CrossRef] [PubMed]
135. Cristancho, A.G.; Lazar, M.A. Forming functional fat: A growing understanding of adipocyte differentiation. *Nat. Rev. Mol. Cell Biol.* **2011**, *12*, 722–734. [CrossRef]
136. Obregon, M.J. Thyroid hormone and adipocyte differentiation. *Thyroid* **2008**, *18*, 185–195. [CrossRef]
137. Mullur, R.; Liu, Y.Y.; Brent, G.A. Thyroid hormone regulation of metabolism. *Physiol. Rev.* **2014**, *94*, 355–382. [CrossRef]
138. Bianco, A.C.; McAninch, E.A. The role of thyroid hormone and brown adipose tissue in energy homoeostasis. *Lancet Diabetes Endocrinol.* **2013**, *1*, 250–258. [CrossRef]
139. Rubio, A.; Raasmaja, A.; Maia, A.L.; Kim, K.R.; Silva, J.E. Effects of thyroid hormone on norepinephrine signaling in brown adipose tissue. I. Beta 1- and beta 2-adrenergic receptors and cyclic adenosine 3′,5′-monophosphate generation. *Endocrinology* **1995**, *136*, 3267–3276. [CrossRef]
140. Tontonoz, P.; Spiegelman, B.M. Fat and beyond: The diverse biology of PPARgamma. *Annu. Rev. Biochem.* **2008**, *77*, 289–312. [CrossRef] [PubMed]
141. Styner, M.; Sen, B.; Xie, Z.; Case, N.; Rubin, J. Indomethacin promotes adipogenesis of mesenchymal stem cells through a cyclooxygenase independent mechanism. *J. Cell. Biochem.* **2010**, *111*, 1042–1050. [CrossRef]
142. Overby, H.; Yang, Y.; Xu, X.; Wang, S.; Zhao, L. Indomethacin promotes browning and brown adipogenesis in both murine and human fat cells. *Pharmacol. Res. Perspect.* **2020**, *8*, e00592. [CrossRef]
143. Levert, K.L.; Waldrop, G.L.; Stephens, J.M. A biotin analog inhibits acetyl-CoA carboxylase activity and adipogenesis. *J. Biol. Chem.* **2002**, *277*, 16347–16350. [CrossRef]
144. Takeda, Y.; Dai, P. Functional roles of pantothenic acid, riboflavin, thiamine, and choline in adipocyte browning in chemically induced human brown adipocytes. *Sci. Rep.* **2024**, *14*, 18252. [CrossRef] [PubMed]
145. Dietz, J.V.; Fox, J.L.; Khalimonchuk, O. Down the Iron Path: Mitochondrial Iron Homeostasis and Beyond. *Cells* **2021**, *10*, 2198. [CrossRef]
146. Moreno-Navarrete, J.M.; Ortega, F.; Moreno, M.; Ricart, W.; Fernández-Real, J.M. Fine-tuned iron availability is essential to achieve optimal adipocyte differentiation and mitochondrial biogenesis. *Diabetologia* **2014**, *57*, 1957–1967. [CrossRef] [PubMed]
147. Yook, J.S.; You, M.; Kim, Y.; Zhou, M.; Liu, Z.; Kim, Y.C.; Lee, J.; Chung, S. The thermogenic characteristics of adipocytes are dependent on the regulation of iron homeostasis. *J. Biol. Chem.* **2021**, *296*, 100452. [CrossRef]

148. Shamsi, F.; Wang, C.-H.; Tseng, Y.-H. The evolving view of thermogenic adipocytes—Ontogeny, niche and function. *Nat. Rev. Endocrinol.* **2021**, *17*, 726–744. [CrossRef]
149. Ye, L.; Wu, J.; Cohen, P.; Kazak, L.; Khandekar, M.J.; Jedrychowski, M.P.; Zeng, X.; Gygi, S.P.; Spiegelman, B.M. Fat cells directly sense temperature to activate thermogenesis. *Proc. Natl. Acad. Sci.* **2013**, *110*, 12480–12485. [CrossRef] [PubMed]
150. Wu, L.; Cai, X.; Dong, H.; Jing, W.; Huang, Y.; Yang, X.; Wu, Y.; Lin, Y. Serum regulates adipogenesis of mesenchymal stem cells via MEK/ERK-dependent PPARγ expression and phosphorylation. *J. Cell. Mol. Med.* **2010**, *14*, 922–932. [CrossRef]
151. Brand, M.D.; Nicholls, D.G. Assessing mitochondrial dysfunction in cells. *Biochem. J.* **2011**, *435*, 297–312. [CrossRef]
152. Divakaruni, A.S.; Rogers, G.W.; Murphy, A.N. Measuring Mitochondrial Function in Permeabilized Cells Using the Seahorse XF Analyzer or a Clark-Type Oxygen Electrode. *Curr. Protoc. Toxicol.* **2014**, *60*, 25.2.1–25.2.16. [CrossRef]
153. Li, Y.; Fromme, T. Uncoupling Protein 1 Does Not Produce Heat without Activation. *Int. J. Mol. Sci.* **2022**, *23*, 2406. [CrossRef]
154. Laurila, S.; Sun, L.; Lahesmaa, M.; Schnabl, K.; Laitinen, K.; Klén, R.; Li, Y.; Balaz, M.; Wolfrum, C.; Steiger, K.; et al. Secretin activates brown fat and induces satiation. *Nat. Metab.* **2021**, *3*, 798–809. [CrossRef] [PubMed]
155. Hill, B.G.; Benavides, G.A.; Lancaster, J.R.; Ballinger, S.; Dell'Italia, L.; Zhang, J.; Darley-Usmar, V.M. Integration of cellular bioenergetics with mitochondrial quality control and autophagy. *Biol. Chem.* **2012**, *393*, 1485–1512. [CrossRef]
156. Ahfeldt, T.; Schinzel, R.T.; Lee, Y.-K.; Hendrickson, D.; Kaplan, A.; Lum, D.H.; Camahort, R.; Xia, F.; Shay, J.; Rhee, E.P.; et al. Programming human pluripotent stem cells into white and brown adipocytes. *Nat. Cell Biol.* **2012**, *14*, 209–219. [CrossRef] [PubMed]
157. Roth, N.; Zilliacus, J.; Beronius, A. Development of the SciRAP Approach for Evaluating the Reliability and Relevance of in vitro Toxicity Data. *Front. Toxicol.* **2021**, *3*, 746430. [CrossRef]
158. OECD. *Guidance Document on Good In Vitro Method Practices (GIVIMP)*; OECD Series on Testing and Assessment, No. 286; OECD Publishing: Paris, France, 2018. [CrossRef]
159. Yin, H.; Pasut, A.; Soleimani, V.D.; Bentzinger, C.F.; Antoun, G.; Thorn, S.; Seale, P.; Fernando, P.; van Ijcken, W.; Grosveld, F.; et al. MicroRNA-133 Controls Brown Adipose Determination in Skeletal Muscle Satellite Cells by Targeting Prdm16. *Cell Metab.* **2013**, *17*, 210–224. [CrossRef] [PubMed]
160. Trajkovski, M.; Ahmed, K.; Esau, C.C.; Stoffel, M. MyomiR-133 regulates brown fat differentiation through Prdm16. *Nat. Cell Biol.* **2012**, *14*, 1330–1335. [CrossRef]
161. Markussen, L.K.; Rondini, E.A.; Johansen, O.S.; Madsen, J.G.S.; Sustarsic, E.G.; Marcher, A.-B.; Hansen, J.B.; Gerhart-Hines, Z.; Granneman, J.G.; Mandrup, S. Lipolysis regulates major transcriptional programs in brown adipocytes. *Nat. Commun.* **2022**, *13*, 1–16. [CrossRef]
162. Waldén, T.B.; Hansen, I.R.; Timmons, J.A.; Cannon, B.; Nedergaard, J. Recruited vs. nonrecruited molecular signatures of brown, "brite," and white adipose tissues. *Am. J. Physiol. Metab.* **2012**, *302*, E19–E31. [CrossRef]
163. Pilkington, A.-C.; Paz, H.A.; Wankhade, U.D. Beige Adipose Tissue Identification and Marker Specificity—Overview. *Front. Endocrinol.* **2021**, *12*, 599134. [CrossRef] [PubMed]
164. Chen, Y.; Zeng, X.; Huang, X.; Serag, S.; Woolf, C.J.; Spiegelman, B.M. Crosstalk between KCNK3-Mediated Ion Current and Adrenergic Signaling Regulates Adipose Thermogenesis and Obesity. *Cell* **2017**, *171*, 836–848.e13. [CrossRef]
165. Lee, K.Y.; Yamamoto, Y.; Boucher, J.; Winnay, J.N.; Gesta, S.; Cobb, J.; Blüher, M.; Kahn, C.R. *Shox2* is a molecular determinant of depot-specific adipocyte function. *Proc. Natl. Acad. Sci.* **2013**, *110*, 11409–11414. [CrossRef]
166. Fu, Q.; Wang, P.; Li, W.; Cai, Z.; Zhao, S.; Ling, W.; Li, M.; Tang, X.; Song, Z. Partial inhibition of adipose CIDEC improves insulin sensitivity and increases energy expenditure in high-fat diet-fed mice via activating ATGL-PPARα pathway. *Biochim. et Biophys. Acta (BBA) - Mol. Cell Biol. Lipids* **2025**, *1870*, 159659. [CrossRef]
167. Politis-Barber, V.; Petrick, H.L.; Raajendiran, A.; DesOrmeaux, G.J.; Brunetta, H.S.; dos Reis, L.M.; A Mori, M.; Wright, D.C.; Watt, M.J.; Holloway, G.P. *Ckmt1* is Dispensable for Mitochondrial Bioenergetics Within White/Beige Adipose Tissue. *Function* **2022**, *3*. [CrossRef] [PubMed]
168. Maurer, S.F.; Fromme, T.; Grossman, L.I.; Hüttemann, M.; Klingenspor, M. The brown and brite adipocyte marker Cox7a1 is not required for non-shivering thermogenesis in mice. *Sci. Rep.* **2015**, *5*, 17704. [CrossRef]
169. Paulo, E.; Wu, D.; Wang, Y.; Zhang, Y.; Wu, Y.; Swaney, D.L.; Soucheray, M.; Jimenez-Morales, D.; Chawla, A.; Krogan, N.J.; et al. Sympathetic inputs regulate adaptive thermogenesis in brown adipose tissue through cAMP-Salt inducible kinase axis. *Sci. Rep.* **2018**, *8*, 11001. [CrossRef] [PubMed]
170. Lee, J.; Ellis, J.M.; Wolfgang, M.J. Adipose Fatty Acid Oxidation Is Required for Thermogenesis and Potentiates Oxidative Stress-Induced Inflammation. *Cell Rep.* **2015**, *10*, 266–279. [CrossRef] [PubMed]
171. Whitehead, A.; Krause, F.N.; Moran, A.; MacCannell, A.D.V.; Scragg, J.L.; McNally, B.D.; Boateng, E.; Murfitt, S.A.; Virtue, S.; Wright, J.; et al. Brown and Beige Adipose Tissue Regulate Systemic Metabolism through a Metabolite Interorgan Signaling Axis. *Nat. Commun.* **2021**, *12*, 1905. [CrossRef]
172. Hüttemann, M.; Frank, V.; Kadenbach, B. The possible role of isoforms of cytochrome c oxidase subunit VIa in mammalian thermogenesis. *Cell. Mol. Life Sci.* **1999**, *55*, 1482–1490. [CrossRef]

173. de Jesus, L.A.; Carvalho, S.D.; Ribeiro, M.O.; Schneider, M.; Kim, S.-W.; Harney, J.W.; Larsen, P.R.; Bianco, A.C. The type 2 iodothyronine deiodinase is essential for adaptive thermogenesis in brown adipose tissue. *J. Clin. Investig.* **2001**, *108*, 1379–1385. [CrossRef]
174. Angueira, A.R.; Shapira, S.N.; Ishibashi, J.; Sampat, S.; Sostre-Colón, J.; Emmett, M.J.; Titchenell, P.M.; Lazar, M.A.; Lim, H.-W.; Seale, P. Early B Cell Factor Activity Controls Developmental and Adaptive Thermogenic Gene Programming in Adipocytes. *Cell Rep.* **2020**, *30*, 2869–2878.e4. [CrossRef] [PubMed]
175. Tan, C.Y.; Virtue, S.; Bidault, G.; Dale, M.; Hagen, R.; Griffin, J.L.; Vidal-Puig, A. Brown Adipose Tissue Thermogenic Capacity Is Regulated by Elovl6. *Cell Rep.* **2015**, *13*, 2039–2047. [CrossRef] [PubMed]
176. Vergnes, L.; Chin, R.; Young, S.G.; Reue, K. Heart-type Fatty Acid-binding Protein Is Essential for Efficient Brown Adipose Tissue Fatty Acid Oxidation and Cold Tolerance. *J. Biol. Chem.* **2011**, *286*, 380–390. [CrossRef]
177. Zhao, X.; Zhao, B.; Li, H.; Liu, Y.; Wang, B.; Li, A.; Zeng, T.; Hui, H.X.; Sun, J.; Cikes, D.; et al. MTCH2 Suppresses Thermogenesis by Regulating Autophagy in Adipose Tissue. *Adv. Sci.* **2025**, *12*, e2416598. [CrossRef]
178. Bartelt, A.; Widenmaier, S.B.; Schlein, C.; Johann, K.; Goncalves, R.L.S.; Eguchi, K.; Fischer, A.W.; Parlakgül, G.; A Snyder, N.; Nguyen, T.B.; et al. Brown adipose tissue thermogenic adaptation requires Nrf1-mediated proteasomal activity. *Nat. Med.* **2018**, *24*, 292–303. [CrossRef] [PubMed]
179. Sellayah, D.; Sikder, D. Orexin receptor-1 mediates brown fat developmental differentiation. *Adipocyte* **2012**, *1*, 58–63. [CrossRef]
180. Razzoli, M.; McGonigle, S.; Sahu, B.S.; Rodriguez, P.; Svedberg, D.; Rao, L.; Ruocco, C.; Nisoli, E.; Vezzani, B.; Frontini, A.; et al. A key role for P2RX5 in brown adipocyte differentiation and energy homeostasis. *Adipocyte* **2024**, *13*, 2421745. [CrossRef]
181. Shu, H.; Zhang, J.; Cheng, D.; Zhao, X.; Ma, Y.; Zhang, C.; Zhang, Y.; Jia, Z.; Liu, Z. The Role of Proton-Coupled Amino Acid Transporter 2 (SLC36A2) in Cold-Induced Thermogenesis of Mice. *Nutrients* **2023**, *15*, 3552. [CrossRef]
182. Long, J.Z.; Svensson, K.J.; Bateman, L.A.; Lin, H.; Kamenecka, T.; Lokurkar, I.A.; Lou, J.; Rao, R.R.; Chang, M.R.; Jedrychowski, M.P.; et al. The Secreted Enzyme PM20D1 Regulates Lipidated Amino Acid Uncouplers of Mitochondria. *Cell* **2016**, *166*, 424–435. [CrossRef]
183. Majeed, Y.; Halabi, N.; Madani, A.Y.; Engelke, R.; Bhagwat, A.M.; Abdesselem, H.; Agha, M.V.; Vakayil, M.; Courjaret, R.; Goswami, N.; et al. SIRT1 promotes lipid metabolism and mitochondrial biogenesis in adipocytes and coordinates adipogenesis by targeting key enzymatic pathways. *Sci. Rep.* **2021**, *11*, 1–19. [CrossRef]
184. Arianti, R.; Vinnai, B.Á.; Tóth, B.B.; Shaw, A.; Csősz, É.; Vámos, A.; Győry, F.; Fischer-Posovszky, P.; Wabitsch, M.; Kristóf, E.; et al. ASC-1 transporter-dependent amino acid uptake is required for the efficient thermogenic response of human adipocytes to adrenergic stimulation. *FEBS Lett.* **2021**, *595*, 2085–2098. [CrossRef] [PubMed]
185. Vernochet, C.; Mourier, A.; Bezy, O.; Macotela, Y.; Boucher, J.; Rardin, M.J.; An, D.; Lee, K.Y.; Ilkayeva, O.R.; Zingaretti, C.M.; et al. Adipose-Specific Deletion of TFAM Increases Mitochondrial Oxidation and Protects Mice against Obesity and Insulin Resistance. *Cell Metab.* **2012**, *16*, 765–776. [CrossRef] [PubMed]
186. Kim, S.H.; Park, W.Y.; Kim, B.; Kim, J.-H.; Song, G.; Park, J.Y.; Jiao, W.; Jung, S.J.; Ahn, K.S.; Kwak, H.J.; et al. FXR-ApoC2 pathway activates UCP1-mediated thermogenesis by promoting the browning of white adipose tissues. *J. Biol. Chem.* **2025**, *301*, 108181. [CrossRef]
187. Yu, J.; Gu, X.; Guo, Y.; Gao, M.; Cheng, S.; Meng, M.; Cui, X.; Zhang, Z.; Guo, W.; Yan, D.; et al. E3 ligase FBXW7 suppresses brown fat expansion and browning of white fat. *Embo Rep.* **2025**, *26*, 748–767. [CrossRef]
188. Arianti, R.; Vinnai, B.Á.; Alrifai, R.; Karadsheh, G.; Al-Khafaji, Y.Q.; Póliska, S.; Győry, F.; Fésüs, L.; Kristóf, E. Upregulation of inhibitor of DNA binding 1 and 3 is important for efficient thermogenic response in human adipocytes. *Sci. Rep.* **2024**, *14*, 1–13. [CrossRef]
189. Bahn, Y.J.; Wang, Y.; Dagur, P.; Scott, N.; Cero, C.; Long, K.T.; Nguyen, N.; Cypess, A.M.; Rane, S.G. TGF-β antagonism synergizes with PPARγ agonism to reduce fibrosis and enhance beige adipogenesis. *Mol. Metab.* **2024**, *90*, 102054. [CrossRef]
190. Bolin, A.P.; Silva, F.d.F.; Salgueiro, R.B.; dos Santos, B.A.; Komino, A.C.M.; Andreotti, S.; de Sousa, É.; de Castro, É.; Real, C.C.; Faria, D.d.P.; et al. Glucocorticoid modulates oxidative and thermogenic function of rat brown adipose tissue and human brown adipocytes. *J. Cell. Physiol.* **2024**, *239*, 1–12. [CrossRef]
191. Di Maio, G.; Alessio, N.; Ambrosino, A.; Al Sammarraie, S.H.A.; Monda, M.; Di Bernardo, G. Irisin influences the in vitro differentiation of human mesenchymal stromal cells, promoting a tendency toward beiging adipogenesis. *J. Cell. Biochem.* **2024**, *125*. [CrossRef] [PubMed]
192. Hayato, R.; Matsumoto, T.; Higure, Y. Ca2+ Depletion in the ER Causes Store-Operated Ca2+ Entry via the TRPC6 Channel in Mouse Brown Adipocytes. *Physiol. Res.* **2024**, *73*, 69–80. [CrossRef]
193. Hong, P.; Wang, D.; Wu, Y.; Zhang, Q.; Liu, P.; Pan, J.; Yu, M.; Tian, W. A novel long noncoding RNA AK029592 contributes to thermogenic adipocyte differentiation. *STEM CELLS Transl. Med.* **2024**, *13*, 985–1000. [CrossRef]
194. Karanfil, A.S.; Louis, F.; Sowa, Y.; Matsusaki, M. Polyelectrolyte nanofilms on cell surface can induce brown adipogenic differentiation of DFATs. *Biochem. Biophys. Res. Commun.* **2024**, *733*, 150432. [CrossRef]

195. Kim, S.; Yazawa, T.; Koide, A.; Yoneda, E.; Aoki, R.; Okazaki, T.; Tomita, K.; Watanabe, H.; Muroi, Y.; Testuka, M.; et al. Potential Role of Pig UCP3 in Modulating Adipocyte Browning via the Beta-Adrenergic Receptor Signaling Pathway. *Biology* **2024**, *13*, 284. [CrossRef]
196. Ma, Y.; Liu, N.; Shao, X.; Shi, T.; Lin, J.; Liu, B.; Shen, T.; Guo, B.; Jiang, Q. Mechanical loading on osteocytes regulates thermogenesis homeostasis of brown adipose tissue by influencing osteocyte-derived exosomes. *J. Orthop. Transl.* **2024**, *48*, 39–52. [CrossRef] [PubMed]
197. Reckziegel, P.; Petrovic, N.; Cannon, B.; Nedergaard, J. Perfluorooctanoate (PFOA) cell-autonomously promotes thermogenic and adipogenic differentiation of brown and white adipocytes. *Ecotoxicol. Environ. Saf.* **2024**, *271*, 115955. [CrossRef]
198. Sakaki, M.; Kamatari, Y.; Kurisaki, A.; Funaba, M.; Hashimoto, O. Activin E upregulates uncoupling protein 1 and fibroblast growth factor 21 in brown adipocytes. *Mol. Cell. Endocrinol.* **2024**, *592*, 112326. [CrossRef] [PubMed]
199. Takeda, Y.; Yoshikawa, T.; Dai, P. Angiotensin II participates in mitochondrial thermogenic functions via the activation of glycolysis in chemically induced human brown adipocytes. *Sci. Rep.* **2024**, *14*, 1–15. [CrossRef]
200. Wang, Q.; Su, Y.; Sun, R.; Xiong, X.; Guo, K.; Wei, M.; Yang, G.; Ru, Y.; Zhang, Z.; Li, J.; et al. MIIP downregulation drives colorectal cancer progression through inducing peri-cancerous adipose tissue browning. *Cell Biosci.* **2024**, *14*, 1–22. [CrossRef] [PubMed]
201. Wen, Q.; Xie, X.; Ren, Q.; Pan, R.; Du, Y. BDE-99 stimulates generation of aberrant brown/beige adipocytes. *Environ. Pollut.* **2024**, *347*, 123761. [CrossRef]
202. Yadav, M.K.; Ishida, M.; Gogoleva, N.; Liao, C.-W.; Salim, F.N.; Kanai, M.; Kuno, A.; Hayashi, T.; Shahri, Z.J.; Kulathunga, K.; et al. MAFB in macrophages regulates cold-induced neuronal density in brown adipose tissue. *Cell Rep.* **2024**, *43*, 113978. [CrossRef]
203. Majeed, S.A.; Dunzendorfer, H.; Weiner, J.; Heiker, J.T.; Kiess, W.; Körner, A.; Landgraf, K. *COBL*, *MKX* and *MYOC* Are Potential Regulators of Brown Adipose Tissue Development Associated with Obesity-Related Metabolic Dysfunction in Children. *Int. J. Mol. Sci.* **2023**, *24*, 3085. [CrossRef]
204. Ali, U.; Wabitsch, M.; Tews, D.; Colitti, M. Effects of allicin on human Simpson-Golabi-Behmel syndrome cells in mediating browning phenotype. *Front. Endocrinol.* **2023**, *14*, 1141303. [CrossRef]
205. Arianti, R.; Vinnai, B.Á.; Győry, F.; Guba, A.; Csősz, É.; Kristóf, E.; Fésüs, L. Availability of abundant thiamine determines efficiency of thermogenic activation in human neck area derived adipocytes. *J. Nutr. Biochem.* **2023**, *119*, 109385. [CrossRef]
206. Bokhari, M.H.; Halleskog, C.; Shabalina, I.; Bengtsson, T. Use of Isothermal Microcalorimetry to Measure Cellular Heat Production in Thermogenic Adipocytes. *Methods Mol Biol* **2023**, *2662*, 77–85. [CrossRef]
207. Carobbio, S.; Vidal-Puig, A. Differentiation of Human Pluripotent Stem Cells (hPSCs) into Brown-Like Adipocytes. *Methods Mol Biol* **2023**, *2662*, 1–9. [CrossRef]
208. Cero, C.; Shu, W.; Reese, A.L.; Douglas, D.; Maddox, M.; Singh, A.P.; Ali, S.L.; Zhu, A.R.; Katz, J.M.; E Pierce, A.; et al. Standardized In Vitro Models of Human Adipose Tissue Reveal Metabolic Flexibility in Brown Adipocyte Thermogenesis. *Endocrinology* **2023**, *164*. [CrossRef]
209. Dong, M.; An, K.; Mao, L. High levels of uric acid inhibit BAT thermogenic capacity through regulation of AMPK. *Am. J. Physiol. Metab.* **2023**, *325*, E376–E389. [CrossRef]
210. Escudero, M.; Vaysse, L.; Eke, G.; Peyrou, M.; Villarroya, F.; Bonnel, S.; Jeanson, Y.; Boyer, L.; Vieu, C.; Chaput, B.; et al. Scalable Generation of Pre-Vascularized and Functional Human Beige Adipose Organoids. *Adv. Sci.* **2023**, *10*, e2301499. [CrossRef]
211. Fu, T.; Sun, W.; Xue, J.; Zhou, Z.; Wang, W.; Guo, Q.; Chen, X.; Zhou, D.; Xu, Z.; Liu, L.; et al. Proteolytic rewiring of mitochondria by LONP1 directs cell identity switching of adipocytes. *Nat. Cell Biol.* **2023**, *25*, 848–864. [CrossRef]
212. Michurina, S.; Stafeev, I.; Boldyreva, M.; Truong, V.A.; Ratner, E.; Menshikov, M.; Hu, Y.-C.; Parfyonova, Y. Transplantation of Adipose-Tissue-Engineered Constructs with CRISPR-Mediated UCP1 Activation. *Int. J. Mol. Sci.* **2023**, *24*, 3844. [CrossRef]
213. Omran, F.; Murphy, A.M.; Younis, A.Z.; Kyrou, I.; Vrbikova, J.; Hainer, V.; Sramkova, P.; Fried, M.; Ball, G.; Tripathi, G.; et al. The impact of metabolic endotoxaemia on the browning process in human adipocytes. *BMC Med.* **2023**, *21*, 154. [CrossRef]
214. Pagnotta, P.; Gantov, M.; Fletcher, S.; Lombardi, A.; Crosbie, M.L.; Santiso, N.; Ursino, A.; Frascarolli, C.; Amato, A.; Dreszman, R.; et al. Peritumoral adipose tissue promotes lipolysis and white adipocytes browning by paracrine action. *Front. Endocrinol.* **2023**, *14*, 1144016. [CrossRef]
215. Rao, J.; Djeffal, Y.; Chal, J.; Marchianò, F.; Wang, C.-H.; Al Tanoury, Z.; Gapon, S.; Mayeuf-Louchart, A.; Glass, I.; Sefton, E.M.; et al. Reconstructing human brown fat developmental trajectory in vitro. *Dev. Cell* **2023**, *58*, 2359–2375.e8. [CrossRef] [PubMed]
216. Spinelli, S.; Cossu, V.; Passalacqua, M.; Hansen, J.B.; Guida, L.; Magnone, M.; Sambuceti, G.; Marini, C.; Sturla, L.; Zocchi, E. The ABA/LANCL1/2 Hormone/Receptor System Controls Adipocyte Browning and Energy Expenditure. *Int. J. Mol. Sci.* **2023**, *24*, 3489. [CrossRef] [PubMed]
217. Vaittinen, M.; Ilha, M.; Herbers, E.; Wagner, A.; Virtanen, K.A.; Pietiläinen, K.H.; Pirinen, E.; Pihlajamäki, J. Liraglutide demonstrates a therapeutic effect on mitochondrial dysfunction in human SGBS adipocytes in vitro. *Diabetes Res. Clin. Pr.* **2023**, *199*, 110635. [CrossRef] [PubMed]

218. Acosta, F.M.; Stojkova, K.; Zhang, J.; Huitron, E.I.G.; Jiang, J.X.; Rathbone, C.R.; Brey, E.M. Engineering Functional Vascularized Beige Adipose Tissue from Microvascular Fragments of Models of Healthy and Type II Diabetes Conditions. *J. Tissue Eng.* **2022**, *13*. [CrossRef]
219. Al-Ali, M.M.; Khan, A.A.; Fayyad, A.M.; Abdallah, S.H.; Khattak, M.N.K. Transcriptomic profiling of the telomerase transformed Mesenchymal stromal cells derived adipocytes in response to rosiglitazone. *BMC Genet.* **2022**, *23*, 17. [CrossRef]
220. Algieri, C.; Bernardini, C.; Trombetti, F.; Schena, E.; Zannoni, A.; Forni, M.; Nesci, S. Cellular Metabolism and Bioenergetic Function in Human Fibroblasts and Preadipocytes of Type 2 Familial Partial Lipodystrophy. *Int. J. Mol. Sci.* **2022**, *23*, 8659. [CrossRef]
221. Christen, L.; Broghammer, H.; Rapöhn, I.; Möhlis, K.; Strehlau, C.; Ribas-Latre, A.; Gebhardt, C.; Roth, L.; Krause, K.; Landgraf, K.; et al. Myoglobin-mediated lipid shuttling increases adrenergic activation of brown and white adipocyte metabolism and is as a marker of thermogenic adipocytes in humans. *Clin. Transl. Med.* **2022**, *12*, e1108. [CrossRef]
222. Colitti, M.; Ali, U.; Wabitsch, M.; Tews, D. Transcriptomic analysis of Simpson Golabi Behmel syndrome cells during differentiation exhibit BAT-like function. *Tissue Cell* **2022**, *77*, 101822. [CrossRef]
223. Cruciani, S.; Garroni, G.; Pala, R.; Coradduzza, D.; Cossu, M.L.; Ginesu, G.C.; Capobianco, G.; Dessole, S.; Ventura, C.; Maioli, M. Metformin and vitamin D modulate adipose-derived stem cell differentiation towards the beige phenotype. *Adipocyte* **2022**, *11*, 356–365. [CrossRef]
224. Dani, V.; Yao, X.; Bruni-Favier, S.; Dani, C. Embryonic origins of the three types of adipocytes and novel in vitro models for studying the development of human adipocytes. *Medecine des Maladies Metaboliques* **2022**, *16*, 689–695. [CrossRef]
225. Davies, M.R.; Garcia, S.; Liu, M.; Chi, H.; Kim, H.T.; Raffai, R.L.; Liu, X.; Feeley, B.T. Muscle-Derived Beige Adipose Precursors Secrete Promyogenic Exosomes That Treat Rotator Cuff Muscle Degeneration in Mice and Are Identified in Humans by Single-Cell RNA Sequencing. *Am. J. Sports Med.* **2022**, *50*, 2247–2257. [CrossRef]
226. Ferrando, M.; Bruna, F.A.; Romeo, L.R.; Contador, D.; Moya-Morales, D.L.; Santiano, F.; Zyla, L.; Gomez, S.; Lopez-Fontana, C.M.; Calvo, J.C.; et al. Renal peritumoral adipose tissue undergoes a browning process and stimulates the expression of epithelial-mesenchymal transition markers in human renal cells. *Sci. Rep.* **2022**, *12*, 1–10. [CrossRef]
227. Gavaldà-Navarro, A.; Mirra, S.; Manso, Y.; Sánchez-Infantes, D.; Giralt, M.; Soriano, E.; Villarroya, F. The armadillo-repeat containing X-linked protein 3, ARMCX3, is a negative regulator of the browning of adipose tissue associated with obesity. *Int. J. Obes.* **2022**, *46*, 1652–1661. [CrossRef] [PubMed]
228. Guijas, C.; To, A.; Montenegro-Burke, J.R.; Domingo-Almenara, X.; Alipio-Gloria, Z.; Kok, B.P.; Saez, E.; Alvarez, N.H.; Johnson, K.A.; Siuzdak, G. Drug-Initiated Activity Metabolomics Identifies Myristoylglycine as a Potent Endogenous Metabolite for Human Brown Fat Differentiation. *Metabolites* **2022**, *12*, 749. [CrossRef] [PubMed]
229. Hong, P.; Wu, Y.; Zhang, Q.; Liu, P.; Zhang, S.; Yu, M.; Tian, W. Identification of thermogenesis-related lncRNAs in small extracellular vesicles derived from adipose tissue. *BMC Genom.* **2022**, *23*, 660. [CrossRef]
230. Jung, I.; Tu-Sekine, B.; Jin, S.; Anokye-Danso, F.; Ahima, R.S.; Brown, T.T.; Kim, S.F. Dolutegravir Suppresses Thermogenesis via Disrupting Uncoupling Protein 1 Expression and Mitochondrial Function in Brown/Beige Adipocytes in Preclinical Models. *J. Infect. Dis.* **2022**, *226*, 1626–1636. [CrossRef]
231. Kasza, I.; Kühn, J.-P.; Völzke, H.; Hernando, D.; Xu, Y.G.; Siebert, J.W.; Gibson, A.L.F.; Yen, C.L.E.; Nelson, D.W.; MacDougald, O.A.; et al. Contrasting recruitment of skin-associated adipose depots during cold challenge of mouse and human. *J. Physiol.* **2021**. [CrossRef]
232. Monfort-Ferré, D.; Caro, A.; Menacho, M.; Martí, M.; Espina, B.; Boronat-Toscano, A.; Nuñez-Roa, C.; Seco, J.; Bautista, M.; Espín, E.; et al. The Gut Microbiota Metabolite Succinate Promotes Adipose Tissue Browning in Crohn's Disease. *J. Crohn's Colitis* **2022**, *16*, 1571–1583. [CrossRef]
233. Nahmgoong, H.; Jeon, Y.G.; Park, E.S.; Choi, Y.H.; Han, S.M.; Park, J.; Ji, Y.; Sohn, J.H.; Han, J.S.; Kim, Y.Y.; et al. Distinct properties of adipose stem cell subpopulations determine fat depot-specific characteristics. *Cell Metab.* **2022**, *34*, 458–472.e6. [CrossRef]
234. Scheele, C.; Henriksen, T.I.; Nielsen, S. Isolation and Characterization of Human Brown Adipocytes. In *Methods in Molecular Biology*; Humana: New York, NY, USA, 2022; Volume 2448, pp. 217–234.
235. So, J.; Taleb, S.; Wann, J.; Strobel, O.; Kim, K.; Roh, H.C. Chronic cAMP activation induces adipocyte browning through discordant biphasic remodeling of transcriptome and chromatin accessibility. *Mol. Metab.* **2022**, *66*, 101619. [CrossRef]
236. Solivan-Rivera, J.; Loureiro, Z.Y.; DeSouza, T.; Desai, A.; Pallat, S.; Yang, Q.; Rojas-Rodriguez, R.; Ziegler, R.; Skritakis, P.; Joyce, S.; et al. A neurogenic signature involving monoamine Oxidase-A controls human thermogenic adipose tissue development. *eLife* **2022**, *11*. [CrossRef] [PubMed]
237. Wang, Q.; Li, H.; Tajima, K.; Verkerke, A.R.P.; Taxin, Z.H.; Hou, Z.; Cole, J.B.; Li, F.; Wong, J.; Abe, I.; et al. Post-translational control of beige fat biogenesis by PRDM16 stabilization. *Nature* **2022**, *609*, 151–158. [CrossRef] [PubMed]
238. Yao, X.; Dani, C. A Simple Method for Generating, Clearing, and Imaging Pre-vascularized 3D Adipospheres Derived from Human iPS Cells. *Methods Mol Biol* **2022**, *2454*, 495–507. [CrossRef]

239. Zhang, P.; Wu, W.; Du, C.; Ji, X.; Wang, Y.; Han, Q.; Xu, H.; Li, C.; Xu, Y. RNA-seq profiling of white and brown adipocyte differentiation treated with epigallocatechin gallate. *Sci. Data* **2022**, *9*, 1–8. [CrossRef] [PubMed]
240. Bové, M.; Monto, F.; Guillem-Llobat, P.; Ivorra, M.D.; Noguera, M.A.; Zambrano, A.; Sirerol-Piquer, M.S.; Requena, A.C.; García-Alonso, M.; Tejerina, T.; et al. NT3/TrkC Pathway Modulates the Expression of UCP-1 and Adipocyte Size in Human and Rodent Adipose Tissue. *Front. Endocrinol.* **2021**, *12*, 630097. [CrossRef]
241. Breining, P.; Pedersen, S.B.; Kjolby, M.; Hansen, J.B.; Jessen, N.; Richelsen, B. Parathyroid hormone receptor stimulation induces human adipocyte lipolysis and browning. *Eur. J. Endocrinol.* **2021**, *184*, 687–697. [CrossRef]
242. Carobbio, S.; Guenantin, A.-C.; Bahri, M.; Rodriguez-Fdez, S.; Honig, F.; Kamzolas, I.; Samuelson, I.; Long, K.; Awad, S.; Lukovic, D.; et al. Unraveling the Developmental Roadmap toward Human Brown Adipose Tissue. *Stem Cell Rep.* **2021**, *16*, 641–655. [CrossRef]
243. Chakraborty, S.; Ong, W.K.; Yau, W.W.Y.; Zhou, Z.; Prakash, K.N.B.; Toh, S.-A.; Han, W.; Yen, P.M.; Sugii, S. CD10 marks non-canonical PPARγ-independent adipocyte maturation and browning potential of adipose-derived stem cells. *Stem Cell Res. Ther.* **2021**, *12*, 1–13. [CrossRef]
244. Chen, X.; He, X.; Guo, Y.; Liu, L.; Li, H.; Tan, J.; Feng, W.; Guan, H.; Cao, X.; Xiao, H.; et al. Glucose-dependent insulinotropic polypeptide modifies adipose plasticity and promotes beige adipogenesis of human omental adipose-derived stem cells. *FASEB J.* **2021**, *35*, e21534. [CrossRef]
245. Lao-On, U.; Cliff, T.S.; Dalton, S.; Jitrapakdee, S. Pyruvate carboxylase supports basal ATP-linked respiration in human pluripotent stem cell-derived brown adipocytes. *Biochem. Biophys. Res. Commun.* **2021**, *569*, 139–146. [CrossRef]
246. Meng, W.; Xiao, T.; Liang, X.; Wen, J.; Peng, X.; Wang, J.; Zou, Y.; Liu, J.; Bialowas, C.; Luo, H.; et al. The miR-182-5p/FGF21/acetylcholine axis mediates the crosstalk between adipocytes and macrophages to promote beige fat thermogenesis. *J. Clin. Investig.* **2021**, *6*. [CrossRef]
247. Senamontree, S.; Lakthan, T.; Charoenpanich, P.; Chanchao, C.; Charoenpanich, A. Betulinic acid decreases lipid accumulation in adipogenesis-induced human mesenchymal stem cells with upregulation of *PGC-1α* and *UCP-1* and post-transcriptional downregulation of adiponectin and leptin secretion. *PeerJ* **2021**, *9*, e12321. [CrossRef]
248. Shaw, A.; Tóth, B.B.; Király, R.; Arianti, R.; Csomós, I.; Póliska, S.; Vámos, A.; Korponay-Szabó, I.R.; Bacso, Z.; Győry, F.; et al. Irisin Stimulates the Release of CXCL1 from Differentiating Human Subcutaneous and Deep-Neck Derived Adipocytes via Upregulation of NFκB Pathway. *Front. Cell Dev. Biol.* **2021**, *9*, 737872. [CrossRef]
249. Takeda, Y.; Yoshikawa, T.; Dai, P. Transcriptome analysis reveals brown adipogenic reprogramming in chemical compound-induced brown adipocytes converted from human dermal fibroblasts. *Sci. Rep.* **2021**, *11*, 1–13. [CrossRef]
250. van Krieken, P.P.; Odermatt, T.S.; Borsigova, M.; Blüher, M.; Wueest, S.; Konrad, D. Oncostatin M suppresses browning of white adipocytes via gp130-STAT3 signaling. *Mol. Metab.* **2021**, *54*, 101341. [CrossRef]
251. Bai, N.; Ma, J.; Alimujiang, M.; Xu, J.; Hu, F.; Xu, Y.; Leng, Q.; Chen, S.; Li, X.; Han, J.; et al. Bola3 Regulates Beige Adipocyte Thermogenesis via Maintaining Mitochondrial Homeostasis and Lipolysis. *Front. Endocrinol.* **2021**, *11*, 592154. [CrossRef]
252. Cattaneo, P.; Mukherjee, D.; Spinozzi, S.; Zhang, L.; Larcher, V.; Stallcup, W.B.; Kataoka, H.; Chen, J.; Dimmeler, S.; Evans, S.M.; et al. Parallel Lineage-Tracing Studies Establish Fibroblasts as the Prevailing In Vivo Adipocyte Progenitor. *Cell Rep.* **2020**, *30*, 571–582.e2. [CrossRef]
253. Colson, C.; Batrow, P.-L.; Gautier, N.; Rochet, N.; Ailhaud, G.; Peiretti, F.; Amri, E.-Z. The *Rosmarinus* Bioactive Compound Carnosic Acid Is a Novel PPAR Antagonist That Inhibits the Browning of White Adipocytes. *Cells* **2020**, *9*, 2433. [CrossRef]
254. Dahlhaus, M.; Roos, J.; Engel, D.; Tews, D.; Halbgebauer, D.; Funcke, J.-B.; Kiener, S.; Schuler, P.J.; Döscher, J.; Hoffmann, T.K.; et al. CD90 Is Dispensable for White and Beige/Brown Adipocyte Differentiation. *Int. J. Mol. Sci.* **2020**, *21*, 7907. [CrossRef]
255. Ferrari, A.; Longo, R.; Peri, C.; Coppi, L.; Caruso, D.; Mai, A.; Mitro, N.; De Fabiani, E.; Crestani, M. Inhibition of class I HDACs imprints adipogenesis toward oxidative and brown-like phenotype. *Biochim. et Biophys. Acta (BBA) - Mol. Cell Biol. Lipids* **2020**, *1865*, 158594. [CrossRef]
256. Frühbeck, G.; Fernández-Quintana, B.; Paniagua, M.; Hernández-Pardos, A.W.; Valentí, V.; Moncada, R.; Catalán, V.; Becerril, S.; Gómez-Ambrosi, J.; Portincasa, P.; et al. FNDC4, a novel adipokine that reduces lipogenesis and promotes fat browning in human visceral adipocytes. *Metabolism* **2020**, *108*, 154261. [CrossRef] [PubMed]
257. Han, K.H.; Arlian, B.M.; Lin, C.-W.; Jin, H.Y.; Kang, G.-H.; Lee, S.; Lee, P.C.-W.; Lerner, R.A. Agonist Antibody Converts Stem Cells into Migrating Brown Adipocyte-Like Cells in Heart. *Cells* **2020**, *9*, 256. [CrossRef]
258. Jung, Y.J.; Kim, H.K.; Cho, Y.; Choi, J.S.; Woo, C.H.; Lee, K.S.; Sul, J.H.; Lee, C.M.; Han, J.; Park, J.H.; et al. Cell reprogramming using extracellular vesicles from differentiating stem cells into white/beige adipocytes. *Sci. Adv.* **2020**, *6*, eaay6721. [CrossRef]
259. Leménager, H.; Fiévet, L.M.A.; Guilloton, F.; Naji, A.; Descamps, J.-G.; Chaput, B.; Suganuma, N.; Pagès, J.-C.; Sensebé, L.; Carrière, A.; et al. Cell immaturity and white/beige adipocyte potential of primary human adipose-derived stromal cells are restrained by culture-medium TGFβ1. *STEM CELLS* **2020**, *38*, 782–796. [CrossRef] [PubMed]
260. Leija, H.A.L.; Velickovic, K.; Bloor, I.; Sacks, H.; Symonds, M.E.; Sottile, V. Cold-induced beigeing of stem cell-derived adipocytes is not fully reversible after return to normothermia. *J. Cell. Mol. Med.* **2020**, *24*, 11434–11444. [CrossRef] [PubMed]

261. Nilsen, M.S.; Jersin, R.Å.; Ulvik, A.; Madsen, A.; McCann, A.; Svensson, P.-A.; Svensson, M.K.; Nedrebø, B.G.; Gudbrandsen, O.A.; Tell, G.S.; et al. 3-Hydroxyisobutyrate, A Strong Marker of Insulin Resistance in Type 2 Diabetes and Obesity That Modulates White and Brown Adipocyte Metabolism. *Diabetes* **2020**, *69*, 1903–1916. [CrossRef]
262. de Oliveira, M.; Mathias, L.S.; Rodrigues, B.M.; Mariani, B.G.; Graceli, J.B.; De Sibio, M.T.; Olimpio, R.M.C.; Moretto, F.C.F.; Deprá, I.C.; Nogueira, C.R. The roles of triiodothyronine and irisin in improving the lipid profile and directing the browning of human adipose subcutaneous cells. *Mol. Cell. Endocrinol.* **2020**, *506*, 110744. [CrossRef]
263. Park, M.; Liao, J.; Kim, D. TC-E 5003, a protein methyltransferase 1 inhibitor, activates the PKA-dependent thermogenic pathway in primary murine and human subcutaneous adipocytes. *FEBS Lett.* **2020**, *594*, 2923–2930. [CrossRef]
264. Takeda, Y.; Dai, P. A developed serum-free medium and an optimized chemical cocktail for direct conversion of human dermal fibroblasts into brown adipocytes. *Sci. Rep.* **2020**, *10*, 1–13. [CrossRef]
265. Vasileva, L.V.; Savova, M.S.; Amirova, K.M.; Balcheva-Sivenova, Z.; Ferrante, C.; Orlando, G.; Wabitsch, M.; Georgiev, M.I. Caffeic and Chlorogenic Acids Synergistically Activate Browning Program in Human Adipocytes: Implications of AMPK- and PPAR-Mediated Pathways. *Int. J. Mol. Sci.* **2020**, *21*, 9740. [CrossRef] [PubMed]
266. Zhang, L.; Avery, J.; Yin, A.; Singh, A.M.; Cliff, T.S.; Yin, H.; Dalton, S. Generation of Functional Brown Adipocytes from Human Pluripotent Stem Cells via Progression through a Paraxial Mesoderm State. *Cell Stem Cell* **2020**, *27*, 784–797.e11. [CrossRef] [PubMed]
267. Zlatska, A.V.; Vasyliev, R.G.; Gordiienko, I.M.; Rodnichenko, A.E.; Morozova, M.A.; Vulf, M.A.; Zubov, D.O.; Novikova, S.N.; Litvinova, L.S.; Grebennikova, T.V.; et al. Effect of the deuterium on efficiency and type of adipogenic differentiation of human adipose-derived stem cells in vitro. *Sci. Rep.* **2020**, *10*, 1–16. [CrossRef]
268. Wu, C.; Zhang, H.; Lin, X.; Zeng, Y.; Zhang, Y.; Ma, X.; Xue, Y.; Guan, M. Role of PDK4 in insulin signaling pathway in periadrenal adipose tissue of pheochromocytoma patients. *Endocrine-Related Cancer* **2020**, *27*, 583–589. [CrossRef]
269. Chen, Y.; Ikeda, K.; Yoneshiro, T.; Scaramozza, A.; Tajima, K.; Wang, Q.; Kim, K.; Shinoda, K.; Sponton, C.H.; Brown, Z.; et al. Thermal stress induces glycolytic beige fat formation via a myogenic state. *Nature* **2019**, *565*, 180–185. [CrossRef] [PubMed]
270. Comas, F.; Martínez, C.; Sabater, M.; Ortega, F.; Latorre, J.; Díaz-Sáez, F.; Aragonés, J.; Camps, M.; Gumà, A.; Ricart, W.; et al. Neuregulin 4 Is a Novel Marker of Beige Adipocyte Precursor Cells in Human Adipose Tissue. *Front. Physiol.* **2019**, *10*, 39. [CrossRef]
271. Christian, M. In vitro models for study of brown adipocyte biology. In *Handbook of Experimental Pharmacology*; Springer: Cham, Switzerland, 2019; Volume 251, pp. 85–96.
272. Fayyad, A.M.; Khan, A.A.; Abdallah, S.H.; Alomran, S.S.; Bajou, K.; Khattak, M.N.K. Rosiglitazone Enhances Browning Adipocytes in Association with MAPK and PI3-K Pathways During the Differentiation of Telomerase-Transformed Mesenchymal Stromal Cells into Adipocytes. *Int. J. Mol. Sci.* **2019**, *20*, 1618. [CrossRef]
273. Harms, M.J.; Li, Q.; Lee, S.; Zhang, C.; Kull, B.; Hallen, S.; Thorell, A.; Alexandersson, I.; Hagberg, C.E.; Peng, X.-R.; et al. Mature Human White Adipocytes Cultured under Membranes Maintain Identity, Function, and Can Transdifferentiate into Brown-like Adipocytes. *Cell Rep.* **2019**, *27*, 213–225.e5. [CrossRef]
274. Klusóczki, Á.; Veréb, Z.; Vámos, A.; Fischer-Posovszky, P.; Wabitsch, M.; Bacso, Z.; Fésüs, L.; Kristóf, E. Differentiating SGBS adipocytes respond to PPARγ stimulation, irisin and BMP7 by functional browning and beige characteristics. *Sci. Rep.* **2019**, *9*, 1–12. [CrossRef]
275. Lee, M.-J.; Jash, S.; Jones, J.E.C.; Puri, V.; Fried, S.K. Rosiglitazone remodels the lipid droplet and britens human visceral and subcutaneous adipocytes ex vivo. *J. Lipid Res.* **2019**, *60*, 856–868. [CrossRef]
276. Pellegrini, C.; Columbaro, M.; Schena, E.; Prencipe, S.; Andrenacci, D.; Iozzo, P.; Guzzardi, M.A.; Capanni, C.; Mattioli, E.; Loi, M.; et al. Altered adipocyte differentiation and unbalanced autophagy in type 2 Familial Partial Lipodystrophy: An in vitro and in vivo study of adipose tissue browning. *Exp. Mol. Med.* **2019**, *51*, 1–17. [CrossRef]
277. Tews, D.; Pula, T.; Funcke, J.; Jastroch, M.; Keuper, M.; Debatin, K.; Wabitsch, M.; Fischer-Posovszky, P. Elevated UCP1 levels are sufficient to improve glucose uptake in human white adipocytes. *Redox Biol.* **2019**, *26*, 101286. [CrossRef]
278. Hafner, A.L.; Mohsen-Kanson, T.; Dani, C. Differentiation of brown adipocyte progenitors derived from human induced pluripotent stem cells. In *Methods in Molecular Biology*; Humana: New York, NY, USA, 2018; Volume 1773, pp. 31–39.
279. Hagberg, C.E.; Li, Q.; Kutschke, M.; Bhowmick, D.; Kiss, E.; Shabalina, I.G.; Harms, M.J.; Shilkova, O.; Kozina, V.; Nedergaard, J.; et al. Flow Cytometry of Mouse and Human Adipocytes for the Analysis of Browning and Cellular Heterogeneity. *Cell Rep.* **2018**, *24*, 2746–2756.e5. [CrossRef]
280. Ju, L.; Chen, S.; Alimujiang, M.; Bai, N.; Yan, H.; Fang, Q.; Han, J.; Ma, X.; Yang, Y.; Jia, W. A novel role for Bcl2l13 in promoting beige adipocyte biogenesis. *Biochem. Biophys. Res. Commun.* **2018**, *506*, 485–491. [CrossRef] [PubMed]
281. Montanari, T.; Colitti, M. Simpson–Golabi–Behmel syndrome human adipocytes reveal a changing phenotype throughout differentiation. *Histochem.* **2018**, *149*, 593–605. [CrossRef]
282. Mukherjee, S.; Zhang, T.; Lacko, L.A.; Tan, L.; Xiang, J.Z.; Butler, J.M.; Chen, S. Derivation and characterization of a UCP1 reporter human ES cell line. *Stem Cell Res.* **2018**, *30*, 12–21. [CrossRef]

283. Nakamura, K.; Kishida, T.; Ejima, A.; Tateyama, R.; Morishita, S.; Ono, T.; Murakoshi, M.; Sugiyama, K.; Nishino, H.; Mazda, O. Bovine lactoferrin promotes energy expenditure via the cAMP-PKA signaling pathway in human reprogrammed brown adipocytes. *BioMetals* **2018**, *31*, 415–424. [CrossRef]
284. Schmidt, E.; Dhaouadi, I.; Gaziano, I.; Oliverio, M.; Klemm, P.; Awazawa, M.; Mitterer, G.; Fernandez-Rebollo, E.; Pradas-Juni, M.; Wagner, W.; et al. LincRNA H19 protects from dietary obesity by constraining expression of monoallelic genes in brown fat. *Nat. Commun.* **2018**, *9*, 1–16. [CrossRef] [PubMed]
285. Tang, Y.; He, Y.; Li, C.; Mu, W.; Zou, Y.; Liu, C.; Qian, S.; Zhang, F.; Pan, J.; Wang, Y.; et al. RPS3A positively regulates the mitochondrial function of human periaortic adipose tissue and is associated with coronary artery diseases. *Cell Discov.* **2018**, *4*, 52. [CrossRef] [PubMed]
286. Zahid, H.; Subbaramaiah, K.; Iyengar, N.M.; Zhou, X.K.; Chen, I.-C.; Bhardwaj, P.; Gucalp, A.; Morrow, M.; A Hudis, C.; Dannenberg, A.J.; et al. Leptin regulation of the p53-HIF1α/PKM2-aromatase axis in breast adipose stromal cells: A novel mechanism for the obesity–breast cancer link. *Int. J. Obes.* **2017**, *42*, 711–720. [CrossRef]
287. Chechi, K.; Voisine, P.; Mathieu, P.; Laplante, M.; Bonnet, S.; Picard, F.; Joubert, P.; Richard, D. Functional characterization of the Ucp1-associated oxidative phenotype of human epicardial adipose tissue. *Sci. Rep.* **2017**, *7*, 1–15. [CrossRef]
288. Finlin, B.S.; Zhu, B.; Confides, A.L.; Westgate, P.M.; Harfmann, B.D.; Dupont-Versteegden, E.E.; Kern, P.A. Mast Cells Promote Seasonal White Adipose Beiging in Humans. *Diabetes* **2017**, *66*, 1237–1246. [CrossRef]
289. Guénantin, A.-C.; Briand, N.; Capel, E.; Dumont, F.; Morichon, R.; Provost, C.; Stillitano, F.; Jeziorowska, D.; Siffroi, J.-P.; Hajjar, R.J.; et al. Functional Human Beige Adipocytes from Induced Pluripotent Stem Cells. *Diabetes* **2017**, *66*, 1470–1478. [CrossRef] [PubMed]
290. Hafner, A.L.; Dani, C. Adipocyte progenitors from human pluripotent stem cells. In *Adipose Tissue Biology*, 2nd ed.; Springer: Cham, Switzerland, 2017; pp. 61–68.
291. Kriszt, R.; Arai, S.; Itoh, H.; Lee, M.H.; Goralczyk, A.G.; Ang, X.M.; Cypess, A.M.; White, A.P.; Shamsi, F.; Xue, R.; et al. Optical visualisation of thermogenesis in stimulated single-cell brown adipocytes. *Sci. Rep.* **2017**, *7*, 1383. [CrossRef]
292. Markussen, L.K.; Isidor, M.S.; Breining, P.; Andersen, E.S.; Rasmussen, N.E.; Petersen, L.I.; Pedersen, S.B.; Richelsen, B.; Hansen, J.B.; Alemany, M. Characterization of immortalized human brown and white pre-adipocyte cell models from a single donor. *PLoS ONE* **2017**, *12*, e0185624. [CrossRef] [PubMed]
293. Maurizi, G.; Poloni, A.; Mattiucci, D.; Santi, S.; Maurizi, A.; Izzi, V.; Giuliani, A.; Mancini, S.; Zingaretti, M.C.; Perugini, J.; et al. Human White Adipocytes Convert Into "Rainbow" Adipocytes In Vitro. *J. Cell. Physiol.* **2016**, *232*, 2887–2899. [CrossRef] [PubMed]
294. Shamsi, F.; Tseng, Y.H. Protocols for Generation of Immortalized Human Brown and White Preadipocyte Cell Lines. *Methods Mol Biol* **2017**, *1566*, 77–85. [CrossRef]
295. Takeda, Y.; Harada, Y.; Yoshikawa, T.; Dai, P. Direct conversion of human fibroblasts to brown adipocytes by small chemical compounds. *Sci. Rep.* **2017**, *7*, 1–11. [CrossRef]
296. Tews, D.; Fromme, T.; Keuper, M.; Hofmann, S.; Debatin, K.; Klingenspor, M.; Wabitsch, M.; Fischer-Posovszky, P. Teneurin-2 (TENM2) deficiency induces UCP1 expression in differentiating human fat cells. *Mol. Cell. Endocrinol.* **2017**, *443*, 106–113. [CrossRef]
297. Yeo, C.R.; Agrawal, M.; Hoon, S.; Shabbir, A.; Shrivastava, M.K.; Huang, S.; Khoo, C.M.; Chhay, V.; Yassin, M.S.; Tai, E.S.; et al. SGBS cells as a model of human adipocyte browning: A comprehensive comparative study with primary human white subcutaneous adipocytes. *Sci. Rep.* **2017**, *7*, 1–12. [CrossRef]
298. Zou, Y.; Lu, P.; Shi, J.; Liu, W.; Yang, M.; Zhao, S.; Chen, N.; Chen, M.; Sun, Y.; Gao, A.; et al. IRX3 Promotes the Browning of White Adipocytes and Its Rare Variants are Associated with Human Obesity Risk. *EBioMedicine* **2017**, *24*, 64–75. [CrossRef] [PubMed]
299. Adeniran-Catlett, A.E.; Weinstock, L.D.; Bozal, F.K.; Beguin, E.; Caraballo, A.T.; Murthy, S.K. Accelerated adipogenic differentiation of hMSCs in a microfluidic shear stimulation platform. *Biotechnol. Prog.* **2015**, *32*, 440–446. [CrossRef] [PubMed]
300. Gavaldà-Navarro, A.; Moreno-Navarrete, J.M.; Quesada-López, T.; Cairó, M.; Giralt, M.; Fernández-Real, J.M.; Villarroya, F. Lipopolysaccharide-binding protein is a negative regulator of adipose tissue browning in mice and humans. *Diabetologia* **2016**, *59*, 2208–2218. [CrossRef]
301. Ghandour, R.A.; Giroud, M.; Vegiopoulos, A.; Herzig, S.; Ailhaud, G.; Amri, E.-Z.; Pisani, D.F. IP-receptor and PPARs trigger the conversion of human white to brite adipocyte induced by carbaprostacyclin. *Biochim. et Biophys. Acta (BBA) - Mol. Cell Biol. Lipids* **2016**, *1861*, 285–293. [CrossRef] [PubMed]
302. Giroud, M.; Pisani, D.F.; Karbiener, M.; Barquissau, V.; Ghandour, R.A.; Tews, D.; Fischer-Posovszky, P.; Chambard, J.-C.; Knippschild, U.; Niemi, T.; et al. miR-125b affects mitochondrial biogenesis and impairs brite adipocyte formation and function. *Mol. Metab.* **2016**, *5*, 615–625. [CrossRef]
303. Hafner, A.-L.; Contet, J.; Ravaud, C.; Yao, X.; Villageois, P.; Suknuntha, K.; Annab, K.; Peraldi, P.; Binetruy, B.; Slukvin, I.I.; et al. Brown-like adipose progenitors derived from human induced pluripotent stem cells: Identification of critical pathways governing their adipogenic capacity. *Sci. Rep.* **2016**, *6*, 32490. [CrossRef]

304. Hankir, M.K.; Kranz, M.; Gnad, T.; Weiner, J.; Wagner, S.; Deuther-Conrad, W.; Bronisch, F.; Steinhoff, K.; Luthardt, J.; Klöting, N.; et al. A novel thermoregulatory role for PDE 10A in mouse and human adipocytes. *EMBO Mol. Med.* **2016**, *8*, 796–812. [CrossRef]
305. Huttala, O.; Mysore, R.; Sarkanen, J.R.; Heinonen, T.; Olkkonen, V.M.; Ylikomi, T. Differentiation of human adipose stromal cells in vitro into insulin-sensitive adipocytes. *Cell Tissue Res.* **2016**, *366*, 63–74. [CrossRef]
306. Laiglesia, L.; Lorente-Cebrián, S.; Prieto-Hontoria, P.; Fernández-Galilea, M.; Ribeiro, S.; Sáinz, N.; Martínez, J.; Moreno-Aliaga, M. Eicosapentaenoic acid promotes mitochondrial biogenesis and beige-like features in subcutaneous adipocytes from overweight subjects. *J. Nutr. Biochem.* **2016**, *37*, 76–82. [CrossRef]
307. Pisani, D.F.; Dumortier, O.; Beranger, G.E.; Casamento, V.; Ghandour, R.A.; Giroud, M.; Gautier, N.; Balaguer, T.; Chambard, J.-C.; Virtanen, K.A.; et al. Visfatin expression analysis in association with recruitment and activation of human and rodent brown and brite adipocytes. *Adipocyte* **2016**, *5*, 186–195. [CrossRef] [PubMed]
308. Shukla, A.; Slater, J.H.; Culver, J.C.; Dickinson, M.E.; West, J.L. Biomimetic Surface Patterning Promotes Mesenchymal Stem Cell Differentiation. *ACS Appl. Mater. Interfaces* **2015**, *8*, 21883–21892. [CrossRef]
309. Zhang, Y.; Xie, C.; Wang, H.; Foss, R.M.; Clare, M.; George, E.V.; Li, S.; Katz, A.; Cheng, H.; Ding, Y.; et al. Irisin exerts dual effects on browning and adipogenesis of human white adipocytes. *Am. J. Physiol. Metab.* **2016**, *311*, E530–E541. [CrossRef]
310. Docanto, M.M.; Ham, S.; Corbould, A.; Brown, K.A. Obesity-Associated Inflammatory Cytokines and Prostaglandin E2 Stimulate Glucose Transporter mRNA Expression and Glucose Uptake in Primary Human Adipose Stromal Cells. *J. Interf. Cytokine Res.* **2015**, *35*, 600–605. [CrossRef] [PubMed]
311. Fernández-Galilea, M.; Pérez-Matute, P.; Prieto-Hontoria, P.L.; Houssier, M.; Burrell, M.A.; Langin, D.; Martínez, J.A.; Moreno-Aliaga, M.J. α-Lipoic acid treatment increases mitochondrial biogenesis and promotes beige adipose features in subcutaneous adipocytes from overweight/obese subjects. *Biochim. et Biophys. Acta (BBA) - Mol. Cell Biol. Lipids* **2015**, *1851*, 273–281. [CrossRef] [PubMed]
312. Guennoun, A.; Kazantzis, M.; Thomas, R.; Wabitsch, M.; Tews, D.; Sastry, K.S.; Abdelkarim, M.; Zilberfarb, V.; Strosberg, A.D.; Chouchane, L. Comprehensive molecular characterization of human adipocytes reveals a transient brown phenotype. *J. Transl. Med.* **2015**, *13*, 1–18. [CrossRef]
313. Lin, W.-C.; Shih, P.-H.; Wang, W.; Wu, C.-H.; Hsia, S.-M.; Wang, H.-J.; Hwang, P.-A.; Wang, C.-Y.; Chen, S.-H.; Kuo, Y.-T. Inhibitory effects of high stability fucoxanthin on palmitic acid-induced lipid accumulation in human adipose-derived stem cells through modulation of long non-coding RNA. *Food Funct.* **2015**, *6*, 2215–2223. [CrossRef]
314. Moisan, A.; Lee, Y.-K.; Zhang, J.D.; Hudak, C.S.; Meyer, C.A.; Prummer, M.; Zoffmann, S.; Truong, H.H.; Ebeling, M.; Kiialainen, A.; et al. White-to-brown metabolic conversion of human adipocytes by JAK inhibition. *Nat. Cell Biol.* **2014**, *17*, 57–67. [CrossRef]
315. Moreno-Navarrete, J.M.; Ortega, F.; Moreno, M.; Xifra, G.; Ricart, W.; Fernández-Real, J.M. PRDM16 sustains white fat gene expression profile in human adipocytes in direct relation with insulin action. *Mol. Cell. Endocrinol.* **2015**, *405*, 84–93. [CrossRef]
316. Nagano, G.; Ohno, H.; Oki, K.; Kobuke, K.; Shiwa, T.; Yoneda, M.; Kohno, N.; Bartolomucci, A. Activation of Classical Brown Adipocytes in the Adult Human Perirenal Depot Is Highly Correlated with PRDM16–EHMT1 Complex Expression. *PLoS ONE* **2015**, *10*, e0122584. [CrossRef]
317. Shinoda, K.; Luijten, I.H.N.; Hasegawa, Y.; Hong, H.; Sonne, S.B.; Kim, M.; Xue, R.; Chondronikola, M.; Cypess, A.M.; Tseng, Y.-H.; et al. Genetic and functional characterization of clonally derived adult human brown adipocytes. *Nat. Med.* **2015**, *21*, 389–394. [CrossRef]
318. Strong, A.L.; Ohlstein, J.F.; Biagas, B.A.; Rhodes, L.V.; Pei, D.T.; Tucker, H.A.; Llamas, C.; Bowles, A.C.; Dutreil, M.F.; Zhang, S.; et al. Leptin produced by obese adipose stromal/stem cells enhances proliferation and metastasis of estrogen receptor positive breast cancers. *Breast Cancer Res.* **2015**, *17*, 1–16. [CrossRef]
319. Yoneshiro, T.; Saito, M. Activation and recruitment of brown adipose tissue as anti-obesity regimens in humans. *Ann. Med.* **2014**, *47*, 133–141. [CrossRef]
320. Bugge, A.; Dib, L.; Collins, S. Measuring Respiratory Activity of Adipocytes and Adipose Tissues in Real Time. In *Methods of Adipose Tissue Biology, Part B*; Academic Press: Cambridge, MA, USA, 2014; Volume 538, pp. 233–247.
321. De Sousa, M.; Porras, D.P.; Perry, C.G.R.; Seale, P.; Scimè, A. p107 Is a Crucial Regulator for Determining the Adipocyte Lineage Fate Choices of Stem Cells. *STEM CELLS* **2014**, *32*, 1323–1336. [CrossRef]
322. Lee, Y.K.; Cowan, C.A. Differentiation of white and brown adipocytes from human pluripotent stem cells. *Methods Enzymol* **2014**, *538*, 35–47. [CrossRef]
323. Li, Y.; Fromme, T.; Schweizer, S.; Schöttl, T.; Klingenspor, M. Taking control over intracellular fatty acid levels is essential for the analysis of thermogenic function in cultured primary brown and brite/beige adipocytes. *Embo Rep.* **2014**, *15*, 1069–1076. [CrossRef]
324. Mohsen-Kanson, T.; Hafner, A.-L.; Wdziekonski, B.; Takashima, Y.; Villageois, P.; Carrière, A.; Svensson, M.; Bagnis, C.; Chignon-Sicard, B.; Svensson, P.-A.; et al. Differentiation of Human Induced Pluripotent Stem Cells into Brown and White Adipocytes: Role of Pax3. *STEM CELLS* **2014**, *32*, 1459–1467. [CrossRef]

325. Obregon, M.-J. *Changing white into brite adipocytes*. Focus on "BMP4 and BMP7 induce the white-to-brown transition of primary human adipose stem cells". *Am. J. Physiol. Physiol.* **2014**, *306*, C425–C427. [CrossRef]
326. Aune, U.L.; Ruiz, L.; Kajimura, S. Isolation and Differentiation of Stromal Vascular Cells to Beige/Brite Cells. *J. Vis. Exp.* **2013**, e50191. [CrossRef]
327. Beranger, G.E.; Karbiener, M.; Barquissau, V.; Pisani, D.F.; Scheideler, M.; Langin, D.; Amri, E.-Z. In vitro brown and "brite"/"beige" adipogenesis: Human cellular models and molecular aspects. *Biochim. et Biophys. Acta (BBA) - Mol. Cell Biol. Lipids* **2013**, *1831*, 905–914. [CrossRef]
328. Chung, S.; Okla, M.; Ha, J.-H.; Lee, M.A. Brown adipocyte commitment of primary human adipose stem cells in vitro. *FASEB J.* **2012**, *26*, 819.9. [CrossRef]
329. Elefanty, A.G.; Stanley, E.G. Efficient generation of adipocytes in a dish. *Nat. Cell Biol.* **2012**, *14*, 126–127. [CrossRef]
330. Nishio, M.; Yoneshiro, T.; Nakahara, M.; Suzuki, S.; Saeki, K.; Hasegawa, M.; Kawai, Y.; Akutsu, H.; Umezawa, A.; Yasuda, K.; et al. Production of Functional Classical Brown Adipocytes from Human Pluripotent Stem Cells using Specific Hemopoietin Cocktail without Gene Transfer. *Cell Metab.* **2012**, *16*, 394–406. [CrossRef]
331. Huang, P.-I.; Chen, Y.-C.; Chen, L.-H.; Juan, C.-C.; Ku, H.-H.; Wang, S.-T.; Chiou, S.-H.; Chiou, G.-Y.; Chi, C.-W.; Hsu, C.-C.; et al. PGC-1α Mediates Differentiation of Mesenchymal Stem Cells to Brown Adipose Cells. *J. Atheroscler. Thromb.* **2011**, *18*, 966–980. [CrossRef]
332. MacKay, D.L.; Tesar, P.J.; Liang, L.; Haynesworth, S.E. Characterizing medullary and human mesenchymal stem cell-derived adipocytes. *J. Cell. Physiol.* **2006**, *207*, 722–728. [CrossRef]
333. Zilberfarb, V.; Piétri-Rouxel, F.; Jockers, R.; Krief, S.; Delouis, C.; Issad, T.; Strosberg, A.D. Human immortalized brown adipocytes express functional β3-adrenoceptor coupled to lipolysis. *J. Cell Sci.* **1997**, *110*, 801–807. [CrossRef]

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