REVIEW

A paracrine role for white thermogenic adipocytes in innervation: an evidence-based hypothesis

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Abstract

White adipose tissue (WAT) stores energy and also plays an important endocrine role in producing adipokines for communication with the peripheral and central nervous system. WAT consists of the major lipogenic unilocular adipocytes and the minor populations of beige and brite multilocular adipocytes. These multilocular adipocytes express thermogenic genes and have phenotypic similarity with thermogenic brown adipose tissue. According to a current paradigm, multilocular adipocytes have a thermogenic function in WAT. In this mini review, we discuss data revealing heterogeneity among multilocular cell subsets in WAT and their functions beyond thermogenesis. We propose a hypothetical neuroendocrine role for multilocular adipocytes subsets in the formation of adaptive sensory-sympathetic circuits between the central nervous system and adipose tissue, which activate lipolysis and thermogenesis in WAT in high energy demand situations.

Key Words: *obesity; thermogenesis; innervation; vitamin A; aldehyde dehydrogenase; paracrine; efferent; afferent; brown adipose tissue*

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Endocrine Lessons Learned from Obesity Epidemics

The obesity epidemic, affecting 35.7% of adults in the United States (CDC.gov), draws an exponential growth in interest to the role of white adipose tissue (WAT). The understanding of WAT's function was advanced beyond insulation and energy storage to its central endocrine role regulating energy homeostasis. The global impact of WAT is achieved after convergence of endocrine signals in the central nervous system (CNS). One of the first mechanisms underlying neuro- and endocrine causes of obesity was linked to the adipokine leptin, or its receptor (LepR or ObR) (reviewed (Rosen and Spiegelman (2014)). Deficient leptin/LepR signaling de-regulates pro-opiomelanocortin neurons in the hypothalamus controlling appetite, glucose metabolism, thermogenesis, and overall energy homeostasis. The endocrine function of WAT and its impact on CNS is now undisputable. Conditions such as metabolic syndrome, type 2 diabetes, cardiovascular disease, stroke, certain cancers, and diseases of the CNS, including depression and dementia, all appear to be linked to specific endocrine proteins, pro-inflammatory cytokines, and metabolites that are produced in WAT and influence CNS. We have performed a PubMed literature search of articles published in the period 1960–July 2018 on adipokines, neuroadipokines, endocrine, beige, brown, brite, thermogenic, thermogenesis, lipolysis, and innervation of adipose tissue.

Paracrine Communication between WAT and Sympathetic Nervous System

The endocrine output depends on the WAT composition [reviewed in Rosen and Spiegelman (2014)]. Preadipocytes and adipocytes produce different endocrine molecules, cytokines, and chemoattractants in response to diet. In obesity, hypertrophic adipocytes and inflammatory cells recruited into hypertrophic WAT secrete additional pro-inflammatory factors into circulation that lead to systemic insulin and leptin resistance and glucose intolerance. High-fat diet, hyperglycemia and oxidative stress in WAT, induce neurodegeneration of sympathetic nervous system (SNS), influencing the norepinephrine/β-adrenergic receptor pathway. Deficiency in SNS signaling reduces lipolysis and thermogenesis in WAT (**Figure 1**). Blockage of α/β-adrenergic pathways markedly reduces (60%) lipolysis during exercise in lean people, compared to obese participants (100%) (Verboven et al., 2018), highlighting reduced contribution of SNS-dependent lipolysis in obesity. However, in response to exercise, both lean and obese participants activate another lipolytic pathway in WAT that is independent of β-adrenergic/SNS axes (Verboven et al., 2018). Thus, partial neurodegeneration in WAT as a result of obesity reduces the contribution of β-adrenergic pathways to energy mobilization.

The transition from storage to lipolysis in WAT during an energy demand state requires remodeling of sympathetic innervation. This plasticity in WAT SNS/β-adrenergic response has been demonstrated in mouse models (Ruohonen et al., 2018), where high-fat diet-induced neurodegeneration decreased lipolytic and thermogenic responses, and exercise restored them in WAT (Ruohonen et al., 2018). Although these responses are indicative for restored innervation, mechanisms regulating innervation plasticity in WAT are not well understood. Paracrine function of white adipocytes

contributes to innervation in WAT; however, this function is associated with lipid storage rather than activation of β-adrenergic pathways for lipolysis. Preadipocytes and adipocytes express nerve growth factor (NGF) [discussed in Shen et al. (2018)], which is augmented in response to inflammatory cytokines. NGF secretion appears to support an obesogenic type of innervation, highlighted by a positive relationship between plasma NGF levels and patients' BMI. Paracrine secretion of leptin by WAT appears to induce sensory innervation that could support vasodilation, though progressive leptin resistance in obese patients may diminish its contribution to innervation; this function of leptin has not been tested *in vivo*. Since white adipocytes cannot produce factors stimulating *de novo* innervation, we investigated paracrine output of a subset of adipocytes from WAT on neurons (Shen et al., 2018).

Minor Cell Populations in WAT

Understanding the role of minor population of adipocytes in WAT and their endocrine contribution has been challenging technically due to the long-lasting misconception of their origin. Abdominal and inguinal WAT contains small interspersed population of multilocular adipocytes of the same mesodermal *Myf5*-lineage as the surrounding main population of unilocular, lipogenic white adipocytes [reviewed in Carobbio et al. (2018)] (**Figure 1**). However, these cells express thermogenic uncoupling protein 1 (UCP1), and higher levels of lipolytic and mitochondrial genes. This gene expression pattern is intermediate between brown and unilocular white adipocytes, therefore, these cells were termed 'beige', 'brite' (brown and white), UCP1 positive (UCP1$^+$), multilocular, or thermogenic WAT adipocytes by different researches (Wang et al., 2016). Ground-breaking studies showed that these cell subsets had a different origin than thermogenic brown adipose tissue (BAT) (Carobbio et al., 2018). However, historically, multilocular white adipocytes are attributed a similar thermogenic function as BAT.

The classical BAT originates from *Myf5*$^+$ mesenchymal precursors, these cells constitutively express *Ucp1*$^+$ and specific markers *Prdm16*$^+$ and *Zic1*$^+$ (Rosen and Spiegelman, 2014; Carobbio et al., 2018). BAT is constitutively innervated by sympathetic neurons during development (**Figure 2**). In response to cold and other sympathetic and β3-adrenergic receptor stimulations, BAT increases *Ucp1* expression for heat production. In this oxygenated tissue, the role of UCP1 in direct defense against oxidative stress is moderate (Shabalina et al., 2006); moreover, increased levels of oxidation are necessary to activate the thermogenic function of UCP1. BAT is located in perivascular and supraclavicular regions in humans and in the subcutaneous scapular regions in mice (Rosen and Spiegelman, 2014). The anatomic location of BAT in humans and mice is permanent and consistent with this thermogenic function.

Paracrine Mediators of BAT Assist SNS in Regulation of Thermogenesis

BAT releases several endocrine factors to control thermogenic responses in conjunction with activation of SNS. BAT expresses and secretes bone morphogenetic protein (BMP)7 and VEGFA that promote BAT differentiation and vascularization, respectively [(reviewed in Carobbio et al. (2018)). Both secreted molecules stimulate *Ucp1* expression, energy expenditure, improve glucose tolerance, and weight loss. However, these effects are seen in context of SNS activation and do not occur at thermoneutrality. Sympathetic activation also mediates glucose flux into BAT that occurs even in the absence of thermogenic response in *Ucp1*$^{-/-}$ mice.

SNS also appears to control a paracrine feedback regulation of thermogenesis in BAT *via* activation of adenosine secretion [reviewed in Carobbio et al. (2018)]. Adenosine, at nanomolar concentrations, stimulates thermogenic function, whereas at high concentrations, adenosine blocks β-adrenergic-dependent lipolysis and thermogenesis. *De novo* innervation is seen mostly in artificial transplants of brown adipocytes, because BAT is innervated during development. Factors responsible for the innervation of BAT implants remain unknown, although in other tissues, BMP7 and VEGFA has been shown to promote innervation. The critical role of innervation in BAT was demonstrated during denervation of BAT in mice overexpressing *Ucp1*. Denervation disrupts thermogenesis and other systemic metabolic effects of BAT, including increase in energy expenditure and glucose uptake (Rosen and Spiegelman, 2014). This loss of function suggests that BAT acts predominantly downstream of CNS as a thermogenic organ and releases endocrine factors to assist SNS.

Different Subsets of UCP1$^+$ Adipocytes of WAT

Multilocular UCP1$^+$ adipocytes in WAT face different challenges than BAT. These multilocular UCP1$^+$ adipocytes reside in WAT, which is a tissue of limited thermoconductivity and sympathetic innervation. Sympathetic response activates a specific subset of cells expressing *Tmem26* and *CD137*. Upon SNS stimulation, these progenitors express *Prdm16* and increased levels of adipose triglyceride lipase (ATGL)/hormone sensitive lipase (HSL) and *Ucp1*/UCP1 to activate lipolysis and thermogenesis. The SNS-dependent subpopulation of UCP1$^+$ adipocytes in WAT is commonly termed 'beige adipocytes' (Wang et al., 2016) (**Figure 1**). Progressive degeneration of peripheral sensory and sympathetic axons in obesity decreases the population of these cells and is associated with decreased lipolysis and thermogenesis in WAT. In the obesity state, the expression of *Ucp1* in UCP1$^+$ adipocytes in WAT is markedly lower compared to that in BAT, a property favoring energy storage in WAT. Under obesogenic neurodegenerative conditions, interspersed beige adipocytes play a progressively decreased role in lipolysis and thermogenesis.

Other subsets of UCP1$^+$ adipocytes can develop without β-adrenergic stimuli and can still respond to SNS stimulation. They are commonly termed 'brite' adipocytes. Stimulation of WAT with peroxisome proliferator-activated receptor (PPAR)γ ligands, cyclin-dependent kinase 5 inhibitors, and other stimuli leads to expression of specific genes Cdsn,

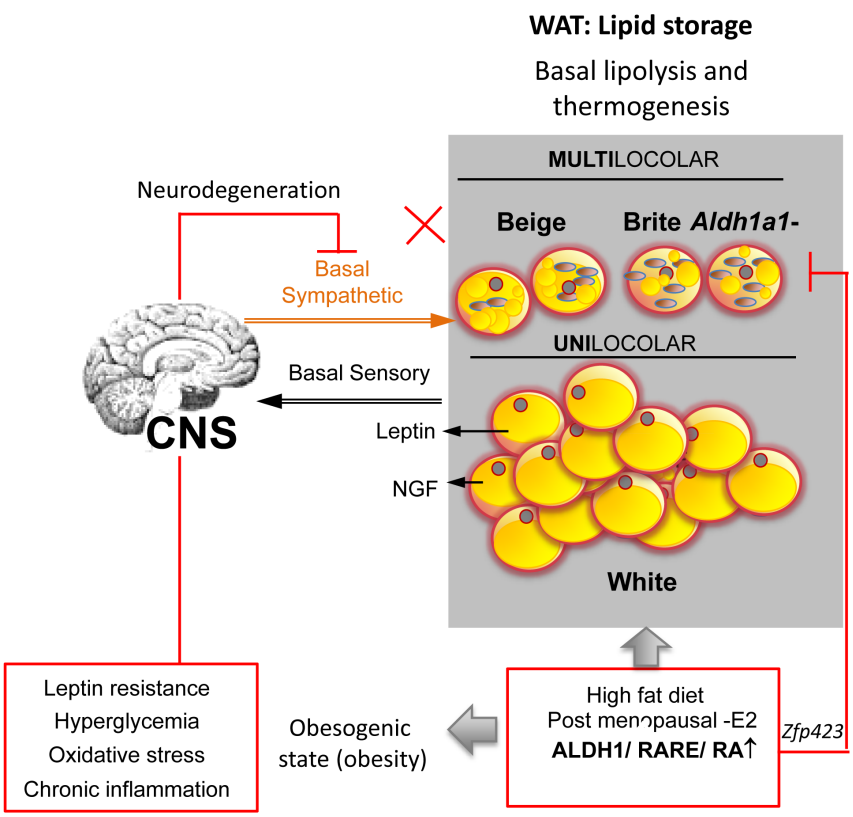

Figure 1 Obesogenic state of white adipose tissue (WAT).
WAT communicates with central nervous system (CNS) with sensory afferent signals and sympathetic efferent neurons. WAT contains predominantly unilocular adipocytes. They can release factors, such as leptin and nerve growth factor (NGF), to communicate with peripheral neurons. WAT also contains minor populations of beige and brite multilocular adipocytes. Beige subset is sympathetic nervous system (SNS)-dependent. Brite subset could be generated by different mechanisms, including removal of thermogenic brakes, such as zinc finger protein transcription factor (ZFP)423. Aldehyde dehydrogenase family 1 member A1 (Aldh1a1) deficiency leads to *Zfp423* deficiency. Obesogenic state of WAT is induced by environmental factors, including a high-fat diet, or hormonal imbalance, such as postmenopausal estrogen (E2) deficiency. These conditions are associated with the activation of retinoic acid receptor (RAR) by retinoic acid (RA), produced in adipocytes by ALDH1 family of enzymes. This activation regulates RAR genes containing RAR response element (RARE) that includes *Zfp423*. This inhibits development of brite cells and promotes differentiation of white adipocytes. Obesity causes leptin resistance, hyperglycemia, oxidative stress and inflammation that lead to neurodegeneration and inhibited development of beige adipocytes.

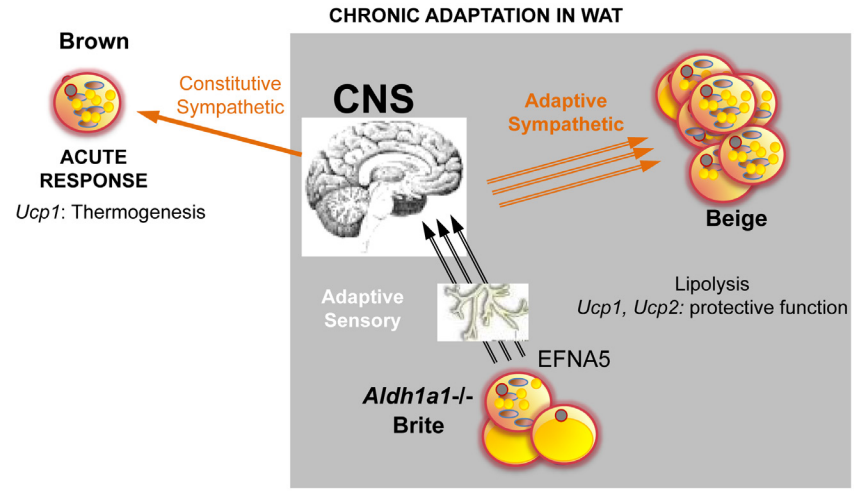

Figure 2 Energy mobilization in energy demanding state.
Brown adipose tissue (BAT) is comprised of multilocular cells and is constitutively innervated during development. BAT is activated for thermogenesis during acute sympathetic stimulations, including cold exposure. Uncoupling protein 1 (*Ucp1*) is expressed at high levels in these tissues and functions primarily to generate heat. Under chronic stimulation, BAT utilizes energy from white adipose tissue (WAT). Different energy demanding conditions require energy from WAT which requires increased innervation. Brite adipocytes, specifically *Aldh1a1*$^{-/-}$ subsets release axon guidance mediators such as ephrin A5 (EFNA5), promoting growth of sensory neurons that establish sensory-sympathetic innervation loops. Activated sympathetic neurons promote lipolysis and thermogenesis leading to the beiging of WAT. Beige multilocular adipocytes express high levels of *Ucp1* and *Ucp2* to protect cells from oxidative stress. CNS: Central nervous system. Aldh1a1: aldehyde dehydrogenase family 1 member A1 (Alias Raldh1).

Rhbg, and Gpx8 (Wang et al., 2016). Another brite adipocyte subset in WAT could be generated by omitting genes suppressing thermogenic programs in WAT, known as thermogenic brakes [reviewed in Carobbio et al., (2018)]. The thermogenic suppressor pathways include Soluble low-density lipoprotein receptor relative LR/sorLA (sLP11)/BMP/transforming growth factor β or Zinc finger protein transcription factor 423 (*Zfp423*)/early B cell factor 2 (*Ebf2*) signaling axes. The inhibition of these pathways induces differentiation of precursors or conversion of white adipocytes into multilocular adipocytes UCP1^{+} with efficient ATGL-mediated lipolysis (Ahmadian et al., 2011), which activates PPARα, its target gene *Ucp1*, and mitochondrial biogenesis. These multilocular adipocytes are also UCP1^{+} and commonly express increased levels of *Ucp2*, to protect them from oxidative stress, and Iodothyronine deiodinase (*Dio2*), to activate thyroid hormone-dependent pathways. Once thermogenic blockers are eliminated in WAT, the lipolytic and moderately thermogenic phenotype is maintained in UCP1^{+} without β-adrenergic/sympathetic stimulation. It is plausible that brite subsets

of UCP1$^+$ cells support basal lipolysis; however, it has been challenging to understand the specific function of minor cell populations. The energy demand signals from the working muscles (irisin) and heart (cardiac natriuretic peptides), inflammation (meteorin/Il4), starvation, digestion and absorption of high fat diets, classic cold- and β-adrenergic stress conditions (Rosen and Spiegelman, 2014) give rise to heterogeneous UCP1$^+$ populations. To meet chronic energy demand under these conditions, *de novo* innervation needs to be developed in WAT for an efficient lipolysis. The understanding of causality between innervation and development of brite and beige subsets holds a key to WAT remodeling.

Nanotechnology for Identification of Paracrine Functions in Cell Subsets

In 1964, Dr. Chang developed technology that captures subsets of endocrine cells producing insulin and allowed their long-term survival after implantation *in vivo*. Encapsulation of cells into porous alginate poly-L-lysine membrane (APL) allows one to inject a desirable number of specific cells into tissues, such as WAT (Shen et al., 2018). Nutrients influx through APL's pores (< 32 kDa) can nourish encapsulated cells which also remain protected by APL from immunoglobulins (> 50 kDa). Therefore, encapsulated cells are biocompatible for implantation into different organisms for a prolonged period of time. Encapsulated cells can communicate with host tissue only *via* paracrine or endocrine factors smaller than pore size (< 32 kDa). For that reason, encapsulated cells can be used to identify signaling factors and their role in systemic metabolism. Moreover, encapsulated cells can help to determine causality of metabolic events initiated by small cell populations. We adapted encapsulation model to study effects of brite UCP1$^+$ adipocytes with adipocytes and neurons *in vitro* as well as *in vivo* in WAT under obesogenic conditions.

Vitamin A Metabolism Controls Transition between White and Brite Phenotype

Different mechanisms have been proposed for induction of 'brite' phenotype in white adipocyte precursors expressing thermogenic blocker *Zfp423* (Wang et al., 2016; Carobbio et al., 2018). In embryonic cells (Huang et al., 2009), *Zfp423* expression is under control of retinoic acid receptor (RAR) activated by its ligand retinoic acid (RA), a vitamin A metabolite. Vitamin A is stored in lipid droplets in white adipocytes, which also express cytosolic enzymes converting retinol to retinaldehyde (Aldehyde dehydrogenase family of enzymes (ADH), retinol dehydrogenase (RDH), and short-chain dehydrogenase/reductase families) as well as retinaldehyde to RA (ALDH1 family, alias RALDH) (**Box 1**). Overexpression of any of *Aldh1* enzymes induces expression of *Zfp423* and its target *Pparg* (Reichert et al., 2011), promoting white phenotype in adipocytes. Deficient expression of *Aldh1*, particularly *Aldh1a1*, decreases expression of *Zfp423 in vitro* in white adipocytes and *in vivo* in WAT. Removal of this thermogenic brake (Reichert et al., 2011), induces lipolytic and thermogenic properties in WAT of *Aldh1a1*$^{-/-}$ mice and render them resistant to obesity induced by high fat diets or ovariectomy (Yasmeen et al., 2013). Importantly, *in vitro*, *Aldh1a1*$^{-/-}$ adipocytes maintained similar heritable lipolytic and thermogenic characteristics and constitutively expressed *Ucp1*, *Ucp2*, *Pgc1a*, *Dio2*, and cell death-inducing DFFA-like effector a (*Cidea*) (Shen et al., 2018). These autonomous lipolytic and thermogenic features of *Aldh1a1*$^{-/-}$ adipocytes are consistent with properties of brite cells in WAT.

Box 1 Pluripotent roles of retinoic acid (RA) in white adipose tissue (WAT)

Intracellular (endogenously-produced) RA has three independent roles:

1. In mitochondria RA acts in conjunction with uncoupling protein 1 (UCP1) to uncouple H$^+$ transport and increase thermogenesis.

2. In cytosol, RA participates in post-translational modification of proteins during adipogenesis.

3. In nucleus, RA acts directly as a ligand for three retinoic acid receptor (RAR) (RARα, RARβ, and RARγ). RAR receptors are expressed in early, intermediate, and late stage of adipogenesis where they regulate expression of different transcription factors, including Zfp423, as well as Krüppel-like family of transcription factor (KLF) and Homeobox transcription factor (HOX) families of transcription factors. RAR receptors also mediate neurogenesis in vascular-resident adipose progenitor cells (APC). Overall, concentrations of RA do not predict its cellular function. The precise regulation of these pathways occurs *via* intracellular RA production by aldehyde dehydrogenase 1 (ALDH1) family of enzymes and transport of RA by binding proteins to different cellular compartments.

Pharmacologic stimulation of RA can elicit different effects (inhibit adipogenesis, cause no effect, or promote obesity) dependent on early, intermediate, and late stage of adipogenesis in WAT or cultured cells, UCP1 expression, diet, or animal species. RA can potentially lead to neurogenesis of APC in WAT. RA induces neurogenesis during central nervous system (CNS) neuronal damage. In contrast, aldehyde dehydrogenase family 1 member A1 (*Aldh1a1*)$^{-/-}$ cells promote growth of dorsal root ganglia axons of preexisting neurons in context of visceral WAT (Shen et al., 2018). This axon growth is inhibited by added RA.

Aldh1a1$^{-/-}$ Adipocytes Can Induce Sensory-Sympathetic WAT Innervation

The genomic comparison between *Aldh1a1*$^{-/-}$ and wild type (WT) adipocytes followed by ingenuity pathway analysis revealed different expression of axon guidance molecules (Shen et al., 2018). The secreted molecules from *Aldh1a1*$^{-/-}$ adipocytes (*Aldh1a1*$^{-/-}$ secretome) induced marked outgrowth of neurites in sensory neurons compared to classic NT3 and NGF inducers. The molecules secreted from WT adipocytes did not influence axon growth consistent with gene expression. Axon guidance activity of *Aldh1a1*$^{-/-}$ adipocytes was mediated in part by ephrinA5/ephrinA4 pathway and was repressed by RA (Shen et al., 2018). EphrinA5/ephrinA4 pathway could also be activated in classic white 3T3-L1 preadipocytes by inhibitors of RAR. This data suggests some of UCP$^+$ subsets of adipocytes could serve as paracrine inducers of innervation. The paracrine regulation of sensory neurons is relevant, because *in vivo* they establish an afferent circuit from the WAT to the brain (Ryu and Bartness, 2014) (**Figure 1**). The comprehensive work by Bartness and

Ryu (Ryu and Bartness, 2014) showed that, following sensory stimulation, CNS establishes long sensory-sympathetic feedback loops that are involved in the control of lipolysis in WAT.

The formation of sensory-sympathetic circuits was tested *in vivo* in encapsulation model. Encapsulated *Aldh1a1*$^{-/-}$ adipocytes (500,000 per depot) were injected once into WAT of obese WT mice fed a high-fat diet (Host). In spite of obesogenic environment, encapsulated *Aldh1a1*$^{-/-}$ adipocytes stimulated outgrowth of peripherin-positive and tyrosine hydroxylase-positive sympathetic axons in host WAT (Shen et al., 2018), demonstrating *de novo* innervation. This WAT remodeling in host obese mice could be attributed to the paracrine action of encapsulated *Aldh1a1*$^{-/-}$ adipocytes communicating signals to the host WAT. Indeed, similar grafts containing encapsulated WT adipocytes did not influence innervation in obese host mice. Non treated obese mice had sparse innervation consistent with neurodegenerative processes in obesity.

The encapsulated *Aldh1a1*$^{-/-}$ subset maintained their thermogenic characteristics *in vivo*. In the proximity of sympathetic axons, host unilocular WAT was also remodeled into multilocular adipocytes expressing ATGL and UCP1. This lipolytic and thermogenic remodeling occurred outside of encapsulated *Aldh1a1*$^{-/-}$ adipocytes in conjunction with *de novo* sympathetic innervation (Shen et al., 2018). Once sympathetic innervation is established, subsequently released norepinephrine could induce lipolysis and thermogenesis producing subsets of adipocytes with beige characteristics. This proposed two-step remodeling mechanism (**Figure 2**) could potentially shed light on differences between acute thermogenesis and chronic adaptation to energy demand, presence of heterogenous populations of *Ucp1*$^{+}$ adipocytes, and the clustered appearance of multilocular adipocytes in proximity of sympathetic axons. More studies would need to test the time course of generation of different UCP^{+} subsets. Cumulatively, WAT's capacity for inducible sensory-sympathetic innervation appears to depend on paracrine function of *Aldh1a1*$^{-/-}$ subsets of thermogenic adipocytes, and probably on the other brite adipocytes.

Conclusion

Investigation of paracrine communication between thermogenic adipocytes and the nervous system could have important translational implications for fundamental understanding and treatment of metabolic diseases and their neurodegenerative complications, as well as injuries in the peripheral nervous system.

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