



Contents lists available at BioMedSciDirect Publications

International Journal of Biological & Medical Research

Journal homepage: www.biomedscidirect.com



Review article

Fighting Fat With Fat: Brown Adipose Tissue

^aSuchismita Panda, ^bManaswini Mangaraj

^aAssistant Professor, Dept. of Biochemistry, SCB Medical College, Cuttack.

^bAdditional Professor, Dept. of Biochemistry, AIIMS, Bhubaneswar.

ARTICLE INFO

*Brown adipose tissue
Uncoupling protein 1
White adipose tissue*

ABSTRACT

Obesity is the most common metabolic disorder that has become a global problem. The serious clinical problems associated with obesity include an increased risk for type 2 diabetes mellitus, atherosclerosis and cancer. Understanding the origin and development of adipocyte and excess adipose tissue resulting from positive energy balance are critical to analysis and treatment of obesity. The calorie burning brown fat and inducible brown fat like adipocyte known as beige fat in adults might prove useful to play a role in fighting against obesity and reducing the metabolic diseases. Many genes, the transcriptional regulators and factors, that regulate brown and beige adipocyte biology have now been identified providing a variety of therapeutic targets for metabolic diseases.

© Copyright 2010 BioMedSciDirect Publications IJBMR -ISSN: 0976:6685. All rights reserved.

1. Introduction

Obesity and weight gain have been a looming pandemic in today's world posing a severe threat to the public health. The pathological accumulation of excess dysfunctional adipose tissue is a major risk factor for the vast array of diseases including Type 2 diabetes mellitus, cardiovascular disease, hypertension, stroke, arthritis and various types of cancer (1). Weight gain that leads to obesity is due to energy imbalance and occurs when energy intake from food chronically exceeds the energy expended by physical activity and metabolic processes (2). That creates an urgent need for new weight loss treatments.

In the recent years, the topic of brown adipose tissue (BAT) has been reinvigorated with many new studies regarding its function and therapeutic promises (3). Brown adipose tissue (BAT) is a key site of heat production (thermogenesis) in mammals that has for many decades been considered as an attractive target to promote weight loss. The heat produced by BAT is essential for the survival of small mammals whenever an organism needs extra heat in cold environments, postnatally, as well as for arousal in hibernators. While White Adipose Tissue (WAT) is characterized by single, large lipid droplet and few mitochondria, BAT contains several small lipid droplets with many mitochondria and uniquely expressed uncoupling protein 1 (UCP1). UCP1 is localized to the inner mitochondrial membrane and acts to uncouple oxidative

phosphorylation from ATP production due to the dissipation of the proton gradient, thereby resulting in the release of energy as heat. When maximally activated, BAT can generate heat up to 300W/kg of tissue compared to 1W/kg from most other tissues (4).

BAT persists as a distinct tissue in small mammals in between the shoulder blades. The major deposit of BAT in the newborn humans regresses shortly after birth and becomes nonexistent and nonfunctional in adult humans. However, recent study by Saito et al (5), Cypess et al (6), van Marken Lichtenbelt et al (7) and Virtanen et al (8) have unambiguously demonstrated that healthy adults have significant depots of metabolically active BAT. During PET imaging studies, symmetrically localized depots of fatty tissue were frequently identified as hotspots for fluorodeoxyglucose (FDG) uptake. Tissue biopsy corresponding to the positron emission tomography have demonstrated positive regions of BAT specific protein UCP1 (9). Most importantly, the tissue identified in adult humans as BAT gets remarkably stimulated to take up glucose on exposure to cold whereas becomes undetectable in people who are kept warm (5).

Consequently, the presence of BAT has now been confirmed in different patient population from across the world. It is now apparent that potentially every human possesses BAT which can be rapidly activated by cold exposure (10), the amount decreases with age (6) and body mass index (11) and it is more likely to be detected in female than male patients (6, 12).

* Corresponding Author : **Dr Suchismita Panda**

Asst. Prof., Dept. of Biochemistry,

SCB Medical College, Cuttack.

Email: dr.suchismitapanda17@gmail.com

Brown adipocytes are derived from a myogenic lineage, separate entirely from white adipose tissue (13) and have a bidirectional cell fate switch between skeletal myoblasts and brown fat cells with help of a transcriptional regulator PRDM16. However, not all of brown fat cells are derived from precursors expressing myogenic makers. In adult life, brown fat cells located in the non-classic sites such as WAT and skeletal muscle are derived from the myf5 negative progenitors. These non-classic brown adipocytes have been named as BROWN in WHITE or BRITE cells or beige cells, that reflects their recruitable and inducible nature. Beige cells resemble white fat cells in having extremely low basal expression of UCP1, but like classical brown fat, they respond to cyclic AMP stimulation with high UCP1 expression and respiration rates. (14). Brown adipocytes are present within the white adipose depots and the transcriptional control of these and classical brown adipocytes remains an area of immense research interest. The developmental regulation of BAT and its subsequent loss into adulthood makes a significant contribution to overall energy balance (15).

However, brown and beige cells should be considered as distinct cell types because of many distinguishing characteristics between them. Beige cells are derived from different embryonic (Myf5 negative) precursors. These cell types are differentially regulated as a number of quantitative trait loci are associated with the induced development of beige but not of brown adipocytes (16). Both of them express distinct and distinguishing gene signatures (17,18). Brown adipocytes express high levels of Ucp1 and other thermogenic genes under basal conditions,

whereas beige adipocytes express these genes only in response to activators such as agonists of the β -adrenergic receptor or peroxisome proliferator-activated receptor- γ (Ppar- γ) (19). Beige fat cells are a distinct cell type and that there is already one polypeptide hormone that preferentially activates beige fat: irisin (20). Fully stimulated brown and beige adipocytes contain comparable amounts of Ucp1, suggesting that they have similar thermogenic capacities, though the relative abundance of UCP1 in beige cells is substantially lower than "classic" BAT. (21)

In formed WAT, whether beige adipocytes come from white adipocytes through transdifferentiation or arise through the de novo differentiation and maturation of precursors remains to be answered. Himms-Hagen et al. (22) found that most beige adipocytes arise from pre-existing (nondividing) cells that they presumed were mature adipocytes. Since then, Cinti and others have provided substantial evidence in support of the idea that large unilocular white adipocytes transform into beige adipocytes in response to cold or β 3-adrenergic agonists (23). The thermogenic profile of beige adipocytes is reversible. Beige adipocytes acquired in WAT during cold exposure express Ucp1. This expression is lost when the mice are moved back to warmer conditions. Re-exposure to cold, induces cells for Ucp1 re-expression (24,25).

Regulation of brown and beige adipocytes by PRDM16

Prdm16 is a large zinc finger-containing transcriptional factor that is highly expressed in mouse BAT and in human BAT relative to visceral WAT (26,27). This Prdm16 acts primarily through binding to and modulating the activity of other transcriptional factors, including c/EBP β , Ppar- γ , Ppar- α and Pgc-1 α . Knockdown of Prdm16 ablates the thermogenic characteristics of brown fat cells while also causing an increase in the expression of white fat-specific and muscle-specific genes (28,29). Multiple factors regulate brown and beige adipocyte differentiation by modulating Prdm16 expression.

Bone morphogenetic proteins (BMPs) regulate the formation and thermogenic activity of BAT. Bone morphogenetic protein 7 (Bmp7) which is a signal for brown fat development, increases the amounts of Prdm16 mRNA in brown and white fat precursor cells, BMP7 singularly promotes differentiation of brown preadipocytes by activating a full program of brown adipogenesis including induction of early regulators of brown fat fate PRDM16 and PGC-1 α , (peroxisome proliferator-activated receptor- γ (PPAR γ) coactivator-1 α ; increased expression of the brown-fat-defining marker uncoupling protein 1 (UCP1) and adipogenic transcription factors PPAR γ with induction of mitochondrial biogenesis, BMP7 triggers commitment of mesenchymal progenitor cells to a brown adipocyte lineage, and implantation of these cells into nude mice resulting in development of adipose tissue containing mostly brown adipocytes. Marked paucity of brown fat and an almost complete absence of UCP1 are seen in Bmp7 knockout embryos, (30-32).

Thiazolidinediones (TZDs), which agonize Ppar- γ , induce thermogenic gene expression in fat cells through its effects on Prdm16 (33,34). miR-133 directly targets and negatively regulates PRDM16, and inhibition of miR-133 promotes differentiation of precursors from BAT and subcutaneous WAT to mature brown adipocytes, thereby leading to increased mitochondrial activity. miRNA133 reduces the amounts of PRDM16 by acting as a central upstream regulator of Prdm16 and hence of brown adipogenesis in response to cold exposure (35). Physiological stimuli, such as cold exposure and sympathetic activation, are also known to induce brown adipogenesis in white depots (36). Cyclooxygenase (COX)2, a rate-limiting enzyme in prostaglandin (PG) synthesis, promote de novo BAT in WAT and increased energy expenditure, and exerts anti-obesity effects in high-fat fed mice (37). peroxisome proliferator-activated receptor gamma (PPAR γ) coactivator 1 α (PGC-1 α), a distinct nuclear factor, controls the thermogenic activation of adipocyte and is now recognized as a master regulator of mitochondrial biogenesis and oxidative metabolism in many cell types. Pgc-1 α expression and activity are regulated directly by the β -adrenergic signaling pathway (38,39) and is a cold induced interacting partner of Ppar γ , providing a link between the physiological activator of brown fat thermogenesis and the transcriptional machinery in brown

adipocytes. The retinoblastoma family members pRb and p107 repress Pgc-1 α transcription to block the expression of brown genes in white adipose tissue, they regulate PGC-1 α expression to control the switch between white and brown adipocyte differentiation from a common pool of presumptive adult progenitors in fat tissue. (40)

The potential beneficial effects of acquiring brown fat cells in non-classic BAT locations, such as WAT and skeletal muscle has got appreciation recently. In addition to thermogenesis, BAT is involved in triglyceride clearance and glucose disposal, serves as a source of adipokines, and possesses distinct inflammatory function compared with WAT(3). Several BAT derived adipokines like fibroblast growth factor(FGF21), is induced upon cold and adrenergic stimulation... FGF21 specifically targets BAT thermogenic activation in neonates and indicate that FGF21 released by the liver may be a novel key signal contributing to neonatal activation of BAT thermogenesis in response to the initiation of milk intake.(41). BAT is more highly innervated by the sympathetic nervous system and contains a more richly developed vasculature, stimulation of which results in the release of norepinephrine that binds to adrenergic receptors and stimulates cAMP production and PKA activation. Downstream of cAMP and PKA, HSL(hormone sensitive lipase) and perilipin are phosphorylated and activated(42). Perilipin A protects the lipid droplet, but after phosphorylation and activation it induces fatty acid cleavage. fatty acid release from triglycerides by hormone sensitive lipase enter into the mitochondria by the carnitine shuttle and activate UCP1 to be metabolized through β -oxidation pathways(3). Beta adrenergic receptor subtypes regulate different physiological responses stimulated by Norepinephrine in brown adipocyte by differentially transducing signals to subcellular compartments. Thyroid hormone enhances facultative thermogenesis by interacting synergistically with the sympathetic nervous system, and directly increasing basal metabolic rate (obligatory thermogenesis). It has a synergistic role with the sympathetic input to the BAT to increase mitochondrial activity and nuclear transcription of genes that affect thermogenesis, including UCP1(43).

The brown fat targeted therapies have been highlighted for its tremendous promise in the treatment of obesity and associated health consequences and serve as an effective sink for disposing of excess glucose and fatty acids. This suggests that such therapies could be very effective for treating insulin resistance, type-2 diabetes, and dyslipidemia without necessarily reducing body weight. The increase in BAT activity can be brought about either through sympathetic stimulation or activation of UCP1 pathways. In addition to sympathetic input, several other hormones and factors have been shown to regulate energy expenditure in adipose tissue. Hormone Irisin, secreted from the myocytes by exercise training, stimulates the browning of WAT through specific action on beige preadipocyte population(17).

A modest increase in the serum concentration of irisin in mice stimulates beige fat development leading to increased glucose tolerance and suppressed weight gain(44). However, the receptors for irisin in beige fat precursors, signal to transcriptional machinery and its effect on other tissues are not known. Fibroblast growth factor(FGF21) expression is increased by cold exposure and adrenergic stimulation. It has an important role in thermogenesis for which it has become a focus of clinical trial for obesity, diabetes and cardiovascular disease(45). High circulating levels of natriuretic peptide have been associated with weight loss in humans. Increased concentration of natriuretic peptide in mice promote beige adipocyte development in WAT and increased thermogenic gene expression in BAT by the direct effect of natriuretic peptide on adipose cells through cGMP dependent protein kinase pathway, the ability of natriuretic peptides together with catecholamines to modulate uncoupled respiration and control white fat mass may serve as a therapeutic target for the management of obesity and the metabolic complications that accompany it (46). Cold increases the concentration of natriuretic peptide, suggesting that this browning system have evolved to safeguard cardiac function in animals during cold exposure, which may allow pharmacological targeting of this pathway(48). Neurotransmitter Orexin plays an integral role in adaptive thermogenesis and body weight regulation via effects on BAT differentiation and function, it may augment BAT function by regulating sympathetic outflow which is an important target(47).

Interestingly, transplantation of BAT into the visceral cavity of recipient mice is able to prevent weight gain and improve glucose homeostasis in diet-induced obese mice(49,50). However, it remains to be determined whether rodent BAT studies are translatable to understanding the biology of human BAT. Since skin fibroblasts or the stromal vascular fraction from adipose tissues are relatively easy to obtain, even from humans, autologous transplantation of engineered brown fat cells generated by expressing PRDM16 and other factors would be a feasible way to generate brown adipose tissue(51). Alternative ways also need to be explored to induce brown fat activity and its development. Screening chemical compounds or drugs to induce dominant brown fat regulators such as PRDM16 or PGC-1 α is certainly plausible. By characterizing the upstream inductive components, such as endogenous hormones/polypeptides that stimulate the formation of brown fat cells during development will also play a valuable role. Future research regarding BAT function will further explore our understanding of its unique physiology as well as its therapeutic promise.

References

- Bray GA, Bellanger T. Epidemiology, trends, and morbidities of obesity and the metabolic syndrome. *Endocrine*. 2006;29:109–117.
- Patrick Seale and Mitchell A. Lazar: Brown Fat in Humans: Turning up the Heat on Obesity. *DIABETES*, 2009;5:1482–1484.
- Townsend KL, Tseng Y H. Brown adipose tissue; recent insights into development, metabolic function and therapeutic potential. *Adipocyte*. 2012;1:13–24.
- Power G.G. Biology of temperature: the mammalian fetus. *Journal of Developmental Physiology*. 1989; 12(6):295–304.
- Saito M, Okamatsu-Ogura Y, Matsushita M, Watanabe K, Yoneshiro T, Nio-Kobayashi J, Iwanaga T, Miyagawa M, Kameya T, Nakada K, Kawai Y, Tsujisaki M. High incidence of metabolically active brown adipose tissue in healthy adult humans: effects of cold exposure and adiposity. *Diabetes*. 2009;58:1526–1531.
- Cypess AM, Lehman S, Williams G, Tal I, Rodman D, Goldfine AB, Kuo FC, Palmer EL, Tseng YH, Doria A, Kolodny GM, Kahn CR. Identification and importance of brown adipose tissue in adult humans. *N Engl J Med*. 2009;360:1509–1517.
- Van Marken Lichtenbelt WD, Vanhomerig JW, Smulders NM, Drossaerts JM, Kemerink GJ, Bouvy ND, Schrauwen P, Teule GJ. Cold-activated brown adipose tissue in healthy men. *N Engl J Med*. 2009;360:1500–1508.
- Virtanen KA, Lidell ME, Orava J, Heglin M, Westergren R, Niemi T, Taittonen M, Laine J, Savisto NJ, Enerback S, Nuutila P. Functional brown adipose tissue in healthy adults. *N Engl J Med*. 2009;360:1518–1525.
- Nedergaard J, Bengtsson T, Cannon B. Unexpected evidence for active brown adipose tissue in adult humans. *Am J Physiol Endocrinol Metab*. 2007;293:E444–E452.
- Symonds M.E, Henderson K, Elvidge L, Bosman C, Sharkey D, Perkins A C, Budge H. Thermal imaging to assess age-related changes of skin temperature within the supraclavicular region co-locating with brown adipose tissue in healthy children. *Journal of Pediatrics*. 2012;161:892–898.
- Vijgen G. H. E. J, Bouvy N. D., Teule G. J. J, Brans B, Schrauwen P, van Marken Lichtenbelt W.D. Brown adipose tissue in morbidly obese subjects. *PLoS ONE*. 2011; 6(2): Article ID e17247.
- Nedergaard J, Bengtsson T, Cannon B. Three years with adult human brown adipose tissue. *Annals of the New York Academy of Sciences*. 2010;1212:E20–E36.
- Seale P, Bjork B, Yang W, Kajimura S, Chin S, Kuang S, Scimè A, Devarakonda S, Conroe HM, Erdjument-Bromage H, Tempst P, Rudnicki MA, Beier DR, Spiegelman BM. PRDM16 controls a brown fat/skeletal muscle switch. *Nature*. 2008;454(7207):961–967.
- Petrovic N, Walden TB, Shabalina IG, Timmons JA, Cannon B, Nedergaard J. Chronic PPAR γ activation of epididymally derived white adipocyte cultures reveals a population of thermogenically competent, ucp1-containing adipocytes molecularly distinct from classical brown adipocytes. *J Biol Chem*. 2010;285:7153–64.
- Symonds M.E, Brown Adipose Tissue Growth and Development, *Scientifica (Cairo)*, 2013:2013(305763)
- Xue B, Rim J S, Hogan J C, Coulter A A, Koza R A, Kozak L P. Genetic variability affects the development of brown adipocytes in white fat but not in interscapular brown fat. *J. Lipid Res*. 2007;48:41–51.
- Wu J, Boström P, Sparks LM, Ye L, Choi JH, Giang AH, Khandekar M, Virtanen KA, Nuutila P, Schaart G, Huang K, Tu H, van Marken Lichtenbelt WD, Hoeks J, Enerbäck S, Schrauwen P, Spiegelman BM. Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. *Cell*. 2012;150:366–376.
- Sharp L.Z., Shinoda K., Ohno H., Scheel D.W., Tomoda E, Ruiz L, Hu .H, Wang L, Pavlova Z, Gilsanz V, Kajimura S. Human BAT possesses molecular signatures that resemble beige/brite cells. *PLoS ONE* 7(11).2012; e49452.
- Petrovic N, Walden TB, Shabalina I.G, Timmons J.A, Cannon B, and Nedergaard J. Chronic peroxisome proliferator-activated receptor γ (PPAR γ) activation of epididymally derived white adipocyte cultures reveals a population of thermogenically competent, UCP1-containing adipocytes molecularly distinct from classic brown adipocytes. *J. Biol. Chem*. 2010;285:7153–7164.
- Wu J., Cohen P., Spiegelman B.M., Adaptive thermogenesis in adipocytes: is beige the new brown?. *Genes Dev*. 2013;27:234–250.
- Nedergaard J, Cannon B. UCP1 mRNA does not produce heat. *Biochimica et Biophysica Acta*. 2013;13:27–29.
- Himms-Hagen . Multilocular fat cells in WAT of CL-316243-treated rats derive directly from white adipocytes. *Am. J. Physiol. Cell Physiol*. 2000;279:C670–C681.
- Vitali, A. , Murano .I., Zingaretti M.C., Frontini .A, Ricquier .D, and Cinti .S. The adipose organ of obesity-prone C57BL/6J mice is composed of mixed white and brown adipocytes. *J. Lipid Res*. 2012;53:619–629.
- Rosenwald M., Perdikari A, Rulicke T , Wolfsum C. Bi-directional interconversion of brite and white adipocytes. *Nat. Cell Biol*. 2013;15:659–667.
- Park A, Kim WK, Boe K-H. Distinction of white, beige and brown adipocytes derived from mesenchymal stem cells. *World J Stem Cells*. 2014;6(1):33–42.
- Seale P, Kajimura S, Yang W, Chin S, Rohas LM, Uldry M, Tavernier G, Langin D, Spiegelman BM. Transcriptional control of brown fat determination by PRDM16. *Cell Metab*. 2007;6:38–54.
- Harms MJ, Ishibashi J, Wang W, Lim H-W, Goyama S, Sato T, Kurokawa M, Won K-J, Seale P . Prdm16 is required for maintenance of brown adipocyte identity and function in adult mice. *Cell Metabolism*, 2014;19(4),593–604.
- Seale P, Bjork B, Yang W, Kajimura S, Chin S, Kuang S, Scimè A, Devarakonda S, Conroe HM, Erdjument-Bromage H, Tempst P, Rudnicki MA, Beier DR, Spiegelman BM. PRDM16 controls a brown fat/skeletal muscle switch. *Nature*. 2008;454:961–967.
- Seale P, Conroe H M, Estall J, Kajimura S, Frontini A, Ishibashi J, Cohen P, Cinti S, Spiegelman B M. Prdm16 determines the thermogenic program of subcutaneous white adipose tissue in mice. *J. Clin. Invest*. 2011;121:96–105.
- Tseng YH, Kokkotou E, Schulz TJ, Huang TL, Winnay JN, Taniguchi CM, Tran TT, Suzuki R, Espinoza DO, Yamamoto Y, Ahrens MJ, Dudley AT, Norris AW, Kulkarni RN, Kahn CR. New role of bone morphogenetic protein 7 in brown adipogenesis and energy expenditure. *Nature*. 2008;454:1000–1004.
- Schulz TJ, Huang TL, Tran TT, Zhang H, Townsend KL, Shadrach JL, Cerletti M, McDougall LE, Giorgadze N, Tchonia T, Schrier D, Falb D, Kirkland JL, Wagers AJ, Tseng YH . Identification of inducible brown adipocyte progenitors residing in skeletal muscle and white fat. *Proc. Natl. Acad. Sci. USA*. 2011;108:143–148.
- Schulz, T.J., Huang, P., Huang, T.L., Xue, R., McDougall, L.E., Townsend, K.L., Cypess, A.M., Mishina, Y., Gussoni, E., and Tseng, Y.H. Brown-fat paucity due to impaired BMP signalling induces compensatory browning of white fat. *Nature*. 2013;495:379–383.
- Ohno H., Shinoda K., Spiegelman, Kajimura B.M. PPAR γ agonists induce a white-to-brown fat conversion through stabilization of PRDM16 protein. *Cell Metab*. 2012;15:395–404.
- Qiang L, Wang L, Kon N, Zhao W, Lee S, Zhang Y, Rosenbaum M, Zhao Y, Gu W, Farmer SR, Accili DB. Brown remodeling of white adipose tissue by SirT1-dependent deacetylation of Ppar γ . *Cell*. 2012;150:620–632.
- Trajkovski M., Ahmed K., Esau C.C, Stoffel M. MyomiR-133 regulates brown fat differentiation through Prdm16. *Nat. Cell Biol*. 2012;14:1330–1335.
- Frontini A, Cinti S. Distribution and development of brown adipocytes in the murine and human adipose organ. *Cell Metabolism*. 2010;11:253–256.

37. Vegiopoulos A, Muller-Decker K, Strzoda D, Schmitt I, Chichelnitskiy E, Ostertag A, et al. Cyclooxygenase-2 controls energy homeostasis in mice by de novo recruitment of brown adipocytes. *Science* 2010; 328:1158-61.
38. Cao W, Daniel KW, Collins S. p38 mitogen-activated protein kinase is the central regulator of cyclic AMP-dependent transcription of the brown fat uncoupling protein 1 gene. *Mol. Cell Biol.* 24, 3057–3067 (2004).
39. Puigserver P, Wu Z, Park CW, Graves R, Wright M, Spiegelman BM. A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. *Cell*. 1998;92:829–839.
40. Scimè A, Grenier G, Huh MS, Gillespie MA, Bevilacqua L, Harper ME, Rudnicki MA. Rb and p107 regulate preadipocyte differentiation into white versus brown fat through repression of PGC-1 α . *Cell Metab.* 2005;2(5):283-95.
41. Hondares E, Rosell M, Gonzalez FJ, Giralto M, Iglesias R, Villarroya F. Hepatic FGF21 expression is induced at birth via PPAR α in response to milk intake and contributes to thermogenic activation of neonatal brown fat. *Cell Metab.* 2010; 11:206-12.
42. Chaudhry A, Granneman JG. Differential regulation of functional responses by beta-adrenergic receptor subtypes in brown adipocytes. *Am J Physiol.* 1999; 277:R147-53.
43. Silva JE. Physiological importance and control of nonshivering facultative thermogenesis. *Front Biosci (Schol Ed)* 2011; 3:352-71.: 352 - 371.
44. Boström P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, Rasbach KA, Boström EA, Choi JH, Long JZ, Kajimura S, Zingaretti MC, Vind BF, Tu H, Cinti S, Højlund K, Gygi SP, Spiegelman BM. A PGC1- α -dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature*. 2012; 481:463–468.
45. Xu J, Lloyd DJ, Hale C, Stanislaus S, Chen M, Sivits G, Vonderfecht S, Hecht R, Li YS, Lindberg RA, Chen JL, Jung DY, Zhang Z, Ko H-J, Kim JK, Véniant MM, et al. Fibroblast growth factor 21 reverses hepatic steatosis, increases energy expenditure, and improves insulin sensitivity in diet-induced obese mice. *Diabetes*. 2009; 58:250–259.
46. Bordicchia M, Liu D, Amri E-Z, Ailhaud G, Dessì-Fulgheri P, Zhang C, Takahashi N, Sarzani R and Collins S et al. Cardiac natriuretic peptides act via p38 MAPK to induce the brown fat thermogenic program in mouse and human adipocytes. *J. Clin. Invest.* 122, 1022–1036 (2012).
47. Sellayah, D., Bharaj, P. & Sikder, D. Orexin is required for brown adipose tissue development, differentiation and function. *Cell Metab.* 14, 478–490 (2011)
48. Harms M, Seale P. Brown and beige fat: development, function and therapeutic potential. *Nature*; 19(10):1252-1262.
49. Stanford KI, Middelbeek RJ-W, An D, Townsend KL, Hitchcox KM, Jung DY. Transplantation of Brown Adipose Tissue Exerts Beneficial Effects on Glucose Homeostasis. *Diabetes*. 2011.
50. Boss O, Farmer SR. Recruitment of Brown Adipose Tissue as a Therapy for Obesity-Associated Diseases. *Frontiers in Endocrinology* .2012;3:14.
51. Kajimura S, Seale P, and Spiegelman B.M. Transcriptional control of brown fat development. *Cell Metabolism* 2010, 11(4):257-262.