REVIEW ARTICLE

Brown adipose tissue and novel therapeutic approaches to treat metabolic disorders

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In humans, 2 functionally different types of adipose tissue coexist: white adipose tissue (WAT) and brown adipose tissue (BAT). WAT is involved in energy storage, whereas BAT is involved in energy expenditure. Increased amounts of WAT may contribute to the development of metabolic disorders, such as obesity-associated type 2 diabetes mellitus and cardiovascular diseases. In contrast, the thermogenic function of BAT allows high consumption of fatty acids because of the activity of uncoupling protein 1 in the internal mitochondrial membrane. Interestingly, obesity reduction and insulin sensitization have been achieved by BAT activation-regeneration in animal models. This review describes the origin, function, and differentiation mechanisms of BAT to identify new therapeutic strategies for the treatment of metabolic disorders related to obesity. On the basis of the animal studies, novel approaches for BAT regeneration combining stem cells from the adipose tissue with active components, such as melatonin, may have potential for the treatment of metabolic disorders in humans. (Translational Research 2015;165:464–479)

Abbreviations: ^{18}F-FDG PET = ^{18}F-fluorodeoxyglucose positron-emission tomography; ADSCs = adipose-derived stem cells; aP2 = adipocyte fatty-acid-binding protein; AR = adrenergic receptor; ASCs = adult stem cells; BAT = brown adipose tissue; BMI = body mass index; BMP = bone morphogenic protein; C/EBP = cytosine-enhancer-binding protein; cAMP = adenosine 3′, 5′-cyclic monophosphate; CNS = central nervous system; CT = computed tomography; ESCs = embryonic stem cells; FAs = fatty acids; FFAs = free FAs; FNDC5 = fibronectin type III domain-containing protein 5; HP = hypothalamus; MEL = melatonin; MSC = mesenchymal stem cell; MT = melatonin receptor; NE = norepinephrine; Necdin = postmitotic neuron-specific growth suppressor; p107 = retinoblastoma-like protein 1; PGC-1α = coactivator 1α of PPAR; PKA = cAMP-dependent protein kinase A; PKA-CREB = PKA-cAMP response element-binding; PPARγ = peroxisome proliferator-activated receptor γ; PRDM16 = positive regulatory domain 16; Rb = retinoblastoma protein; Runx2 = osteogeneic key transcriptional factor; RXR = retinoid X receptor; SCs = stem cells; SNS = sympathetic nervous system; SRC = steroid recep-

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tor coactivators 1, 2 and 3; T2DM = type 2 diabetes mellitus; TGs = triglycerides; UCP1 = uncoupling protein 1; WAT = white adipose tissue; Wnt = embryogenic signaling pathway

INTRODUCTION

Adipose tissue is one of the largest organs in the body and plays an important role in central energy balance and lipid homeostasis.[1] Two types of adipose tissue are found in mammals, white adipose tissue (WAT) and brown adipose tissue (BAT). WAT functions to store energy, whereas BAT specializes in energy expenditure.[2]

In WAT cells, energy is stored via synthesis of triglycerides (TGs) that accumulate in lipid vesicles. WAT is composed of visceral and subcutaneous fat and represents 10% of healthy body weight.[3,4] Excess WAT is related to several metabolic disorders. Although visceral fat is less sensitive to insulin than subcutaneous fat, both fat tissues play a role in the development of type 2 diabetes mellitus (T2DM) and cardiovascular complications.[5-8] In addition, an increase in fatty acids (FAs), derived from excessive WAT energy storage, leads to an increased liver glucose output and consequent production of atherogenic lipids such as very low-density lipoproteins.[9]

In contrast, BAT plays an important thermogenic function in neonatal mammals, rodents, and hibernators, helping to counteract the cold stress of birth.[2,3] In adult mammals, BAT has the capacity to modulate energy balance by metabolizing FAs and dissipating the energy produced as heat.[10] The ability of BAT to burn fat could be used as a novel therapeutic strategy to combat obesity and metabolic diseases.

Therefore, the goal of this review is to identify therapeutic approaches with the potential to regenerate BAT in humans to treat metabolic disorders.

After a brief overview of BAT in terms of its origin, its physiological properties, and the key molecular signals for BAT differentiation, this review summarizes the pathways currently used in the research community for BAT regeneration in animals and new routes that need to be investigated.

ORIGIN AND ROLE OF BAT

It was believed that white and brown adipocytes arise from the same precursor cells.[11] However, DNA microarray studies revealed that brown adipocytes do not share a progenitor with white adipose cells but rather have the same origin as skeletal muscle cells.[12,13] Lineage-tracing experiments suggested a model in which tripotent cells in the central dermomyotome give rise to dermis, epaxial muscle, and brown fat.[14] BAT precursor cells express myogenic factor 5, suggesting their close localization to skeletal muscle cells during fetal development.[15]

Brown fat depots were also found in the WAT of the Siberian dwarf hamster, in which 10% of adipocytes express the specific BAT marker uncoupling protein 1 (UCP1).[16] Other authors reported a 17% increase in brown fat within WAT after administering adrenergic agonists. They observed a rise in the number of brown adipocytes but not in preadipocytes, suggesting that brown adipocytes can differentiate from mature white adipocytes.

The fact that brown fat depots can be found in a pool of white adipocyte precursors[16] and that this population can be increased by administration of adrenergic agonists led to the hypothesis that 2 distinct brown adipocyte lineages exist.[17] One shares precursors with skeletal muscle cells and localizes to interscapular areas and skeletal muscle, and the other derives from white adipocytes and localizes in the WAT itself.[1]

BAT is responsible for nonshivering thermogenesis to maintain body temperature in cold environments[18] and can be found in rodents and newborn humans, mainly in interscapular, paraspinal, and supraclavicular sites (Fig 1). BAT is highly vascularized and innervated in comparison with WAT[1] and is composed of brown adipocytes, which contain multilocular lipid droplets and large numbers of mitochondria (Fig 1). In a cold atmosphere, the hypothalamus (HP) drives the release of norepinephrine (NE) in BAT via sympathetic nervous system (SNS) activation[19] (Fig 1). The high innervation of BAT allows rapid stimulation of the adipocyte membrane. The adrenergic receptor (AR) is a 7-transmembrane G protein–coupled receptor. On activation, lipolysis is stimulated via the adenosine 3′,5′-cyclic monophosphate (cAMP)-dependent protein kinase A (PKA) signaling pathway.[20]

Free FAs (FFAs) derived from TG lipolysis via cytochrome c oxidase activation (Fig 2) stimulate mitochondrial biogenesis in brown adipocyte nuclei.[1] These FFAs undergo β-oxidation, and respiratory chain proteins from the mitochondrial internal membrane generate a proton electrochemical gradient between the mitochondrial matrix and the intermembrane space.[21] The presence of UCP1, which belongs to a superfamily of anion carrier proteins, in the internal membrane of the mitochondria mediates the re-entry of protons into the mitochondria and dissipates energy as heat instead of producing adenosine triphosphate[22] (Fig 2). The high