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Fighting obesity by targeting factors regulating beige adipocytes

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Abstract

Purpose of review—The current review provides an update on secreted factors and mechanisms that promote a thermogenic program in beige adipocytes, and their potential roles as therapeutic targets to fight obesity.

Recent findings—We outline recent studies revealing unrecognized mechanisms controlling beige adipocyte physiology, and summarize in particular those that underlie beige thermogenesis independently of classical uncoupling. We also update strategies aimed at fostering beige adipogenesis and white-to beige adipocyte conversion. Finally, we summarize newly identified endogenous secreted factors that promote the thermogenic activation of beige adipocytes and discuss their therapeutic potential.

Summary—The identification of novel endogenous factors that promote beiging and regulate beige adipocyte-specific physiological pathways opens up new avenues for therapeutic engineering targeting obesity and related metabolic disorders.

Keywords

beige adipocyte; brown adipose tissue; metabolic disease; obesity; secreted factors; thermogenesis; uncoupling protein-1

INTRODUCTION

Obesity and consequent metabolic disorders, such as type 2 diabetes, are an increasingly serious global health problem and reflect a need for more comprehensive and effective strategies for prevention, treatment, and even reversal. Given that obesity results when bodily energy intake exceeds expenditure, one potential solution would be to increase energy expenditure. Indeed, tunable strategies to minimally enhance energy expenditure over prolonged periods of time could both prevent and potentially reverse obesity without

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substantial risk for unwanted off-target effects. This review discusses several avenues of progress towards this goal.

Adipose tissue maintains the critical balance between lipid storage and utilization for energy. Two basic types of adipose tissue have been identified – white adipose tissue (WAT), which is responsible for storage of excess triglycerides, and brown adipose tissue (BAT), which is specialized to dissipate energy by producing heat. One key difference between WAT and BAT is that the latter expresses uncoupling protein-1 (UCP1), a transmembrane protein in mitochondria that is responsible for heat generation.

Additionally, precursor cells existing mainly within subcutaneous WAT depots can be stimulated to differentiate into thermogenic 'beige' or 'brite' adipocytes [1–3]. Conversion to a thermogenic phenotype or 'beiging' in these cells can be triggered by cold exposure and by β3-adrenergic receptor or peroxisome proliferator-activated receptor γ (PPAR γ) agonists, promoting UCP1 expression and β -oxidation, and uncoupled respiration [1,2]. Activated beige adipocytes burn free fatty acids to generate heat similar to a bona fide brown adipocyte within the BAT [2,4]. Although it is estimated that beige adipocytes only contribute about one-fifth of the thermogenic capacity generated by BAT, at least in rodents, their physiological contribution to energy homeostasis and systemic metabolism is still important [4]. Stimulating WAT beiging increases energy expenditure, produces antiobesity effects, and improves glucose tolerance and insulin sensitivity in several mouse models [2–4]. Moreover, the recruitable nature of beige cells operant within the WAT makes them attractive therapeutic targets, prompting interest in the factors and pathways regulating their number and function.

CLINICAL RELEVANCE OF BEIGE ADIPOSE TISSUE

With the goal of identifying factors capable of inducing WAT beiging to treat metabolic disorders, the important question is whether humans are capable of such a phenomenon. Several studies have now identified that classical 'brown' adipocytes and recruitable beige adipocytes differentiate from distinct developmental lineages and exhibit distinct gene expression signatures [5,6]. Humans are born with BAT located in the interscapular region that contains adipocytes expressing the classical brown profile [7,8]. This BAT involutes over the next several months, and traditional thinking held that humans, unlike rodents, are devoid of true BAT after the newborn period [9]. However, more recent metabolic tracer studies using PET imaging demonstrate that adult human participants have considerably sized depots of metabolically active adipose tissue that avidly take up glucose [10,11]. Indeed, it is now known that thermogenic fat stores increase within the body over the first decade of life, and in response to puberty [12,13].

Adult human BAT, however, exhibits differences when compared with newborn human BAT or interscapular BAT in adult rodents. First, the thermogenic capacity of adult BAT is highly inducible by cold and adrenergic stimulation [14,15]. Indeed, several studies on human subjects have shown that daily, mild (e.g. 19 °C), short-term (2 h) cold exposure increases energy expenditure, reduces fat mass, and improves insulin sensitivity in association with activation of intra-thoracic BAT [15,16]. Consistent with this, BAT mass is higher in adult

humans who live in cold climates, and in the winter versus summer [17]. Moreover, the amount and activity of adult BAT is decreased in obese individuals [2,18]. Taken together, this information highlights the energetic and metabolic importance of adult human BAT, and the potential clinical benefit of developing strategies to promote BAT recruitment and thermogenic activation.

The functional differences between the BAT of adult humans and rodents have been probed at the cellular level. This work revealed that adipocytes from supraclavicular fat, which was thought to represent classical BAT, in fact express a gene profile reminiscent of beige adipocytes [1–3]. Genome-wide analysis shows that $UCP1^+$ adipocytes derived from human BAT samples display a transcriptional profile more similar to murine beige adipocytes than classical interscapular brown adipocytes. Thus, human adult 'BAT' depots are in fact mainly constituted of beige-like adipocytes that are competent for ligand-stimulated activation [5]. This conclusion has led to a proliferation of research focused on finding secreted factors that control the beiging process.

SECRETED FACTORS MODULATE BEIGE ADIPOCYTE ACTIVATION

Space limitations preclude us from discussing all the signaling molecules regulating beige adipogenesis and function here. Several of these have already been reviewed [3,19]. Instead, we will focus specifically on endogenously synthesized and physiologically important secreted factors that may be effectively targeted from a therapeutic standpoint.

Secreted factors and their corresponding receptors have become attractive therapeutic targets against metabolic diseases because by manipulating endogenous endocrine, paracrine, and/or autocrine pathways that are already in place, we may achieve clinically relevant outcomes without all the undesirable off-target effects associated with traditional drug discovery. For example, catecholamines acting via the β3-adrenergic receptor directly stimulate the classical pathway that activates beige adipocytes. However, developing adrenergic ligands for obesity and metabolic disease applications could produce unwanted autonomic, bone, and cardiovascular effects over time. Similarly, bone morphogenetic proteins 4, 7, and 8b (BMP4, BMP7, BMP8b), atrial and brain-type natriuretic peptides, FGF21, VEGF-A, and prostaglandins, have all been shown to promote beiging *in vivo* [20–25]. However, these factors may also exert potentially unwanted pleiotropic effects when translated into drugs. Indeed, the development of FGF21 mimetics was halted after phase I trials because of adverse effects [26]. By contrast, several more recently identified endogenous factors show promise as beiging agents and examination of their therapeutic potential is thus continuing aggressively. Below we summarize intriguing endogenous secreted factors identified in the last 2 years and discuss their therapeutic potential.

Slit2

Slit2 is a factor secreted by beige adipocytes under transcriptional control of PRDM16, a master-regulator of beige/brown adipocyte differentiation [27■]. Slit2 is posttranslationally cleaved, and functional studies reveal that the C-terminal fragment of Slit2 promotes thermogenesis cultured white adipocytes and in mice by activating the PKA-p38 MAP kinase pathway (Fig. 1) [27■].

Interestingly, adenoviral overexpression of C-terminal Slit2 in the livers of diet-induced obese mice increased whole-body energy expenditure and improved glucose tolerance, suggesting that systemically administering purified Slit2 C-terminal protein in isolation could produce beneficial effects [27■]. Previous studies showed that Slit proteins bind to the Robo family of receptors through their N-terminal region to activate the small GTPase Cdc42 [28], whereas the receptor for the C-terminus of Slit2 is unknown. Notably, although full-length Slit2 also promotes beiging, the truncated C-terminal Slit2 protein might provide a more specific effect therapeutically.

Angiopoietin-like 4

Angiopoietin-like 4 (ANGPTL4) is a secreted protein highly expressed in liver and adipose tissues, whose expression is induced by environmental cues including fasting, hypoxia, and glucocorticoids. As with Slit2, ANGPTL4 has distinct structural and functional domains corresponding with its N-terminal and C-terminal halves. Initial studies of ANGPTL4 focused on its ability to inhibit lipoprotein lipase, an activity that is specifically exerted by its N-terminal coiled-coil domain (CCD) [29]. However, ANGPTL4 also promotes intracellular triacylglycerol hydrolysis (lipolysis) in adipocytes by stimulating cAMP production (Fig. 1) [30]. This action is independent of the CCD, and is now known to be exerted specifically by the C-terminal fibrinogen-like domain (FLD) of ANGPTL4 [31■]. Increasing circulating ANGPTL4 FLD levels in isolation induced in-vivo adipose tissue lipolysis, protected mice against high-fat diet-induced obesity, ectopic steatosis, and glucose intolerance [31■]. In addition, ANGPTL4 FLD increased oxygen consumption and the expression of thermogenic genes, such as *UCP1* and *PGC-1α*, in inguinal WAT, an indication of beiging [31■]. These effects resulted in increased whole-body energy expenditure [31■]. The receptor mediating ANGPTL4 FLD effects on adipocytes is unknown, however, previous studies showed that ANGPTL4 FLD associates with integrins, including β1, β3, and β5, to stimulate cell migration and apoptosis in cancer cells and keratinocytes [29]. The role of integrin-dependent signaling in ANGPTL4 FLD-induced beiging, however, is unclear. Although full-length ANGPTL4 also likely induces beiging, the C-terminal ANGPTL4 FLD could be more beneficial therapeutically, as administering it would avoid the inhibition of lipoprotein lipase and consequent hypertriglyceridemia stimulated by the N-terminal CCD [10].

Adrenomedullin 2

Adrenomedullin 2 (ADM2) is a secreted peptide from the *calcitonin* gene-related peptide family. Plasma ADM2 levels are inversely correlated with obesity in humans [32■]. Adipose-specific ADM2 transgenic mice are resistant to diet-induced obesity, have increased whole body energy expenditure, and increased beiging in subcutaneous WAT [32■]. AMD2 exerts two mechanisms to promote beiging. First, treating rat primary subcutaneous adipocytes and human adipocytes with ADM2 increased expression of genes encoding UCP1 and other thermogenic proteins, and promoted uncoupled mitochondrial respiration [32■]. The receptor for ADM2 is composed of a calcitonin receptor-like receptor (CRLR) and one of the three receptor activity-modifying proteins (RAMPs) (Fig. 1) [33]. ADM2-stimulated beiging was shown to be mediated by RAMP1 and its downstream effectors, PKA and p38 MAPK [32■]. In addition, ADM2 promotes the polarization of resident subcutaneous WAT macrophages to

an M2-like state, which has recently been implicated in regulating catecholamine levels and action in the WAT [32■,34]. ADM2-activated WAT macrophages are suggested to be important to the mechanism by which ADM2 promotes beiging, perhaps by producing paracrine factors that functionally modulate neighboring adipocytes [32■,35]. However, ADM2 also impacts the cardiovascular system and can produce hypotension in animal models [33]. Therefore, targeting ADM2-dependent signaling to curb obesity will require a strategy to do so in a WAT-specific manner.

Kynurenic acid

Kynurenine is a neurotoxic metabolite of tryptophan [36]. Exercise increases conversion of kynurenine to kynurenic acid in skeletal muscle and in the circulation [37■]. Unlike kynurenine, kynurenic acid cannot cross the blood–brain barrier. Daily kynurenic acid injection in C57BL/6 mice increased energy expenditure [37■]. Global gene expression analysis in this context shows that kynurenic acid induces a beige adipocyte signature and increases expression of lipid metabolism and anti-inflammatory genes [37■]. Kynurenic acid acts through its receptor, G protein-coupled receptor 35 (Gpr35), to activate ERK and CREB, and to subsequently increase PGC-1α expression and cellular respiration (Fig. 1) [37■]. Kynurenic acid-Gpr35 signaling also increases intracellular levels of Rgs14, leading to enhanced β-adrenergic receptor signaling [37■]. Notably, Gpr35-deficient mice are resistant to exercise-induced beiging of subcutaneous WAT [37■]. Interestingly, 2 weeks of daily kynurenic acid treatment in mice with diet-induced obesity reduced body weight and inguinal WAT mass, and improved glucose tolerance and plasma triglyceride levels [37■]. Overall, tissue-selective Gpr35 agonists could be an intriguing antiobesity approach.

TGR5

TGR5 is a G protein-coupled receptor for bile acids [38], and cold-induced WAT beiging was attenuated in TGR5-deficient mice [39■]. Under thermoneutral conditions, at which there is no ambient temperature-associated thermogenic stress, activating TGR5 with systemic TGR5-selective bile acid mimetics promotes subcutaneous WAT beiging in wild-type, but not TGR5-null mice [39■]. Not surprisingly, TGR5-selective bile acid mimetics also induce beiging and reduce body weight gain in mice with diet-induced obesity [39■]. Adding the TGR5 agonist INT-777 to differentiation media bathing adipogenic precursor cells from the WAT stromal vascular fraction of wild-type mice augmented the expression of thermogenic genes [39■]. INT-777 was shown to induce mitochondrial fission and respiration in an ERK/DRP1-dependent manner (Fig. 1) [39■]. Although TGR5 is a potentially desirable therapeutic target, TGR5 agonists also produce several unwanted effects as well, including gallbladder expansion, impaired immune function, and alterations in heart rate [40,41]. These off-target effects could limit the development of TGR5-based therapies. As such, any potential antiobesity approach focused on TGR5 may have to be engineered to be WAT specific.

Immune signals

Group 2 innate lymphoid cells (ILC2s) and M2 macrophages remain an active focus in metabolic research [32■,34], though the specific role of macrophages in catecholamine metabolism has been recently questioned [42]. A recent study found that FGF21 activates

type 2 immunologic responses in the WAT by inducing adipocytes to express the chemokine CCL11 [43]. Moreover, the activation of histamine receptor has been shown to induce PKA signaling, leading to UCP1 expression and sub-cutaneous WAT beiging [44]. In targeting immune signals to stimulate beiging, however, effective strategies will require that this targeting is specific to the WAT and/or BAT, and to metabolic and temperature-sensitive triggers, to lessen the possibility of either autoimmunity or immunosuppression in a broader sense.

NEW INSIGHTS ON BEIGE ADIPOCYTE PHYSIOLOGY

Most studies of secreted factor effects on beige adipocyte differentiation and physiology use rodent models. Notably, as we discussed above, there are differences between rodent and human BAT and they could respond to secreted factors differently. Recent studies show that human BAT is activated by acute glucocorticoid treatment, whereas in rodent BAT, glucocorticoids significantly suppress thermogenesis [45]. Moreover, human BAT does not respond to certain β3-adrenergic receptor agonists as well as rodent BAT [46]. Thus, it is important to establish human stem cell models to study the effects of secreted factors on beige adipocyte differentiation. Recently, one group had success differentiating human pluripotent stem cells (hPSCs) through mesenchymal stem cells to thermogenically active adipocytes most closely, physiologically resembling beige adipocytes [47]. The current progress of developing human stem cell-based models of thermogenic adipocytes has been reviewed in a recent article [48].

Most of the secreted factors described thus far promote beiging through activation of the cAMP-PKA pathway (Fig. 1). Recent studies, however, have revealed additional, previously unrecognized physiological pathways that induce WAT beiging without altering the function of bona fide brown adipocytes. These pathways provide new directions in screening for secreted factors that promote beige differentiation and activation.

One such pathway underlies a UCP1-independent thermogenic mechanism newly identified in beige adipocytes residing in WAT, which express UCP1 at much lower levels than do brown adipocytes residing BAT. This discovery stemmed from the initial observation that mice lacking UCP1 contain beige adipocytes capable of thermogenesis [49▪▪]. In these mice, enhanced ATP-dependent calcium cycling in beige adipocytes by the sarco/endoplasmic reticulum Ca^{2+}-ATPase 2b (SERCA2b) and the type 2 ryanodine receptor (RyR2) promotes thermogenesis, whereas this pathway is expendable in BAT thermogenesis [49▪▪]. The mechanism for this cell type specificity is unclear, but may hinge on the higher cellular availability of ATP in beige, as opposed to brown adipocytes [49▪▪]. PKA enhances this thermogenic mechanism by phosphorylating RyR2, potentiating calcium release from the sarco/endoplasmic reticulum.

Creatine metabolism has also been shown to play a role in maintaining thermogenesis independently of UCP1. The expression of genes regulating creatine metabolism was elevated in UCP1-deficient mice, and reducing creatine levels in these mice decreased core body temperature and oxygen consumption by WAT beige cells [50]. Reducing creatine

levels also decreased cold-inducible and catecholamine-inducible energy expenditure in both WAT and BAT [50].

Beige adipocytes spontaneously revert to a classical white-like phenotype, including development of hallmark unilocular lipid droplets, without the constant presence of stimuli to maintain their thermogenic phenotype [18]. This beige-to-white conversion may be because of autophagy-mediated mitochondrial degradation [51∎]. Parkin, an E3 ubiquitin ligase that initiates mitophagy, has been identified as a crucial mediator of adipocyte beige-to-white transition [51∎]. Beige adipocytes in mice lacking Parkin do not responsively degrade their mitochondria upon cessation of external beiging stimuli. Notably, Parkin is not relevant to mitochondrial maintenance in bona fide brown adipocytes or BAT [51∎]. Interestingly, UCP1 is not required to recruit Parkin to mitochondria, or for mitophagy during beige-white adipocyte conversion, indicating that this control of beige adipocyte maintenance is UCP1-independent [51∎].

Warming also induces the 'whitening' of beige adipocytes. Epigenomic studies reveal that warming beige adipocytes in culture shifts their chromatin state to one resembling lipid-storing white adipocytes [52∎]. However, these whitened beige adipocytes retain an array of 'poised' transcriptional enhancers that prime thermogenic genes for a rapid transcriptional conversion back to a beige pheno-type upon the next cold exposure. The glucocorticoid receptor and the zinc finger protein Zfp423 have been identified as key transcriptional regulators of the whitening of beige adipocytes. Interestingly, bona fide interscapular brown adipocytes do not significantly change chromatin state during warming despite morphological indicators of whitening [52∎].

The identification of functionally important UCP1-independent thermogenic mechanisms employed by beige adipocytes expands the number of approaches targeting adipocytes to fight obesity (Fig. 1). However, whereas enhancing Ca^{2+}-cycling to promote thermogenesis could have therapeutic potential, forcing Ca^{2+}-cycling in cells beyond adipocytes could have adverse effects on cardiac and skeletal muscle function. Thus, stimulating these UCP1-independent pathways in an adipose-specific manner is critical. Minimizing beige-to-white adipocyte conversion could be another approach to enhance beige adipocyte activity.

CONCLUSION

We have summarized some newly identified endogenous secreted factors that promote beige adipocyte activation. The identification of Slit2 and ANGPTL4, in this regard, are especially intriguing, as targeting specific functional domains of each of these factors may hold therapeutic promise without the adverse effects that might be attendant with the entire full-length proteins. The identification of UCP1-independent mechanisms for adipose tissue thermogenesis and pathways governing beige-to-white adipocyte conversion provide alternative therapeutic avenues as well. Regardless, a key remaining task is confining the action of any beiging-oriented therapeutics specifically to the adipose tissue, and avoiding effects on tissues elsewhere in the body.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■■ of outstanding interest

1. Gulyaeva O, Dempersmier J, Sul HS. Genetic and epigenetic control of adipose development. Biochim Biophys Acta 2018; doi:10.1016/j.bbalip.2018.04.016 [Epub ahead of print]

2. Inagaki T, Sakai J, Kajimura S. Transcriptional and epigenetic control of brown and beige adipose cell fate and function. Nat Rev Mol Cell Biol 2016; 17:480–495. [PubMed: 27251423]

3. Wang W, Seale P. Control of brown and beige fat development. Nat Rev Mol Cell Biol 2016; 17:691–702. [PubMed: 27552974]

4. Kajimura S, Spiegelman BM, Seale P. Brown and beige fat: physiological roles beyond heat generation. Cell Metab 2015; 22:546–559. [PubMed: 26445512]

5. Sidossis L, Kajimura S. Brown and beige fat in humans: thermogenic adipocytes that control energy and glucose homeostasis. J Clin Invest 2015; 125:478–486. [PubMed: 25642708]

6. Lidell ME, Betz MJ, Dahlqvist Leinhard O, et al. Evidence for two types of brown adipose tissue in humans. Nat Med 2013; 19:631–634. [PubMed: 23603813]

7. Lee P, Werner CD, Kebebew E, Celi FS. Functional thermogenic beige adipogenesis is inducible in human neck fat. Int J Obes (Lond) 2014; 38:170–176. [PubMed: 23736373]

8. Sharp LZ, Shinoda K, Ohno H, et al. Human BAT possesses molecular signatures that resemble beige/brite cells. PloS One 2012; 7:e49452. [PubMed: 23166672]

9. Hany TF, Gharehpapagh E, Kamel EM, et al. Brown adipose tissue: a factor to consider in symmetrical tracer uptake in the neck and upper chest region. Eur J Nucl Med Mol Imaging 2002; 29:1393–1398. [PubMed: 12271425]

10. Soderlund V, Larsson SA, Jacobsson H. Reduction of FDG uptake in brown adipose tissue in clinical patients by a single dose of propranolol. Eur J Nucl Med Mol Imaging 2007; 34:1018–1022. [PubMed: 17225118]

11. Vijgen GH, Sparks LM, Bouvy ND, et al. Increased oxygen consumption in human adipose tissue from the 'brown adipose tissue' region. J Clin Endocrinol Metab 2013; 98:E1230–E1234. [PubMed: 23783102]

12. Gilsanz V, Smith ML, Goodarzian F, et al. Changes in brown adipose tissue in boys and girls during childhood and puberty. J Pediatr 2012; 160: 604.e1–609.e1. [PubMed: 22048045]

13. Gilsanz V, Hu HH, Kajimura S. Relevance of brown adipose tissue in infancy and adolescence. Pediatr Res 2013; 73:3–9. [PubMed: 23090604]

14. van der Lans AA, Hoeks J, Brans B, et al. Cold acclimation recruits human brown fat and increases nonshivering thermogenesis. J Clin Invest 2013; 123:3395–3403. [PubMed: 23867626]

15. Yoneshiro T, Aita S, Matsushita M, et al. Recruited brown adipose tissue as an antiobesity agent in humans. J Clin Invest 2013; 123:3404–3408. [PubMed: 23867622]

16. Lee P, Smith S, Linderman J, et al. Temperature-acclimated brown adipose tissue modulates insulin sensitivity in humans. Diabetes 2014; 63:3686–3698. [PubMed: 24954193]

17. Saito M, Okamatsu-Ogura Y, Matsushita M, et al. High incidence of metabolically active brown adipose tissue in healthy adult humans: effects of cold exposure and adiposity. Diabetes 2009; 58:1526–1531. [PubMed: 19401428]

18. Kiefer FW. The significance of beige and brown fat in humans. Endocr Connect 2017; 6:R70–R79. [PubMed: 28465400]

19. Harms M, Seale P. Brown and beige fat: development, function and therapeutic potential. Nat Med 2013; 19:1252–1263. [PubMed: 24100998]

20. Qian SW, Tang Y, Li X, et al. BMP4-mediated brown fat-like changes in white adipose tissue alter glucose and energy homeostasis. Proc Natl Acad Sci USA 2013; 110:E798–E807. [PubMed: 23388637]

21. Tseng YH, Kokkotou E, Schulz TJ, et al. New role of bone morphogenetic protein 7 in brown adipogenesis and energy expenditure. Nature 2008; 454:1000–1004. [PubMed: 18719589]

22. Tomlinson E, Fu L, John L, et al. Transgenic mice expressing human fibroblast growth factor-19 display increased metabolic rate and decreased adiposity. Endocrinology 2002; 143:1741–1747. [PubMed: 11956156]

23. Fisher FM, Kleiner S, Douris N, et al. FGF21 regulates PGC-1alpha and browning of white adipose tissues in adaptive thermogenesis. Genes Dev 2012; 26:271–281. [PubMed: 22302939]

24. Madsen L, Pedersen LM, Lillefosse HH, et al. UCP1 induction during recruitment of brown adipocytes in white adipose tissue is dependent on cyclooxygenase activity. PloS One 2010; 5:e11391. [PubMed: 20613988]

25. Vegiopoulos A, Muller-Decker K, Strzoda D, et al. Cyclooxygenase-2 controls energy homeostasis in mice by de novo recruitment of brown adipocytes. Science (New York, NY) 2010; 328:1158–1161.

26. Kusminski CM, Bickel PE, Scherer PE. Targeting adipose tissue in the treatment of obesity-associated diabetes. Nat Rev Drug Discov 2016; 15:639–660. [PubMed: 27256476]

■ 27. Svensson KJ, Long JZ, Jedrychowski MP, et al. A secreted Slit2 fragment regulates adipose tissue thermogenesis and metabolic function. Cell Metab 2016; 23:454–466. [PubMed: 26876562] The recent article from Svensson et al. identify Slit2 as a factor secreted from beige adipocytes, transcriptionally regulated by PRDM16, which promotes a thermogenic, PKA-dependent pathway in adipocytes and improves overall metabolic parameters in response to high-fat diet challenge.

28. Hussain SA, Piper M, Fukuhara N, et al. A molecular mechanism for the heparan sulfate dependence of slit-robo signaling. J Biol Chem 2006; 281:39693–39698. [PubMed: 17062560]

29. Zhu P, Goh YY, Chin HF, et al. Angiopoietin-like 4: a decade of research. Biosci Rep 2012; 32:211–219. [PubMed: 22458843]

30. Gray NE, Lam LN, Yang K, et al. Angiopoietin-like 4 (Angptl4) protein is a physiological mediator of intracellular lipolysis in murine adipocytes. J Biol Chem 2012; 287:8444–8456. [PubMed: 22267746]

■ 31. McQueen AE, Kanamaluru D, Yan K, et al. The C-terminal fibrinogen- like domain of angiopoietin-like 4 stimulates adipose tissue lipolysis and promotes energy expenditure. J Biol Chem 2017; 292:16122–16134. [PubMed: 28842503] The recent article from McQueen et al. identified the c-terminal fibrinogen-like domain of angiopoietin-like 4 as a secreted factor, which induces cAMP-PKA-dependent lipolysis in white adipocytes leading the upregulation of a thermogenic program and subsequent protection against weight gain, increase in energy expenditure and improvement in glucose tolerance in high-fat diet-fed mice.

■ 32. Lv Y, Zhang SY, Liang X, et al. Adrenomedullin 2 enhances beiging in white adipose tissue directly in an adipocyte-autonomous manner and indirectly through activation of M2 macrophages. J Biol Chem 2016; 291: 23390–23402. [PubMed: 27621315] The recent article from Lv et al. identified that adrenomedullin 2 enhances beiging of adipocytes via calcitonin receptor-like receptor-receptor activity-modifying protein 1 complex and the PKA and p38 MAPK signaling as well as by stimulation of alternative M2 polarization in macrophages.

33. Zhang SY, Xu MJ, Wang X. Adrenomedullin 2/intermedin: a putative drug candidate for treatment of cardiometabolic diseases. Br J Pharmacol 2018; 175:1230–1240. [PubMed: 28407200]

34. Uhm M, Saltiel AR. White, brown, and beige; type 2 immunity gets hot. Immunity 2015; 42:15–17. [PubMed: 25607455]

35. Zhang H, Zhang SY, Jiang C, et al. Intermedin/adrenomedullin 2 polypeptide promotes adipose tissue browning and reduces high-fat diet-induced obesity and insulin resistance in mice. Int J Obes (Lond) 2016; 40:852–860. [PubMed: 26786353]

36. Schwarcz R, Bruno JP, Muchowski PJ, Wu HQ. Kynurenines in the mammalian brain: when physiology meets pathology. Nat Rev Neurosci 2012; 13:465–477. [PubMed: 22678511]

■ 37. Agudelo LZ, Ferreira DMS, Cervenka I, et al. Kynurenic acid and Gpr35 regulate adipose tissue energy homeostasis and inflammation. Cell Metab 2018; 27:378.e5–392.e5. [PubMed: 29414686] The recent article from Agudelo et al. shows that kynurenic acid increases energy expenditure by activating G-protein-coupled receptor Gpr35, which in turn stimulates a thermogenic program in adipose tissue and increases levels of Rgs14 in adipocytes leading to enhanced b-adrenergic receptor signaling.

38. Malhi H, Camilleri M. Modulating bile acid pathways and TGR5 receptors for treating liver and GI diseases. Curr Opin Pharmacol 2017; 37:80–86. [PubMed: 29102744]

■ 39. Velazquez-Villegas LA, Perino A, Lemos V, et al. TGR5 signalling promotes mitochondrial fission and beige remodelling of white adipose tissue. Nat Commun 2018; 9:245. [PubMed: 29339725] The recent article from Velazquez-Villegas et al. has identified TGR5, a bile acid responsive membrane receptor, as a mediator of beiging during cold exposure or under high-fat diet challenge. In addition, signaling through TGR5 induces mitochondrial fission through the ERK/DRP1-signaling pathway leading to further increased mitochondrial respiration.

40. Li T, Holmstrom SR, Kir S, et al. The G protein-coupled bile acid receptor, TGR5, stimulates gallbladder filling. Mol Endocrinol 2011; 25:1066–1071. [PubMed: 21454404]

41. Stepanov V, Stankov K, Mikov M. The bile acid membrane receptor TGR5: a novel pharmacological target in metabolic, inflammatory and neoplastic disorders. J Recept Signal Transduct Res 2013; 33:213–223. [PubMed: 23782454]

42. Fischer K, Ruiz HH, Jhun K, et al. Alternatively activated macrophages do not synthesize catecholamines or contribute to adipose tissue adaptive thermo-genesis. Nat Med 2017; 23:623–630. [PubMed: 28414329]

43. Huang Z, Zhong L, Lee JTH, et al. The FGF21-CCL11 axis mediates beiging of white adipose tissues by coupling sympathetic nervous system to type 2 immunity. Cell Metab 2017; 26:493.e4–508.e4. [PubMed: 28844880]

44. Finlin BS, Zhu B, Confides AL, et al. Mast cells promote seasonal white adipose beiging in humans. Diabetes 2017; 66:1237–1246. [PubMed: 28250021]

45. Ramage LE, Akyol M, Fletcher AM, et al. Glucocorticoids acutely increase brown adipose tissue activity in humans, revealing species-specific differences in UCP-1 regulation. Cell Metab 2016; 24:130–141. [PubMed: 27411014]

46. Liu X, Cervantes C, Liu F. Common and distinct regulation of human and mouse brown and beige adipose tissues: a promising therapeutic target for obesity. Protein Cell 2017; 8:446–454. [PubMed: 28220393]

47. Guenantin AC, Briand N, Capel E, et al. Functional human beige adipocytes from induced pluripotent stem cells. Diabetes 2017; 66:1470–1478. [PubMed: 28270520]

48. Singh AM, Dalton S. What can 'Brown-ing' do for you? Trends in endocrinology and metabolism: TEM 2018; 29:349–359. [PubMed: 29606342]

■■ 49. Ikeda K, Kang Q, Yoneshiro T, et al. UCP1-independent signaling involving SERCA2b-mediated calcium cycling regulates beige fat thermogenesis and systemic glucose homeostasis. Nat Med 2017; 23:1454–1465. [PubMed: 29131158] The recent article from Ikeda et al. has identified a UCP1-independent mechanism that promotes thermogenesis in a beige-adipocyte specific manner. Activation of the SERCA2b-RyRr signaling pathway enhances calcium cycling and stimulates UCP1-independent thermogenesis in beige adipoctyes.

50. Kazak L, Chouchani ET, Jedrychowski MP, et al. A creatine-driven substrate cycle enhances energy expenditure and thermogenesis in beige fat. Cell 2015; 163:643–655. [PubMed: 26496606]

■ 51. Lu X, Altshuler-Keylin S, Wang Q, et al. Mitophagy controls beige adipocyte maintenance through a Parkin-dependent and UCP1-independent mechanism. Sci Signal 2018; 11:527.The

recent article from Lu et al. has identified a mechanism of beige adipocyte maintenance. Parkin has been identified as a factor responsible for mitophagy in beige adipocytes, which triggers their reversion back to white adipocytes.

■ 52. Roh HC, Tsai LTY, Shao M, et al. Warming induces significant reprogramming of beige, but not brown, adipocyte cellular identity. Cell Metab 2018; 27:1121.e5–1137.e5. [PubMed: 29657031] The recent article from Roh et al. has identified a new 'whitening' mechanism in beige adipose tissue. They have shown that, upon warming, beige adipocytes exhibit a shift in cellular identity, namely a conversion from a brown to white chromatin state driven by a glucocorticoid receptor and Zfp423-dependent signaling cascade.

KEY POINTS

- Human beings have a substantial reservoir of beige adipocytes that can be recruited to enhance energy expenditure; targeting these cells represents a clear opportunity to improve metabolic health.

- The identification of unrecognized endogenous factors that promote beiging offer new potential avenues for therapeutic engineering targeting obesity and related metabolic disorders.

- Recent studies have identified UCP1-independent pathways that promote beige adipogenesis, thermogenesis, and/or conversion between beige and white adipocyte phenotypes, highlighting the complexity of adipose tissue energetics and the number of different strategies that may be leveraged for clinical purposes.
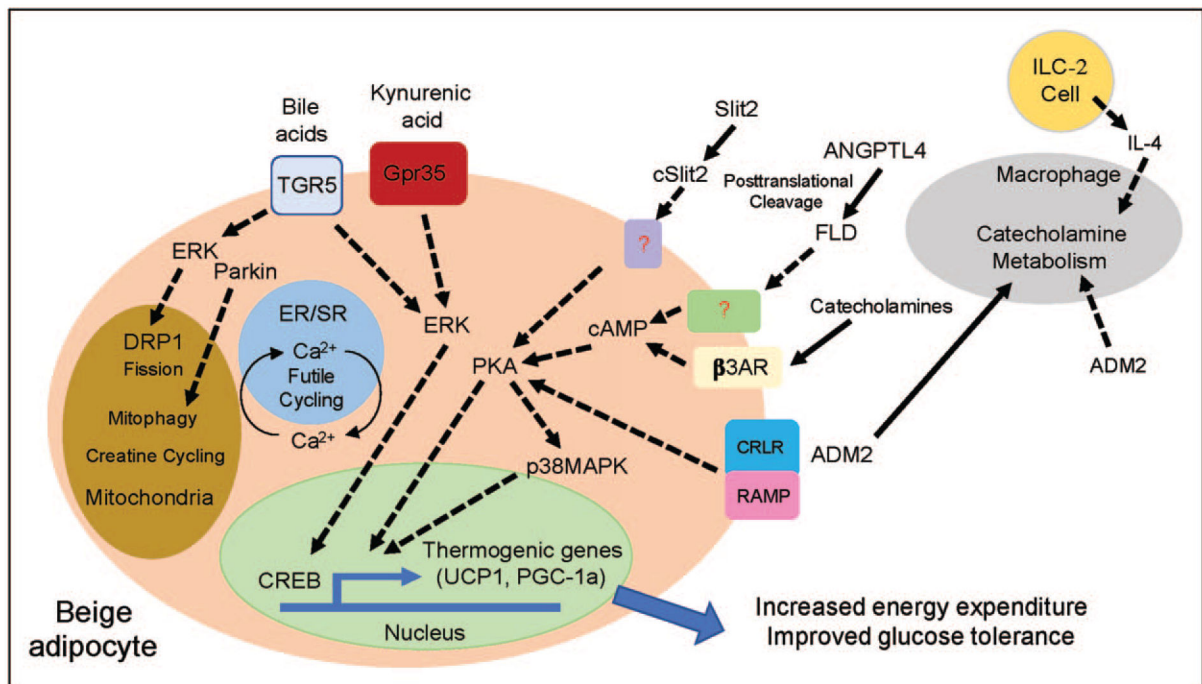
FIGURE 1.
Newly discovered pathways in the physiology of beige adipocytes. Shown are several recently identified endogenous secreted factors that regulate beige thermogenesis. Note that these factors, acting via recognized and as yet unknown receptors, converge primarily onto the PKA-p38MAPK and ERK-signaling pathways. Interestingly, two of these factors, Slit2 and ANGPTL4, are cleaved, with the pro-thermogenic domain of each protein being confined to the C-terminal fragment. These factors have been shown to augment classical (UCP1-dependent) uncoupling to produce metabolically desirable effects. Shown also are UCP1-independent pathways recently found to operate in beige adipocytes as well. These include thermogenesis resulting from futile calcium cycling into and out of intracellular stores, Parkin-dependent mitophagy during beige-to-white adipocyte interconversion, and futile creatine cycling within the mitochondrial outer matrix. These factors and pathways greatly expand the number of potential therapeutic targets that may be exploited to reverse obesity and associated metabolic diseases. UCP-1, uncoupling protein-1.