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Brown and Beige Adipose Thermogenesis

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Summary

Brown and beige adipose tissues have been identified as potential therapeutic targets for combating diet-induced obesity and metabolic disease. Here, we review transcriptional and developmental regulation of brown and beige adipose tissue, as well as critical physiological and pharmaceutical activators of thermogenesis in both tissues.

Transcriptional Regulation of brown and beige adipogenesis

Brown and beige adipocytes are highly adapted to expend chemical energy in the form of heat through the action of Uncoupling Protein-1 (UCP1). Brown adipocytes develop prenatally within distinct brown fat depots and arise from a population of multipotent precursors in the embryonic dermomyotome. By contrast, beige adipocytes arise sporadically within white adipose tissue (WAT) in response to cold exposure and certain other stimuli. In mice, brown fat is predominantly found in the interscapular, cervical, axillary, and perirenal depots, whereas beige fat is most prominent in subcutaneous white fat depots. In humans, the delineation between brown and beige adipose is less well defined; however, depots of brown adipose have been identified in the neck and interscapular regions (particularly in newborns), whereas beige adipose has been found in the supraclavicular region (Bartelt and Heeren, 2014).

Brown and beige adipocyte differentiation from precursor cells (adipogenesis) is regulated by an overlapping set of both pan-adipogenic and brown fat-specific transcription factors. The nuclear receptor peroxisome proliferator-activated receptor gamma (PPARγ) controls the general process of adipogenesis in all fat lineages and also acts in concert with lineage-specific factors to regulate brown fat-specific characteristics. The brown and beige fat precursor marker Early B-Cell Factor 2 (EBF2) drives a brown adipocyte-specific program of gene transcription in fat cells by cooperating with PPARγ. In addition, the transcriptional co-regulator PR Domain-containing Protein 16 (PRDM16) binds with EBF2, C/EBPβ, and PPARy at brown fat-specific regulatory regions and promotes transcription through the recruitment of co-activators such as the Mediator complex. Conversely, many transcription factors including ZFP423, FOXO1, TWIST1, p107, LXRa, pRB, and RIP140 repress brown fat-selective genes either directly or by repressing activators such as PPARy coactivator-1α (PGC1α) (Shao et al., 2016; Seale, 2015). We speculate that many of the transcriptional

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events that control brown adipogenesis are also conserved in beige adipocytes, however, whether a stable mature beige adipocyte exists in an unstimulated state is currently unclear.

Norepinephrine (NE) released by nerve fibers or macrophages in adipose tissue activates thermogenesis in brown/beige adipocytes. This stimulation is also accompanied by adaptive transcriptional changes to support maximal induction of thermogenic capacity. Increased intracellular concentrations of cycle AMP (cAMP) initiate a signaling cascade in which Protein Kinase A (PKA) phosphorylates and activates CREB and the p38/MAPK pathway. p38/MAPK phosphorylates and activates PGC1α, which interacts with PPARγ and PPARα to stimulate the transcription of *Ucp1* and other key thermogenic genes (Cao et al., 2004).

Adrenergic Activation of Brown and Beige Thermogenesis

Brown and beige adipose tissues provide a critical source of heat to protect mammals against hypothermia in the cold. Cold exposure, sensed by the central nervous system, elicits sympathetic outflow to brown and white adipose depots. NE, secreted by sympathetic neurons, binds to beta-adrenergic receptors (βARs) on brown and beige fat cells and triggers a signaling cascade leading to an increase in thermogenic gene expression and lipolysis. Free fatty acids released by lipolysis are both oxidized by mitochondria and bind to UCP1 to activate its function. When activated, UCP1 catalyzes the leak of protons across the inner mitochondrial membrane, resulting in the production of heat rather than ATP from the oxidation of available substrates. Notably, reactive oxygen species (ROS) produced by the mitochondria during cold-induced thermogenesis sensitize UCP1 for activation (Chouchani et al., 2016). In addition to activating thermogenesis in brown and beige fat cells, adrenergic agonists stimulate the differentiation of new brown and beige fat cells from resident precursor cells.

Innate immune regulation of beige fat thermogenesis

Type 2 cytokine signaling plays a major role in beige fat activation. Specifically, upon cold exposure eosinophils expand within WAT and release the cytokine interleukin-4 (IL4). IL4 stimulates alternatively activated macrophages to produce NE, providing a nerve-independent source of catecholamines for beige fat activation (Qiu et al., 2014). IL4 also acts directly on precursor cells in white fat to promote beige adipogenesis. Group 2 innate lymphoid cells (ILC2) also contribute to the induction of beige adipocytes. The cytokine IL33, secreted from adipocytes and endothelial cells, stimulates ILC2 cells to produce IL5 which acts on eosinophils to release IL4 (Lee et al., 2015). In addition to the aforementioned effects of IL4, activated ILC2 cells secrete the peptide methionine-enkephalin (Met-Enk) that binds to the opioid receptor on beige adipogenic cells to promote differentiation and thermogenesis (Brestoff et al., 2015). These innate immune cell pathways present promising targets for inducing the development of beige adipose.

A creatine-dependent energetic uncoupling pathway in beige adipocytes

Beige adipocytes are able to expend energy in a UCP1-independent manner by running a futile creatine-cycle (Kazak et al., 2015). Specifically, creatine kinase activity and a creatine

metabolism gene signature are coordinately elevated by cold-exposure in beige adipocytes. Creatine increases mitochondrial ATP production as well as increasing flux of substrate through the respiratory chain. Depletion of creatine level in mice significantly blunts β3-adrenergic mediates increases in whole body oxygen consumption, suggesting that this pathway plays a critical natural role in beige fat thermogenesis.

References

Bartelt A, Heeren J. Adipose tissue browning and metabolic health. Nature reviews Endocrinology. 2014; 10:24–36.

Brestoff JR, Kim BS, Saenz SA, Stine RR, Monticelli LA, Sonnenberg GF, Thome JJ, Farber DL, Lutfy K, Seale P, et al. Group 2 innate lymphoid cells promote beiging of white adipose tissue and limit obesity. Nature. 2015; 519:242–246. [PubMed: 25533952]

Cao W, Daniel KW, Robidoux J, Puigserver P, Medvedev AV, Floering LM, Spiegelman BM, Collins S. p38 mitogen-activated protein kinase is the central regulator of cyclic AMP-dependent transcription of the brown fat uncoupling protein 1 gene. Molecular Cell Biology. 2004; 24:3057–3067.

Chouchani ET, Kazak L, Jedrychowski MP, Lu GZ, Erickson BK, Szpyt J, Pierce KA, Laznik-Bogoslavski D, Vetrivelan R, Clish CB, et al. Mitochondrial ROS regulate thermogenic energy expenditure and sulfenylation of UCP1. Nature. 2016; 532:112–116. [PubMed: 27027295]

Harms M, Seale P. Brown and beige fat: development, function and therapeutic potential. Nature medicine. 2013; 19:1252–1263.

Kazak L, Chouchani ET, Jedrychowski MP, Erickson BK, Shinoda K, Cohen P, Vetrivelan R, Lu GZ, Laznik-Bogoslavski D, Hasenfuss SC, et al. A creatine-driven substrate cycle enhances energy expenditure and thermogenesis in beige fat. Cell. 2015; 163:643–655. [PubMed: 26496606]

Lee MW, Odegaard JI, Mukundan L, Qiu Y, Molofsky AB, Nussbaum JC, Yun K, Locksley RM, Chawla A. Activated type 2 innate lymphoid cells regulate beige fat biogenesis. Cell. 2015; 160:74–87. [PubMed: 25543153]

Qiu Y, Nguyen KD, Odegaard JI, Cui X, Tian X, Locksley RM, Palmiter RD, Chawla A. Eosinophils and type 2 cytokine signaling in macrophages orchestrate development of functional beige fat. Cell. 2014; 157:1292–1308. [PubMed: 24906148]

Shao M, Ishibashi J, Kusminksi CM, Wang QA, Hepler C, Vishvanath L, MacPherson KA, Spurgin SB, Sun K, Holland WL, Seale P, Gupta RK. Zfp423 maintains white adipocyte identity through suppression of the beige cell thermogenic gen program. Cell Metabolism. 2016; 23:1167–1184. [PubMed: 27238639]

Seale P. Transcriptional Regulatory Circuits Controlling Brown Fat Development and Activation. Diabetes. 2015; 64:2369–2375. [PubMed: 26050669]