Short Communication

Resurgence in the interest of brown fat physiology

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Abstract

Brown adipose tissue was considered as a thermogenic organ only in hibernating mammals and human neonates for so long time until its presence was confirmed in human adults as an incidental finding. Apart from its well-known label as a 'thermogenic organ', recent interest in this field has led to the discovery of various other vital functions of brown adipocytes. In this short communication with a brief introduction about the morphology, development and differentiation of brown adipose tissue and the non-shivering thermogenesis mechanism, we intend to describe the recent findings in the field of brown fat research studies. A brief description has been given about the key role played by brown adipose tissue in the regulation of whole-body energy expenditure by maintaining glucose and lipid homeostasis, the 'Batokines' released by brown fat, its immune role and the link between thyroid hormones and brown fat. The key finding for the resurgence of interest in this field is the existence of two different types of brown adipose tissue, the classical brown fat and the beige or inducible brown fat and various factors which cause activation of brown fat and trans-differentiation of white adipose tissue to brown adipose tissue. Wider knowledge of brown fat physiology would help to modulate the body energy expenditure which could be a promising way to manage the global threat of metabolic syndrome.

Key words: batokines, beige fat, brown adipose tissue (BAT), thermogenesis.

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Introduction

"Neither fat nor flesh, it is something in between" This was how Conrad Gesner gave his description when he observed brown fat in a marmot in 1551.[1] Brown adipose tissue (BAT), then called as 'hibernating gland' was considered as a thermogenic organ only in hibernating mammals for so long time until its presence was confirmed in human neonates. Sufficient exploration was done in the non-shivering thermogenesis mechanism taking place in newborns. Though enormous research works had been done in brown adipose tissue for many centuries, this organ has gained its importance in research field recently when scientists showed the presence of metabolically active BAT in healthy human adults by Fluorodeoxyglucose PET-CT Fusion scan studies. [2-6] Brown fat was found as an incidental finding in PET scan done for carcinoma patients in regions like neck and shoulder which was believed to be due to muscle uptake. But this has been confirmed as brown fat by injecting a radioactive tracer 18F-Fluorodeoxyglucose, and measuring the increased uptake in adipose tissue depots using physiological and morphological imaging modalities, the Positron emission tomography/Computed tomography (PET/CT) after exposing the subject to cold stimulus. Wider knowledge of brown fat physiology would help in developing strategies to enhance energy expenditure and to combat the global pandemic threat of metabolic syndrome.

Morphology of brown adipose tissue

Brown adipose tissue stands distinct from white adipose tissue by its polygonal shape, smaller size, multi-loculated appearance with a central nucleus.[7] It has enormous mitochondria with the specialised uncoupling protein UCP1 on its membrane. Brown fat shows presence of multiple intracellular lipid droplets. It has a rich network of blood supply and sympathetic innervation. Evidence of dense perivascular mesenchymal cells has been observed in BAT. The rich blood supply and abundant cytochrome enzymes in the mitochondrial membrane with iron as cofactor give it the peculiar brown appearance.

Adult bat & infant bat

In human adults, activated Brown fat tissue has been identified in six anatomical locations like cervical, supraclavicular, Axillary, Mediastinal, Paraspinal and Abdominal regions.[8] The main depot in adults is the supraclavicular area. Adult BAT has more lipid droplets and less mitochondrial density when compared to infant BAT. Adult BAT is less active. The mRNA expression of the uncoupling protein UCP1 and other thermogenic genes expression are also found to be less in adult BAT.

Development of bat

Both the brown and white adipose tissues arise from common precursor cells of the embryonic mesoderm. These progenitor cells also give rise to the development of skeletal muscle, bone and other connective tissue lineages.[9-11]

Beige or brite fat

Special type of adipocytes named as “Beige”, “Brite”(Brown in white),” have been delineated in between the White adipose tissue and brown adipose tissue which also express the UCP1 and these are Induced BAT” or “Recruitable BAT”.[9] Because of their differential expression of genes they stood unique from Classical Brown adipose tissue

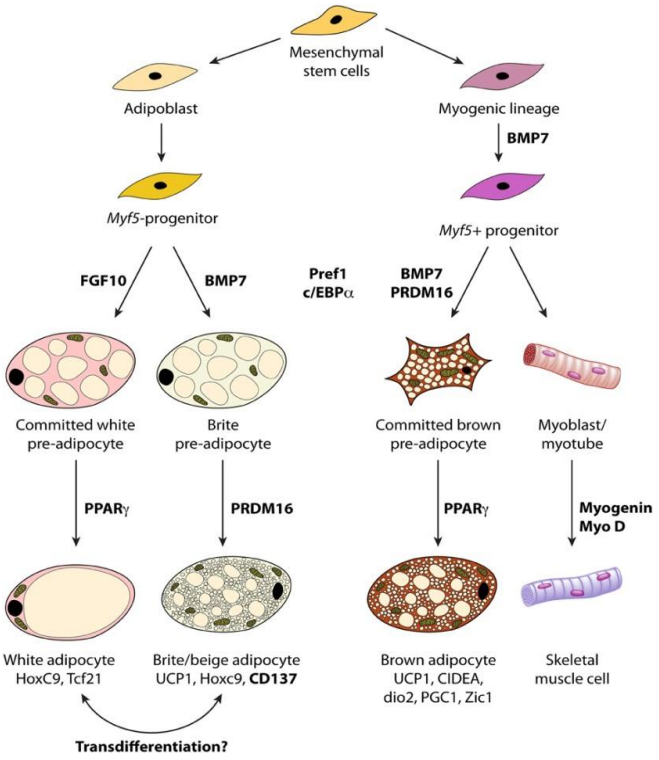

Fig: 1 Embryogenesis of White, Beige & Brown Adipose tissue. Maria Jesus Obregon, Adipose tissues and thyroid hormones, Frontiers in Physiology 2014. Copyright © 2014 Obregon

Non-shivering thermogenesis mechanism

The ventro-medial nucleus of hypothalamus senses the changes in body temperature and feeding status. Whenever there is a need to increase the rate of heat production, the sympathetic nervous system is activated and Nor epinephrine is released at the nerve terminals in brown adipose tissue. The ß3 adrenergic receptors are activated and via the cyclic AMP – Protein kinase A pathway there is an increased stimulation of Hormone Sensitive Lipase activity. This hormone breaks down the stored triglycerides into free fatty acids which then undergo oxidation in mitochondria. The combustion of free fatty acids in the Electron transport chain leads to release of protons into the inter-membrane space of mitochondria. The proton motive force thus created drives back the protons again into the mitochondrial matrix with the help of the uncoupling protein present in the inner mitochondrial membrane named as UCP1 or thermogenin. The energy stored in the proton motive force is then dissipated as heat.[12,13]

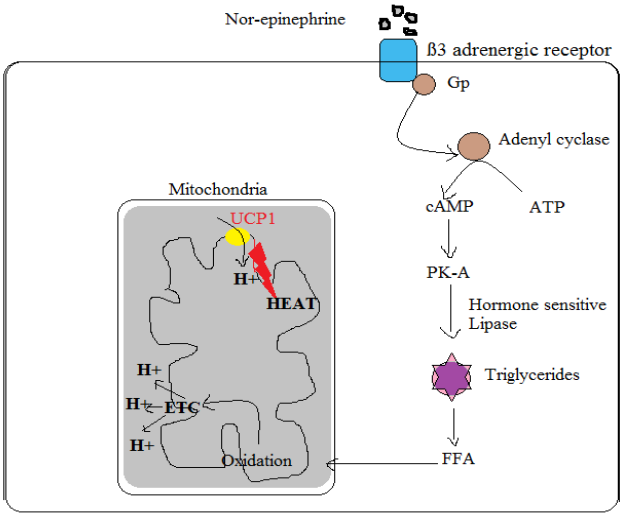

Fig: 2 Non-Shivering Thermogenesis mechanism taking place in brown adipose tissue and the role of UCP1 as uncoupler.Gp – G Protein, PK-A Protein kinase A, FFA-Free fatty acids, ETC – Electron transport chain, UCP1-Uncoupling protein 1.

Enhancing brown fat activation – potential role in obesity prevention

- To combat obesity, various factors which stimulate energy expenditure in brown fat are being studied. The well-known stimulus to activate brown fat is exposure to cold environment. It has been found that, "succinate", an intermediate metabolite in TCA cycle is one such trigger factor. This has been proved by administering succinate to mice which failed to gain weight even while on high-fat diet.[14]
- Recent study in humans concluded the fact that intake of a carbohydrate-rich meal could activate brown fat almost equivalent to exposure to cold.[15]

Brown fat – as an endocrine organ

During thermogenic induction brown fat releases certain signaling biomolecules which are termed as "Batokines".[16,17] These substances are believed to have both autocrine and paracrine action. They would have a role in causing systemic adaptation during thermogenesis. The following are some of the batokines and their role.

- Vascular endothelial growth factor-A(VEGF-A): Favours angiogenesis
- Insulin-like Growth Factor-1 (IGF1)& Fibroblast Growth Factor-2(FGF2): Proliferation of brown fat precursor cells
- Bone morphogenetic protein 8b: Sensitizes brown fat to sympathetic stimulation
- Interleukins 1&6: Proinflammatory cytokines
- Irisin & Fibroblast Growth Factor-21: Upregulates brown adipocyte gene expression
- Neuregulin 4 (NRG4): BAT- liver cross talk. Inhibits lipogenesis in the liver thereby reducing the occurrence of Non-Alcoholic fatty liver disease. [18]
- Retinol-binding protein 4: Retinol transporter

Thyroid hormones & bat

Brown adipocytes are rich in Type II Deiodinase (D2) which converts T4 to active T3. Thyroid hormone is needed for both the functioning of BAT and brown adipogenesis. Thyroid hormone activates thermogenesis in BAT in two ways.[19]

(i) Adaptive thermogenesis – Thyroid hormone causes increased expression of UCP1 in BAT thereby stimulating the mitochondrial uncoupling.

(ii) Obligatory thermogenesis – Thyroid hormone enhances ATP hydrolysis via various pathways with heat generation.

Role of bat in glucose homeostasis

Though the brown adipose tissue burns the stored triglycerides for its thermogenesis process initially it, later on, seeks out the circulating substrates for heat dissipation. It utilizes circulating glucose and fats. According to recent studies in humans, brown fat plays an important role in whole-body glucose disposal and in increasing insulin sensitivity. This suggests that brown adipose tissue could act as an antidiabetic tissue in adults and functions as a "metabolic sink" for glucose and fatty acids [20,21]

Mechanism of glucose uptake in brown fat is a two-step process:

(i) ß3 adrenergic receptor stimulation induced cAMP activation leading to de novo synthesis of Glucose Transporter-1(GLUT-1)

(ii) Translocation of GLUT-1 to cell membrane via mTORC2 (mechanistic target of rapamycin complex 2)[22]

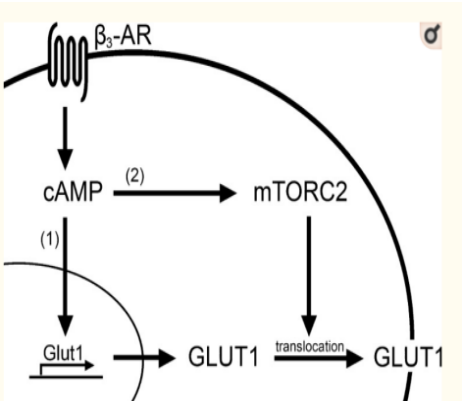

Fig:3 Mechanism of Glucose uptake in BAT. Adapted from Jessica M. Olsen and Masaaki Sato, Glucose uptake in brown fat cells is dependent on mTOR complex 2–promoted GLUT1 translocation. J Cell Biol. 2014 Nov 10; 207(3): 365–374

Exercise and bat

During exercise, as a result of enormous heat production due to muscle contraction transient decrease in thermogenic activity was observed in classical brown adipose tissue which was confirmed by the reduced mass of UCP1 in endurance-trained rats. To compensate this, at the same time browning of subcutaneous white adipose tissue occurs which under microscopic observation showed more of multilocular appearance rather than their usual unilocular appearance.[23]

Immune cells on bat

Brown adipose tissue has been recently found to play an important role in immunity.[24-26]

- Evidence suggest that immune cells like Eosinophils and Macrophages are recruited within adipose tissues and control inflammatory responses.[27,28]
- Eosinophils produce type 2 cytokines Interleukin 4 and 13 which is needed for adipogenesis
- Alternatively activated macrophage has a role in the development of brite fat

White to brown conversion ("browning")

- Exposure to cold, ß3 selective agonists, Serotonin, peroxisome proliferator-activated receptor γ (PPARγ) agonists, Triiodothyronine
- Capsaicin, Carotenoids, PUFA[29]
- Inhibition of Vascular Endothelial Growth Factor-1 (VEGFR-1) would increase adipose angiogenesis and browning of white adipose tissue[30]

Conclusion

The brown adipose tissue which was considered to have no significant role in humans has gained importance recently after the confirmation of their presence in adult humans in the last decade. Apart from its well known label as a 'thermogenic organ', brown adipocytes significantly regulate the whole-body energy expenditure and maintain glucose and lipid homeostasis. Further exploration on this would be possible by finding a simple, affordable and non-invasive method to quantify the brown tissue mass. Future researches should focus on identifying better serological markers to assess brown adipose tissue activity. Understanding the methods to increase white to BAT transdifferentiation and knowledge on signaling pathways involved, would help to modulate the body energy expenditure which could be a promising way to manage the global threat of metabolic syndrome.

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