Front. Med.
https://doi.org/10.1007/s11684-017-0555-2

REVIEW

Role of brown adipose tissue in metabolic syndrome, aging, and cancer cachexia

Meng Dong[1,2,*], Jun Lin[1,2,*], Wonchung Lim[3], Wanzhu Jin[1], Hyuek Jong Lee (✉)[1,4]

[1]*Key Laboratory of Animal Ecology and Conservation Biology, Institute of Zoology, Chinese Academy of Sciences, Beijing 100101, China;* [2]*The University of the Chinese Academy of Sciences, Beijing 100049, China;* [3]*Department of Sports Medicine, College of Health Science, Cheongju University, Cheongju 363-764, Republic of Korea;* [4]*Center for Vascular Research, Institute for Basic Science (IBS), Daejeon 34141, Republic of Korea*

© Higher Education Press and Springer-Verlag GmbH Germany 2017

Abstract **Brown adipose tissue (BAT) plays a fundamental role in maintaining body temperature by producing heat. BAT that had been know to exist only in mammals and the human neonate has received great attention for the treatment of obesity and diabetes due to its important function in energy metabolism, ever since it is recently reported that human adults have functional BAT. In addition, beige adipocytes, brown adipocytes in white adipose tissue (WAT), have also been shown to take part in whole body metabolism. Multiple lines of evidence demonstrated that transplantation or activation of BAT or/and beige adipocytes reversed obesity and improved insulin sensitivity. Furthermore, many genes involved in BAT activation and/or the recruitment of beige cells have been found, thereby providing new promising strategies for future clinical application of BAT activation to treat obesity and metabolic diseases. This review focuses on recent advances of BAT function in the metabolic aspect and the relationship between BAT and cancer cachexia, a pathological process accompanied with decreased body weight and increased energy expenditure in cancer patients. The underlying possible mechanisms to reduce BAT mass and its activity in the elderly are also discussed.**

Keywords brown adipose tissue; beige adipocyte; anti-obesity; anti-diabetes; cancer cachexia; aging

Introduction

Adipose tissue is an essential organ in regulating energy homeostasis. Human and small mammals exhibit mainly two different types of fat tissue, namely, white adipose tissue (WAT) and brown adipose tissue (BAT). BAT, as a thermogenic organ, is involved in the maintenance of body temperature. BAT consumes energy by generating heat through the expression of uncoupling protein 1 (UCP1) in its inner mitochondrial membrane [1]. BAT, as an endocrine organ, also plays a key role in glucose and lipid metabolism by consuming fatty acids (FAs) and glucose and regulating energy homeostasis [2,3]. Human adults possess functional BAT and the presence and/or activity of BAT is negatively related to age, body mass index (BMI), and glucose level [4–6]. Thermogenesis is a major function of BAT in rodent and human adult [7–9]. In terms of human neonates, the core and skin temperature can decrease immediately after delivery at a rate of approximately 0.1 and 0.3 °C per minute, respectively, due to physical characteristics and environmental factor [10]. To prevent hypothermia, the neonate should activate nonshivering thermogenesis (NST), which is associated with lipolysis in BAT to accelerate heat production [11]. In newborn sheep, impaired BAT thermogenesis results in life-threatening hypothermia [12]. Human neonates who died of cold syndrome also show BAT depletion, whereas healthy neonates exhibit a considerable amount of BAT [13]. Therefore, BAT might also be important for human neonates to maintain body temperature. However, the thermogenic function of BAT in human neonates is not well studied due to the absence of safe protocol for temperature challenge.

Brown adipocyte arises from progenitor cell that shares common myogenic transcriptional characteristic, such as Myf5 and Pax7 [14–16]. PRD1-BF-1-RIZ1 homologous domain 16 (PRDM16) and CCAAT/enhancer binding

Received July 12, 2016; accepted April 29, 2017
Correspondence: leehj@ioz.ac.cn

*These authors have contributed equally to this work.

protein-β (C/EBPβ) complexes that induce the expression of peroxisome proliferator-activated receptor γ (PPARγ) and peroxisome proliferator-activated receptor-γ coactivator-1 (PGC-1), key regulators of the brown fat programming, are responsible for the differentiation of brown adipocyte from myoblast [14,17]. As a third type of adipocyte, beige cells that are recruited in WAT by cold exposure or β3-adrenoceptor agonist treatment express large amount of UCP1, a specific marker of brown adipocyte [18,19]. Beige cell originates from $PDGFR\alpha^{+}CD34^{+}Sca1^{+}$ precursor cell rather than from Myf5-positive myoblast [15,20], but its gene characteristics show a similarity to that of classical BAT [21]. For the brown adipogenesis, brown adipocyte-specific proteins such as PGC-1α, PRDM16, and UCP1 are essential [22]. UCP1, mainly expressed in brown adipocytes and beige cells, releases chemical energy as heat by dissipating pH gradient generated by oxidative phosphorylation [23,24]. Originally, UCP1-deficient mouse has an impairment of thermoregulation, whereas UCP1 deficiency is not associated with hyperphagia or obesity due to a compensation mechanism of UCP2 induction [25]. However, UCP1 ablation results in obesity and impairment of diet-induced thermogenesis at thermoneutrality [26]. Thus, UCP1 is essential for thermoregulation and control of metabolism in thermoneutral condition.

Although the different functions between classical brown adipocytes and beige cells should be elucidated, both cells express thermogenic genes and thereby play a critical role in the maintenance of body temperature under cold environment. Therefore, brown and beige adipocytes are promising targets for the treatment of obesity and its related metabolic disorders.

Anti-obesity effect of BAT and beige fat

When energy intake exceeds energy consumption, obesity occurs as a result of caloric imbalance. Although decreasing energy intake is the primary option to prevent and treat obesity, the effort is not effective. BAT, as a thermogenic organ, provides a new therapeutic strategy for the treatment of obesity because BAT activity is negatively correlated with BMI in human [4,27–29].

When the BAT from healthy mouse is transplanted in mouse to simply increase its mass, increased BAT mass prevents and reverses obesity in high-fat diet (HFD)-induced obese mice [30–32] and Ob/Ob mice [33]. Transplanted BAT increases the activity of endogenous BAT by secreting IL-6 [30], adiponectin [33], or unknown potential cytokines [31,32]. These findings suggested that increased BAT mass enhances energy expenditure, which results in an anti-obesity effect. Nevertheless, BAT transplantation is not applicable to human. Cell-based strategy, such as transplantation of thermogenic adipocytes that are differentiated *in vitro* from autologous cells after autopsy, is considered an alternative option to overcome this issue [34].

Cold exposure-induced NST remarkably reduces body weight in HFD-induced rodent models or fat mass in human subjects [35–37], since cold exposure activates BAT and induces the recruitment of beige adipocytes in WAT. Cold challenge activates sympathetic nervous system (SNS) to release noradrenaline (NE) that binds to β3-adrenergic receptor (β3-AR) and eventually promotes the expression of UCP1 in BAT [38,39] and WAT [40,41]. The treatment of CL-316243, a β3-AR agonist, also reduces adiposity in rodent models through activating BAT thermogenesis [42,43]. In addition, eosinophils, type II cytokines, and group 2 innate lymphoid cells (ILC2) play important roles in beige fat formation [44–46]. Fibroblast growth factor 21 (FGF21) [47,48], bone morphogenetic proteins (BMPs) [49–51], and cardiac natriuretic peptide [52] also regulate brown and beige fat activity, thereby reducing body weight by activating thermogenesis in rodent models. In obese human subjects, a clinical study with LY2405319, a FGF21 mimetic, shows beneficial metabolic effects with modest body weight reduction [53]. In addition to a β3-AR agonist and FGF21 mimetic, natural compounds, such as capsaicin and capsinoid, can reduce body fat mass in small rodents and humans [54] by activating transient receptor potential cation channel, subfamily V, member 1, which stimulates SNS to release NE and enhances the activity of BAT [54–58]. For clinical usage of these compounds, defined clinical studies are required because BAT activation could induce adverse effects on other metabolic diseases such as atherosclerosis.

In spite of the anti-obesity potential of BAT, BAT activation-induced lipolysis increases more plasma lipoprotein remnant than that of hepatic clearance capacity, thereby aggravating the atherosclerotic plaque development and instability in ApoE- or LDLR-deficient mice [59]. However, BAT activation in APOE*3-Leiden.CETP transgenic mice, which preserves hepatic remnant clearance, protects atherosclerosis. It indicates that BAT activation attenuates atherosclerosis only when the liver can clear lipoprotein remnants [60]. Therefore, clinical application with chemicals or natural compounds for the activation of BAT should be carefully considered yet for patients who possess metabolic complications, except for simple obesity.

Role of BAT and beige fat in diabetes mellitus (DM)

BAT tightly regulates the systemic level of FA and glucose that are the main fuel for UCP1-mediated BAT thermogenesis [2,8,61]. The BAT mass ranging from ~30 g to 300 g is able to contribute to 20% of daily resting energy

expenditure (REE) [4,62]. In addition, BAT mass and its ability to uptake glucose in basal and cold environment are decreased in obese and diabetes patients [27–29], indicating that decreased BAT activity is associated with DM. The number of studies describing that BAT mass or its activity mediates insulin resistance has been increasing in recent years. In streptozotocin-induced and autoimmune-mediated type 1 DM (T1DM) mice, BAT transplantation improves glucose tolerance and reverses polydipsia, polyphagia, and polyuria that are major symptoms of T1DM, resulting in euglycemia [63,64]. Furthermore, BAT transplantation in HFD and Ob/Ob mice significantly enhances glucose tolerance and insulin sensitivity [30–33]. Implantation of differentiated human UCP1-positive beige adipocytes or functional brown adipocytes differentiated from human pluripotent stem cells (hPSCdBA) also enhances glucose tolerance in mice [65–67]. Additionally, prolonged exposure to cold or CL-316,243 treatment increases BAT mass and results in improved glucose intolerance in obese rat [36,42,43]. In humans, cold-induced BAT activation also increases glucose uptake by ~12 folds [68] and enhances glucose homeostasis and insulin sensitivity [69]. These studies supported that activated BAT markedly increases the uptake rate of triglyceride, ameliorating the insulin resistance in mice [61].

These beneficial effects are, at least in part, from batokines defined as cytokines released from BAT. BAT expresses FGF21, IL-6, adiponectin, T3, BMP8B, prostaglandin D2 synthase (PTGDS), Nrg4, VEGFA, and VEGFB [70–72]. In particular, FGF21 [73–75], IL-6 [30,76,77], adiponectin [33], PTGDs [78], and BMP8B [51] reverse hyperglycemia and improve insulin sensitivity through autocrine and/or endocrine mechanisms. Nrg4 regulates glucose homeostasis by activating ErbB3 and ErbB4 signaling pathway in the liver [79]. Additionally, VEGFA and VEGFB exhibit antidiabetic effect through endocrine and paracrine mechanisms [80–83].

For the clinical application of BAT activation on obesity or DM, determining molecules with remarkable efficiency as that of cold exposure or CL-316,243 would be a valuable therapeutic approach.

Mass and activity of BAT in aging

According to the ^{18}F-FDG PET-CT imaging analysis, most prominent ^{18}F-FDG uptake regions are cervical-supraclavicular and paracervical adipose tissues in human [4–6]. The gene characteristics of human UCP1^{+} brown adipocytes are more similar to those of mouse beige adipocytes than those of mouse classical brown adipocytes [19,84]. The amount of BAT after cold stimulus is inversely correlated with age, and BAT is barely detected in the elderly who is more than 60 years old [85]. The reason why BAT mass is reduced in human is unknown. Wide distribution of BATs in human neonates is associated with NST for protection against cold because they possess an immature heat generation mechanism. However, adults exhibit another mechanism to produce heat from shivering and voluntary muscular activity in cold environment. Therefore, a transition from nonshivering to shivering thermogenic mechanism might exist with aging [86,87].

The proposed mechanisms for the reduction of BAT in the elderly include defective hormonal signals (pituitary growth hormone and sex hormones) [85], BAT stem cell alteration [88], mitochondrial dysfunction [89], and decreased brain activity [90]. Sex hormones, such as estrogens and androgens, decline in late adulthood and inhibit the activity of glucocorticoids that negatively regulate BAT activity [85]. Aging is accompanied with progressive impairment of stem cell function, which leads to the regenerative defect of BAT in the elderly [88]. Reduced sensitivity to sympathetic tone, accumulated DNA mutations and ROS damages could be possible explanations for the defective function of stem cell in the elderly [88,89]. Recently, the central nervous system is suggested to be responsible for the decreased BAT activity in aging. After cold exposure, regional brain FDG uptake analyzed by ^{18}F-FDG PET-CT imaging is remarkably attenuated in an old man compared with that in a young man [90]. Given that brain circuit mediates the autonomic nervous system that is dysfunctional in obesity and aging, impairment of central nervous activity could have caused BAT inactivity in the elderly. Liver-derived FGF21 regulates insulin sensitivity, mitochondrial activity, lipid metabolism, ketogenesis, and lifespan extension in mice. More than 30% of female FGF21-Tg mice extend their lifespan to approximately 44 months [91] by activating AMPK and Sirt1 [92], that promote longevity [93]. BAT increases FGF21 secretion after cold exposure or chemical compound administration [94]. In addition, FGF21 overexpression increases the perithymic BAT and protects age-related thymic lipoatrophy, thereby delaying immune senescence. The reduction of thymic lipotoxicity induced by BAT lipid uptake can be regarded as one of the most important mechanisms for the delay of immune senescence [95]. The cause of attenuated BAT activity in the elderly is multifactorial. Thus, considerable amount of work is needed to understand the underlying mechanisms for the reduction of BAT in the elderly.

Role of BAT in cancer cachexia

BAT activation has received considerable attention for the development of cancer cachexia in animal model. Cancer cachexia is a multifactorial syndrome defined as a continuous loss of skeletal muscle and fat mass that cannot be completely reversed by conventional nutritional

support. Therefore, cancer cachexia eventually leads to progressive functional impairment. The diagnostic criteria for cachexia in clinic include weight loss of higher than 5% of stable body weight over the past six months, ongoing weight loss that is higher than 2% in patients with a BMI of less than 20 kg/m^2, or depletion of skeletal muscle mass (sarcopenia) [96]. Cancer patients who lose weight show higher REE than those of patients with a stable weight [97].

Enhanced thermogenesis in BAT is suggested as a primary reason for increased REE in certain cancer patients [98], since elevation of BAT activity results in hypermetabolic diseases and is partially responsible for the weight loss in tumor-bearing mice [99]. In C26 colon carcinoma-induced cachectic mice, β3-AR that is responsible for the activation of BAT, is activated and thereby induces delipidation in BAT with a higher induction of UCP1 at the protein level [100]. Furthermore, ^{18}F-FDG PET imaging shows more BAT positive sites in cachectic C26 colon carcinoma-bearing mouse than that of nontumor-bearing mouse [101], supporting that cancer cachexia could be associated with increased BAT activity in animal models. Adipose tissue browning, the recruitment of beige cells in WAT, is also found in cachexia mouse model. Adipose tissue specific Prdm16 deficient mouse inhibits adipose tissue wasting in Lewis lung carcinoma (LLC)-bearing tumorigenesis [102]. Tumor-derived IL-6 and β3-AR activation is associated with cancer cachexia-mediated adipose tissue browning in genetically engineered cancer cachexia mice, and neutralization of IL-6 or β3-AR significantly ameliorates cancer cachexia [103]. Although the main role of IL-6 on metabolism remains poorly understood, IL-6, at least in part, contributes to systemic metabolism by regulating BAT activation and adipose tissue browning [76,104]. Introduction of IL-6 in brain using adenoviral system significantly increases UCP1 expression only in sympathetic innervated BAT, not denervated one, indicating that IL-6 activates BAT through β3-AR signaling pathway [76]. Additionally, tumor cell-derived parathyroid-hormone-related protein (PTHrP) is responsible for cancer cachexia [102]. While PTHrP treatment does not alter tumor size, it leads to cancer cachexia-associated weight loss with skeletal muscle wasting in LLC-bearing mouse. Instead, blocking PTHrP with neutralizing antibody prevents adipose tissue and skeletal muscle wasting. Furthermore, PTHrP shares G-protein-couple receptor signaling pathway with β3 agonists to upregulate UCP1 expression at protein level in white and brown adipocytes [102]. Therefore, tumor cell-derived IL-6 and PTHrP might play an important role in cancer cachexia by activating BAT and/or adipose tissue browning at least in mouse tumor models.

However, it is not clear yet whether BAT activation contributes to cancer cachexia in human. In human periadrenal tissue, BATs are observed in 80% of total 25 cancer patients compared with the 13% of total 16 age-matched healthy subjects [105]. ^{18}F-FDG PET-CT study with a small number of cancer patients revealed that the prevalence of activated BAT in cancer patients (~50%) is similar to that in healthy control subjects (~56%) [29]. Discrepancies in previous results may result from the individual difference in BAT activity because BAT activation is regulated by various factors such as age, sex, outdoor temperature, obesity, and exercise [4,106]. Therefore, well-designed studies with a large number of cancer patients and appropriate control subjects are required to investigate the effect of BAT activation on cancer cachexia.

Signaling pathways for BAT activation and browning

The activation of β3-AR and its downstream signaling is a major signaling pathway for thermogenic gene induction. FGF21, an endocrine hormone, belongs to the FGF family and regulates BAT activation through β3-AR signaling. To induce thermogenic ability, FGF21 directly binds to adipocytes [107] and consequently activates BAT or inguinal adipocytes by increasing sympathetic activity [108] and/or enhancing PGC-1α, a key factor of browning [109]. Type II cytokine plays an important role in beige formation during cold exposure and exercise by adrenergic regulation [44]. Cold exposure or excise induces beige formation by increasing the expression level of eosinophil-derived IL-4 and activates M2 macrophage-derived catecholamine through IL4Ra signal pathway [110,111]. In particular, IL-33-mediated activation of type 2 innate lymphoid cells (ILC2s) promotes the expansion of PDGFRα$^+$ bipotential adipocyte precursors and the commitment to beige adipocytes via IL4Ra pathway [111]. Alternatively, activated ILC2s also secrete methionine-enkephalin peptides that directly induce UCP1 expression and browning in the IL4Ra independent pathway [46]. Adiponectin also regulates cold-induced browning by promoting M2 macrophage in WAT with unknown mechanism [112].

However, BMPs induce thermogenic genes without adrenergic pathways. BMPs, as pleiotropic members of the transforming growth factor β superfamily, regulate adipogenesis through BMP receptors (type I and II) rather than β3-AR, as evidenced by the fact that the ablation of type 1A BMP receptor in brown adipogenic progenitor cells prevents brown adipogenesis in BAT. Instead, the ablation of BAM receptor promotes beige cell recruitment by increased sympathetic input to WAT [113]. BMP4 requires PGC-1β and PGC-1α for white to brown transition of mouse WAT and human adipose stem cells, respectively [49,114]. BMP7 is originally identified as a hormone for

bone formation, but it regulates BAT growth and activation *in vitro* and *in vivo* through p38 MAP kinase-mediated PGC-1α and PGC-1β [50]. In addition, BMP7 also enhances white-to-beige transition in primary adipocytes [114].

Although various signaling pathways and cell types involved in BAT activation and browning have been uncovered, better understanding of crosstalk among signaling pathways is required for the development of drugs that stimulate BAT activation on the purpose of clinical application in the near future.

Conclusions

BAT plays an important role in human physiology and metabolic diseases. BAT transplantation or its activation enhances energy expenditure, reduces weight loss, improves insulin sensitivity, and reverses hyperinsulinemia in animal and human studies. The recruitment of beige cells in WAT also shows similar effects. However, BAT activation could deteriorate cancer cachexia. From the pathophysiological point of view, BAT activation is associated with cancer cachexia in animal models. In addition, direct evidence between BAT activity and human cancer cachexia has not been observed yet. In the elderly, BAT mass and activity are negatively correlated with aging. Therefore, BAT activation with chemicals or natural compounds could be a new therapeutic strategy to treat obesity and metabolic diseases and extend life span.

Acknowledgements

This work was supported by the Strategic Priority Research Program (No. XDB13030000), the Ministry of Science and Technology of China (Nos. 2015CB943102, 2012CBA01301, and 2012CB944701), and the National Natural Science Foundation of China (No. 81370951).

Compliance with ethics guidelines

Meng Dong, Jun Lin, Wonchung Lim, Wanzhu Jin, and Hyuek Jong Lee declare no conflict of interest. They also declare no financial relationship with the organization that sponsored this research. This manuscript is a review article, and it involves no research protocol requiring approval by relevant institutional review board or ethics committee.

References

1. Schulz TJ, Tseng YH. Emerging role of bone morphogenetic proteins in adipogenesis and energy metabolism. Cytokine Growth Factor Rev 2009; 20(5-6): 523–531
2. Townsend KL, Tseng YH. Brown fat fuel utilization and thermogenesis. Trends Endocrinol Metab 2014; 25(4): 168–177
3. Shen YY, Liu XM, Dong M, Lin J, Zhao QW, Lee H, Jin WZ. Recent advances in brown adipose tissue biology. Chin Sci Bull 2014; 59(31): 4030–4040
4. 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(15): 1509–1517
5. van Marken Lichtenbelt WD, Vanhommerig 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(15): 1500–1508
6. Virtanen KA, Lidell ME, Orava J, Heglind M, Westergren R, Niemi T, Taittonen M, Laine J, Savisto NJ, Enerbäck S, Nuutila P. Functional brown adipose tissue in healthy adults. N Engl J Med 2009; 360(15): 1518–1525
7. Oelkrug R, Polymeropoulos ET, Jastroch M. Brown adipose tissue: physiological function and evolutionary significance. J Comp Physiol B 2015; 185(6): 587–606
8. Cannon B, Nedergaard J. Brown adipose tissue: function and physiological significance. Physiol Rev 2004; 84(1): 277–359
9. Astrup A. Thermogenesis in human brown adipose tissue and skeletal muscle induced by sympathomimetic stimulation. Acta Endocrinol Suppl (Copenh) 1986; 278: 1–32
10. Adamson SK Jr, Towell ME. Thermal homeostasis in the fetus and newborn. Anesthesiology 1965; 26(4): 531–548
11. Asakura H. Fetal and neonatal thermoregulation. J Nippon Med Sch 2004; 71(6): 360–370
12. Symonds ME. Pregnancy, parturition and neonatal development: interactions between nutrition and thyroid hormones. Proc Nutr Soc 1995; 54(2): 329–343
13. Aherne W, Hull D. Brown adipose tissue and heat production in the newborn infant. J Pathol Bacteriol 1966; 91(1): 223–234
14. Timmons JA, Wennmalm K, Larsson O, Walden TB, Lassmann T, Petrovic N, Hamilton DL, Gimeno RE, Wahlestedt C, Baar K, Nedergaard J, Cannon B. Myogenic gene expression signature establishes that brown and white adipocytes originate from distinct cell lineages. Proc Natl Acad Sci USA 2007; 104(11): 4401–4406
15. 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
16. Lepper C, Fan CM. Inducible lineage tracing of Pax7-descendant cells reveals embryonic origin of adult satellite cells. Genesis 2010; 48(7): 424–436
17. Kajimura S, Seale P, Kubota K, Lunsford E, Frangioni JV, Gygi SP, Spiegelman BM. Initiation of myoblast to brown fat switch by a PRDM16-C/EBP-β transcriptional complex. Nature 2009; 460 (7259): 1154–1158
18. Ohno H, Shinoda K, Spiegelman BM, Kajimura S. PPARγ agonists induce a white-to-brown fat conversion through stabilization of PRDM16 protein. Cell Metab 2012; 15(3): 395–404
19. 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(2): 366–376

20. Lee YH, Petkova AP, Mottillo EP, Granneman JG. *In vivo* identification of bipotential adipocyte progenitors recruited by β3-adrenoceptor activation and high-fat feeding. Cell Metab 2012; 15 (4): 480–491
21. Jespersen NZ, Larsen TJ, Peijs L, Daugaard S, Homøe P, Loft A, de Jong J, Mathur N, Cannon B, Nedergaard J, Pedersen BK, Møller K, Scheele C. A classical brown adipose tissue mRNA signature partly overlaps with brite in the supraclavicular region of adult humans. Cell Metab 2013; 17(5): 798–805
22. 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(1): 38–54
23. Dalgaard LT, Pedersen O. Uncoupling proteins: functional characteristics and role in the pathogenesis of obesity and Type II diabetes. Diabetologia 2001; 44(8): 946–965
24. Ricquier D. Respiration uncoupling and metabolism in the control of energy expenditure. Proc Nutr Soc 2005; 64(1): 47–52
25. Enerbäck S, Jacobsson A, Simpson EM, Guerra C, Yamashita H, Harper ME, Kozak LP. Mice lacking mitochondrial uncoupling protein are cold-sensitive but not obese. Nature 1997; 387(6628): 90–94
26. Feldmann HM, Golozoubova V, Cannon B, Nedergaard J. UCP1 ablation induces obesity and abolishes diet-induced thermogenesis in mice exempt from thermal stress by living at thermoneutrality. Cell Metab 2009; 9(2): 203–209
27. Orava J, Nuutila P, Noponen T, Parkkola R, Viljanen T, Enerbäck S, Rissanen A, Pietiläinen KH, Virtanen KA. Blunted metabolic responses to cold and insulin stimulation in brown adipose tissue of obese humans. Obesity (Silver Spring) 2013; 21(11): 2279–2287
28. Jacene HA, Cohade CC, Zhang Z, Wahl RL. The relationship between patients' serum glucose levels and metabolically active brown adipose tissue detected by PET/CT. Mol Imaging Biol 2011; 13(6): 1278–1283
29. Lee P, Greenfield JR, Ho KK, Fulham MJ. A critical appraisal of the prevalence and metabolic significance of brown adipose tissue in adult humans. Am J Physiol Endocrinol Metab 2010; 299(4): E601–E606
30. Stanford KI, Middelbeek RJ, Townsend KL, An D, Nygaard EB, Hitchcox KM, Markan KR, Nakano K, Hirshman MF, Tseng YH, Goodyear LJ. Brown adipose tissue regulates glucose homeostasis and insulin sensitivity. J Clin Invest 2013; 123(1): 215–223
31. Liu X, Zheng Z, Zhu X, Meng M, Li L, Shen Y, Chi Q, Wang D, Zhang Z, Li C, Li Y, Xue Y, Speakman JR, Jin W. Brown adipose tissue transplantation improves whole-body energy metabolism. Cell Res 2013; 23(6): 851–854
32. Zhu Z, Spicer EG, Gavini CK, Goudjo-Ako AJ, Novak CM, Shi H. Enhanced sympathetic activity in mice with brown adipose tissue transplantation (transBATation). Physiol Behav 2014; 125: 21–29
33. Liu X, Wang S, You Y, Meng M, Zheng Z, Dong M, Lin J, Zhao Q, Zhang C, Yuan X, Hu T, Liu L, Huang Y, Zhang L, Wang D, Zhan J, Jong Lee H, Speakman JR, Jin W. Brown adipose tissue transplantation reverses obesity in Ob/Ob mice. Endocrinology 2015; 156(7): 2461–2469
34. Kim EH, Heo CY. Current applications of adipose-derived stem cells and their future perspectives. World J Stem Cells 2014; 6(1): 65–68
35. Harms M, Seale P. Brown and beige fat: development, function and therapeutic potential. Nat Med 2013; 19(10): 1252–1263
36. Vallerand AL, Lupien J, Bukowiecki LJ. Cold exposure reverses the diabetogenic effects of high-fat feeding. Diabetes 1986; 35(3): 329–334
37. Yoneshiro T, Aita S, Matsushita M, Kayahara T, Kameya T, Kawai Y, Iwanaga T, Saito M. Recruited brown adipose tissue as an antiobesity agent in humans. J Clin Invest 2013; 123(8): 3404–3408
38. Murano I, Barbatelli G, Giordano A, Cinti S. Noradrenergic parenchymal nerve fiber branching after cold acclimatisation correlates with brown adipocyte density in mouse adipose organ. J Anat 2009; 214(1): 171–178
39. Collins S. b-Adrenoceptor signaling networks in adipocytes for recruiting stored fat and energy expenditure. Front Endocrinol (Lausanne) 2012; 2: 102
40. Giordano A, Frontini A, Murano I, Tonello C, Marino MA, Carruba MO, Nisoli E, Cinti S. Regional-dependent increase of sympathetic innervation in rat white adipose tissue during prolonged fasting. J Histochem Cytochem 2005; 53(6): 679–687
41. Barbatelli G, Murano I, Madsen L, Hao Q, Jimenez M, Kristiansen K, Giacobino JP, De Matteis R, Cinti S. The emergence of cold-induced brown adipocytes in mouse white fat depots is determined predominantly by white to brown adipocyte transdifferentiation. Am J Physiol Endocrinol Metab 2010; 298(6): E1244–E1253
42. Liu X, Pérusse F, Bukowiecki LJ. Mechanisms of the antidiabetic effects of the β 3-adrenergic agonist CL-316243 in obese Zucker-ZDF rats. Am J Physiol 1998; 274(5 Pt 2): R1212–R1219
43. de Souza CJ, Hirshman MF, Horton ES. CL-316,243, a β3-specific adrenoceptor agonist, enhances insulin-stimulated glucose disposal in nonobese rats. Diabetes 1997; 46(8): 1257–1263
44. 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(6): 1292–1308
45. Lee SD, Tontonoz P. Eosinophils in fat: pink is the new brown. Cell 2014; 157(6): 1249–1250
46. Brestoff JR, Kim BS, Saenz SA, Stine RR, Monticelli LA, Sonnenberg GF, Thome JJ, Farber DL, Lutfy K, Seale P, Artis D. Group 2 innate lymphoid cells promote beiging of white adipose tissue and limit obesity. Nature 2015; 519(7542): 242–246
47. 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 HJ, Kim JK, Véniant MM. Fibroblast growth factor 21 reverses hepatic steatosis, increases energy expenditure, and improves insulin sensitivity in diet-induced obese mice. Diabetes 2009; 58(1): 250–259
48. Coskun T, Bina HA, Schneider MA, Dunbar JD, Hu CC, Chen Y, Moller DE, Kharitonenkov A. Fibroblast growth factor 21 corrects obesity in mice. Endocrinology 2008; 149(12): 6018–6027
49. Qian SW, Tang Y, Li X, Liu Y, Zhang YY, Huang HY, Xue RD, Yu HY, Guo L, Gao HD, Liu Y, Sun X, Li YM, Jia WP, Tang QQ. BMP4-mediated brown fat-like changes in white adipose tissue alter glucose and energy homeostasis. Proc Natl Acad Sci USA 2013; 110(9): E798–E807

50. 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(7207): 1000–1004
51. Whittle AJ, Carobbio S, Martins L, Slawik M, Hondares E, Vázquez MJ, Morgan D, Csikasz RI, Gallego R, Rodriguez-Cuenca S, Dale M, Virtue S, Villarroya F, Cannon B, Rahmouni K, López M, Vidal-Puig A. BMP8B increases brown adipose tissue thermogenesis through both central and peripheral actions. Cell 2012; 149(4): 871–885
52. Bordicchia M, Liu D, Amri EZ, Ailhaud G, Dessì-Fulgheri P, Zhang C, Takahashi N, Sarzani R, Collins S. Cardiac natriuretic peptides act via p38 MAPK to induce the brown fat thermogenic program in mouse and human adipocytes. J Clin Invest 2012; 122 (3): 1022–1036
53. Gaich G, Chien JY, Fu H, Glass LC, Deeg MA, Holland WL, Kharitonenkov A, Bumol T, Schilske HK, Moller DE. The effects of LY2405319, an FGF21 analog, in obese human subjects with type 2 diabetes. Cell Metab 2013; 18(3): 333–340
54. Kawabata F, Inoue N, Yazawa S, Kawada T, Inoue K, Fushiki T. Effects of CH-19 sweet, a non-pungent cultivar of red pepper, in decreasing the body weight and suppressing body fat accumulation by sympathetic nerve activation in humans. Biosci Biotechnol Biochem 2006; 70(12): 2824–2835
55. Kawada T, Watanabe T, Takaishi T, Tanaka T, Iwai K. Capsaicin-induced beta-adrenergic action on energy metabolism in rats: influence of capsaicin on oxygen consumption, the respiratory quotient, and substrate utilization. Proc Soc Exp Biol Med 1986; 183(2): 250–256
56. Kawada T, Hagihara K, Iwai K. Effects of capsaicin on lipid metabolism in rats fed a high fat diet. J Nutr 1986; 116(7): 1272–1278
57. Ohnuki K, Haramizu S, Oki K, Watanabe T, Yazawa S, Fushiki T. Administration of capsiate, a non-pungent capsaicin analog, promotes energy metabolism and suppresses body fat accumulation in mice. Biosci Biotechnol Biochem 2001; 65(12): 2735–2740
58. Masuda Y, Haramizu S, Oki K, Ohnuki K, Watanabe T, Yazawa S, Kawada T, Hashizume S, Fushiki T. Upregulation of uncoupling proteins by oral administration of capsiate, a nonpungent capsaicin analog. J Appl Physiol (1985) 2003;95(6): 2408–2415
59. Dong M, Yang X, Lim S, Cao Z, Honek J, Lu H, Zhang C, Seki T, Hosaka K, Wahlberg E, Yang J, Zhang L, Länne T, Sun B, Li X, Liu Y, Zhang Y, Cao Y. Cold exposure promotes atherosclerotic plaque growth and instability via UCP1-dependent lipolysis. Cell Metab 2013; 18(1): 118–129
60. Berbée JF, Boon MR, Khedoe PP, Bartelt A, Schlein C, Worthmann A, Kooijman S, Hoeke G, Mol IM, John C, Jung C, Vazirpanah N, Brouwers LP, Gordts PL, Esko JD, Hiemstra PS, Havekes LM, Scheja L, Heeren J, Rensen PC. Brown fat activation reduces hypercholesterolaemia and protects from atherosclerosis development. Nat Commun 2015; 6: 6356
61. Bartelt A, Bruns OT, Reimer R, Hohenberg H, Ittrich H, Peldschus K, Kaul MG, Tromsdorf UI, Weller H, Waurisch C, Eychmüller A, Gordts PL, Rinninger F, Bruegelmann K, Freund B, Nielsen P, Merkel M, Heeren J. Brown adipose tissue activity controls triglyceride clearance. Nat Med 2011; 17(2): 200–205
62. Carey AL, Kingwell BA. Brown adipose tissue in humans: therapeutic potential to combat obesity. Pharmacol Ther 2013; 140 (1): 26–33
63. Gunawardana SC, Piston DW. Reversal of type 1 diabetes in mice by brown adipose tissue transplant. Diabetes 2012; 61(3): 674–682
64. Gunawardana SC, Piston DW. Insulin-independent reversal of type 1 diabetes in nonobese diabetic mice with brown adipose tissue transplant. Am J Physiol Endocrinol Metab 2015; 308(12): E1043–E1055
65. Min SY, Kady J, Nam M, Rojas-Rodriguez R, Berkenwald A, Kim JH, Noh HL, Kim JK, Cooper MP, Fitzgibbons T, Brehm MA, Corvera S. Human 'brite/beige' adipocytes develop from capillary networks, and their implantation improves metabolic homeostasis in mice. Nat Med 2016; 22(3): 312–318
66. Nishio M, Yoneshiro T, Nakahara M, Suzuki S, Saeki K, Hasegawa M, Kawai Y, Akutsu H, Umezawa A, Yasuda K, Tobe K, Yuo A, Kubota K, Saito M, Saeki K. Production of functional classical brown adipocytes from human pluripotent stem cells using specific hemopoietin cocktail without gene transfer. Cell Metab 2012; 16(3): 394–406
67. Nishio M, Saeki K. Differentiation of human pluripotent stem cells into highly functional classical brown adipocytes. Methods Enzymol 2014; 537: 177–197
68. Orava J, Nuutila P, Lidell ME, Oikonen V, Noponen T, Viljanen T, Scheinin M, Taittonen M, Niemi T, Enerbäck S, Virtanen KA. Different metabolic responses of human brown adipose tissue to activation by cold and insulin. Cell Metab 2011; 14(2): 272–279
69. Chondronikola M, Volpi E, Børsheim E, Porter C, Annamalai P, Enerbäck S, Lidell ME, Saraf MK, Labbe SM, Hurren NM, Yfanti C, Chao T, Andersen CR, Cesani F, Hawkins H, Sidossis LS. Brown adipose tissue improves whole-body glucose homeostasis and insulin sensitivity in humans. Diabetes 2014; 63(12): 4089–4099
70. Peirce V, Vidal-Puig A. Regulation of glucose homoeostasis by brown adipose tissue. Lancet Diabetes Endocrinol 2013; 1(4): 353–360
71. Villarroya J, Cereijo R, Villarroya F. An endocrine role for brown adipose tissue? Am J Physiol Endocrinol Metab 2013; 305(5): E567–E572
72. Wang GX, Zhao XY, Lin JD. The brown fat secretome: metabolic functions beyond thermogenesis. Trends Endocrinol Metab 2015; 26(5): 231–237
73. Hondares E, Iglesias R, Giralt A, Gonzalez FJ, Giralt M, Mampel T, Villarroya F. Thermogenic activation induces FGF21 expression and release in brown adipose tissue. J Biol Chem 2011; 286(15): 12983–12990
74. Kharitonenkov A, Shiyanova TL, Koester A, Ford AM, Micanovic R, Galbreath EJ, Sandusky GE, Hammond LJ, Moyers JS, Owens RA, Gromada J, Brozinick JT, Hawkins ED, Wroblewski VJ, Li DS, Mehrbod F, Jaskunas SR, Shanafelt AB. FGF-21 as a novel metabolic regulator. J Clin Invest 2005; 115(6): 1627–1635
75. Inagaki T, Dutchak P, Zhao G, Ding X, Gautron L, Parameswara V, Li Y, Goetz R, Mohammadi M, Esser V, Elmquist JK, Gerard RD, Burgess SC, Hammer RE, Mangelsdorf DJ, Kliewer SA. Endocrine regulation of the fasting response by PPARα-mediated induction of fibroblast growth factor 21. Cell Metab 2007; 5(6):

415–425

76. Li G, Klein RL, Matheny M, King MA, Meyer EM, Scarpace PJ. Induction of uncoupling protein 1 by central interleukin-6 gene delivery is dependent on sympathetic innervation of brown adipose tissue and underlies one mechanism of body weight reduction in rats. Neuroscience 2002; 115(3): 879–889
77. Wallenius V, Wallenius K, Ahrén B, Rudling M, Carlsten H, Dickson SL, Ohlsson C, Jansson JO. Interleukin-6-deficient mice develop mature-onset obesity. Nat Med 2002; 8(1): 75–79
78. Virtue S, Feldmann H, Christian M, Tan CY, Masoodi M, Dale M, Lelliott C, Burling K, Campbell M, Eguchi N, Voshol P, Sethi JK, Parker M, Urade Y, Griffin JL, Cannon B, Vidal-Puig A. A new role for lipocalin prostaglandin d synthase in the regulation of brown adipose tissue substrate utilization. Diabetes 2012; 61(12): 3139–3147
79. Wang GX, Zhao XY, Meng ZX, Kern M, Dietrich A, Chen Z, Cozacov Z, Zhou D, Okunade AL, Su X, Li S, Blüher M, Lin JD. The brown fat-enriched secreted factor Nrg4 preserves metabolic homeostasis through attenuation of hepatic lipogenesis. Nat Med 2014; 20(12): 1436–1443
80. Elias I, Franckhauser S, Ferré T, Vilà L, Tafuro S, Muñoz S, Roca C, Ramos D, Pujol A, Riu E, Ruberte J, Bosch F. Adipose tissue overexpression of vascular endothelial growth factor protects against diet-induced obesity and insulin resistance. Diabetes 2012; 61(7): 1801–1813
81. Sun K, Kusminski CM, Luby-Phelps K, Spurgin SB, An YA, Wang QA, Holland WL, Scherer PE. Brown adipose tissue derived VEGF-A modulates cold tolerance and energy expenditure. Mol Metab 2014; 3(4): 474–483
82. Hagberg CE, Falkevall A, Wang X, Larsson E, Huusko J, Nilsson I, van Meeteren LA, Samen E, Lu L, Vanwildemeersch M, Klar J, Genove G, Pietras K, Stone-Elander S, Claesson-Welsh L, Ylä-Herttuala S, Lindahl P, Eriksson U. Vascular endothelial growth factor B controls endothelial fatty acid uptake. Nature 2010; 464 (7290): 917–921
83. Robciuc MR, Kivelä R, Williams IM, de Boer JF, van Dijk TH, Elamaa H, Tigistu-Sahle F, Molotkov D, Leppänen VM, Käkelä R, Eklund L, Wasserman DH, Groen AK, Alitalo K. VEGFB/VEGFR1-induced expansion of adipose vasculature counteracts obesity and related metabolic complications. Cell Metab 2016; 23 (4): 712–724
84. Sharp LZ, Shinoda K, Ohno H, Scheel DW, 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 2012; 7(11): e49452
85. Rogers NH. Brown adipose tissue during puberty and with aging. Ann Med 2015; 47(2): 142–149
86. Heaton JM. The distribution of brown adipose tissue in the human. J Anat 1972; 112(Pt 1): 35–39
87. Brooke OG, Harris M, Salvosa CB. The response of malnourished babies to cold. J Physiol 1973; 233(1): 75–91
88. Graja A, Schulz TJ. Mechanisms of aging-related impairment of brown adipocyte development and function. Gerontology 2015; 61 (3): 211–217
89. Wallace DC, Fan W, Procaccio V. Mitochondrial energetics and therapeutics. Annu Rev Pathol 2010; 5(1): 297–348
90. Kindred JH, Tuulari JJ, Simon S, Luckasen GJ, Bell C, Rudroff T. Brown adipose and central nervous system glucose uptake is lower during cold exposure in older compared to young men: a preliminary PET study. Aging Clin Exp Res 2016; 28(3): 557–560
91. Zhang Y, Xie Y, Berglund ED, Coate KC, He TT, Katafuchi T, Xiao G, Potthoff MJ, Wei W, Wan Y, Yu RT, Evans RM, Kliewer SA, Mangelsdorf DJ. The starvation hormone, fibroblast growth factor-21, extends lifespan in mice. eLife 2012; 1: e00065
92. Chau MD, Gao J, Yang Q, Wu Z, Gromada J. Fibroblast growth factor 21 regulates energy metabolism by activating the AMPK-SIRT1-PGC-1α pathway. Proc Natl Acad Sci USA 2010; 107(28): 12553–12558
93. Solon-Biet SM, Mitchell SJ, de Cabo R, Raubenheimer D, Le Couteur DG, Simpson SJ. Macronutrients and caloric intake in health and longevity. J Endocrinol 2015; 226(1): R17–R28
94. Lee P, Linderman JD, Smith S, Brychta RJ, Wang J, Idelson C, Perron RM, Werner CD, Phan GQ, Kammula US, Kebebew E, Pacak K, Chen KY, Celi FS. Irisin and FGF21 are cold-induced endocrine activators of brown fat function in humans. Cell Metab 2014; 19(2): 302–309
95. Youm YH, Horvath TL, Mangelsdorf DJ, Kliewer SA, Dixit VD. Prolongevity hormone FGF21 protects against immune senescence by delaying age-related thymic involution. Proc Natl Acad Sci USA 2016; 113(4): 1026–1031
96. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, Jatoi A, Loprinzi C, MacDonald N, Mantovani G, Davis M, Muscaritoli M, Ottery F, Radbruch L, Ravasco P, Walsh D, Wilcock A, Kaasa S, Baracos VE. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011; 12(5): 489–495
97. Cao DX, Wu GH, Zhang B, Quan YJ, Wei J, Jin H, Jiang Y, Yang ZA. Resting energy expenditure and body composition in patients with newly detected cancer. Clin Nutr 2010; 29(1): 72–77
98. Tisdale MJ. Mechanisms of cancer cachexia. Physiol Rev 2009; 89 (2): 381–410
99. Brooks SL, Neville AM, Rothwell NJ, Stock MJ, Wilson S. Sympathetic activation of brown-adipose-tissue thermogenesis in cachexia. Biosci Rep 1981; 1(6): 509–517
100. Tsoli M, Moore M, Burg D, Painter A, Taylor R, Lockie SH, Turner N, Warren A, Cooney G, Oldfield B, Clarke S, Robertson G. Activation of thermogenesis in brown adipose tissue and dysregulated lipid metabolism associated with cancer cachexia in mice. Cancer Res 2012; 72(17): 4372–4382
101. Fueger BJ, Czernin J, Hildebrandt I, Tran C, Halpern BS, Stout D, Phelps ME, Weber WA. Impact of animal handling on the results of 18F-FDG PET studies in mice. J Nucl Med 2006; 47(6): 999–1006
102. Kir S, White JP, Kleiner S, Kazak L, Cohen P, Baracos VE, Spiegelman BM. Tumour-derived PTH-related protein triggers adipose tissue browning and cancer cachexia. Nature 2014; 513 (7516): 100–104
103. Petruzzelli M, Schweiger M, Schreiber R, Campos-Olivas R, Tsoli M, Allen J, Swarbrick M, Rose-John S, Rincon M, Robertson G, Zechner R, Wagner EF. A switch from white to brown fat increases energy expenditure in cancer-associated cachexia. Cell Metab 2014; 20(3): 433–447
104. Knudsen JG, Murholm M, Carey AL, Biensø RS, Basse AL, Allen TL, Hidalgo J, Kingwell BA, Febbraio MA, Hansen JB, Pilegaard H. Role of IL-6 in exercise training- and cold-induced UCP1

expression in subcutaneous white adipose tissue. PLoS One 2014; 9(1): e84910

105. Shellock FG, Riedinger MS, Fishbein MC. Brown adipose tissue in cancer patients: possible cause of cancer-induced cachexia. J Cancer Res Clin Oncol 1986; 111(1): 82–85
106. Vosselman MJ, Hoeks J, Brans B, Pallubinsky H, Nascimento EB, van der Lans AA, Broeders EP, Mottaghy FM, Schrauwen P, van Marken Lichtenbelt WD. Low brown adipose tissue activity in endurance-trained compared with lean sedentary men. Int J Obes 2015; 39(12): 1696–1702
107. Hondares E, Rosell M, Gonzalez FJ, Giralt M, Iglesias R, Villarroya F. Hepatic FGF21 expression is induced at birth via PPARα in response to milk intake and contributes to thermogenic activation of neonatal brown fat. Cell Metab 2010; 11(3): 206–212
108. Douris N, Stevanovic DM, Fisher FM, Cisu TI, Chee MJ, Nguyen NL, Zarebidaki E, Adams AC, Kharitonenkov A, Flier JS, Bartness TJ, Maratos-Flier E. Central fibroblast growth factor 21 browns white fat via sympathetic action in male mice. Endocrinology 2015; 156(7): 2470–2481
109. Fisher FM, Kleiner S, Douris N, Fox EC, Mepani RJ, Verdeguer F, Wu J, Kharitonenkov A, Flier JS, Maratos-Flier E, Spiegelman BM. FGF21 regulates PGC-1α and browning of white adipose tissues in adaptive thermogenesis. Genes Dev 2012; 26(3): 271–281
110. Rao RR, Long JZ, White JP, Svensson KJ, Lou J, Lokurkar I, Jedrychowski MP, Ruas JL, Wrann CD, Lo JC, Camera DM, Lachey J, Gygi S, Seehra J, Hawley JA, Spiegelman BM. Meteorin-like is a hormone that regulates immune-adipose interactions to increase beige fat thermogenesis. Cell 2014; 157 (6): 1279–1291
111. 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 (1-2): 74–87
112. Hui X, Gu P, Zhang J, Nie T, Pan Y, Wu D, Feng T, Zhong C, Wang Y, Lam KS, Xu A. Adiponectin enhances cold-induced browning of subcutaneous adipose tissue via promoting M2 macrophage proliferation. Cell Metab 2015; 22(2): 279–290
113. Schulz TJ, Huang P, Huang TL, Xue R, McDougall LE, Townsend KL, Cypess AM, Mishina Y, Gussoni E, Tseng YH. Brown-fat paucity due to impaired BMP signalling induces compensatory browning of white fat. Nature 2013; 495(7441): 379–383
114. Elsen M, Raschke S, Tennagels N, Schwahn U, Jelenik T, Roden M, Romacho T, Eckel J. BMP4 and BMP7 induce the white-to-brown transition of primary human adipose stem cells. Am J Physiol Cell Physiol 2014; 306(5): C431–C440