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Regulation of brown and beige fat by microRNAs

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ABSTRACT

MicroRNAs (miRNAs) are small non-coding RNA molecules consisting of approximately 20 to 22 nucleotides. They play a very important role in the regulation of gene expression. miRNAs can be found in different species and a variety of organs and tissues including adipose tissue. There are two types of adipose tissue in mammals: White adipose tissue (WAT) is the largest energy storage, whereas brown adipose tissue (BAT) dissipates energy to maintain body temperature. BAT was first identified in hibernating animals and newborns as a defense against cold. Later on, it was also discovered in human adults, suggesting its potential role in energy balance and metabolism. Moreover, "brown-like" adipocytes present in WAT depots, so called beige or brite (brown-in-white) cells, were discovered by several groups. In recent years, miRNAs were found to have important regulatory function during brown fat differentiation, brown fat activation and white fat "browning". In this review, we focus on the regulation of brown and beige fat by miRNAs including the role in their differentiation and function, providing evidence for their therapeutic potential in metabolic diseases.

Contents

1. Introduction

Nowadays, more and more people are suffering from obesity worldwide. Obesity is characterized by a high body mass index (BMI) with a disturbed energy balance (Spiegelman & Flier, 2001). It is associated with diseases, such as hypertension, hyperlipidemia, type 2 diabetes, cardiovascular diseases and certain types of cancer (Must et al., 1999). Treatments of obesity have been focused on diet, physical exercise,

Abbreviations: ADAM17, ADAM metallopeptidase domain 17; ADINR, adipogenic differentiation induced noncoding RNA; ADNCR, adipocyte differentiation-associated long noncoding RNA; AMPK, AMP-activated protein kinase; aP2, fatty-acid binding protein 4; BAT, brown adipose tissue; Blnc1, brown fat lncRNA 1; BMI, body mass index; BMP7, bone morphogenetic protein 7; BMPR1A, bone morphogenetic protein receptor-1α; C/EBP, CCAAT/enhancer-binding protein; cGMP, cyclic GMP; Cidea, cell death-inducing DNA fragmentation factor alpha-like effector A; Creb, cAMP response element binding protein; CtBPs, C-terminal-binding proteins; EBF2, early B cell factor-2; EHMT1, euchromatic histone-lysine *N*-methyltransferase 1; FABP4, fatty-acid binding protein 4; HFD, high fat diet; HIF1an, hypoxia-inducible factor 1, alpha subunit inhibitor; hnRNPU, heterogeneous nuclear ribonucleoprotein U; HOTAIR, HOX antisense intergenic RNA; HoxC8, Homeobox C8; igWAT, inguinal white adipose tissue; Insig1, insulin induced gene 1; lncRNA, long non-coding RNA; MAPK, p38 mitogen activated protein kinase; miRNA, microRNA; Myf5, myogenic factor 5; NPs, natriuretic peptides; Pdgfr2, platelet-derived growth factor receptor 2; PDGFRα, platelet-derived growth factor receptor alpha; PGC-1α, peroxisome-proliferator-activated receptor γ-coactivator 1α; PGC-1β, peroxisome-proliferator-activated receptor γ-coactivator 1β; PPAR, peroxisome-proliferator-activated receptor; PRDM16, protein PR domain containing 16; pri-miRNA, primary miRNA; PU.1 AS, antisense long non-coding RNA; RIP140, receptor-interacting protein 140; Runx1t1, Runt-related transcription factor 1, translocated to, 1; slincRAD, super-long intergenic non-coding RNA functioning in adipocyte differentiation; SIRT1, Sirtuin 1; SVFs, stromal vascular fraction; TGFβ1, transforming growth factor-β1; UCP1, uncoupling protein 1; vWAT, visceral white adipose tissue; WAT, white adipose tissue.

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medications taking and even bariatric surgery. However, due to the lack of efficient pharmacological therapies, gastrointestinal or cardiovascular side-effects of the medications and complications after surgery, it is necessary to search for novel ways to efficiently prevent or reduce obesity.

1.1. Definition and classification of adipose tissue

In mammals, there are two kinds of adipose tissue, white adipose tissue (WAT) which stores energy in the form of lipids, and brown adipose tissue (BAT) which consumes energy to generate heat (Lowell & Flier, 1997). Brown adipocytes contain a large amount of mitochondria and less lipids in comparison to white adipocytes.

WAT is distributed widely throughout the whole body. According to its location, it can be classified as visceral white adipose tissue (vWAT) which is mainly surrounding internal organs, and superficial or inguinal white adipose tissue (igWAT).

BAT has been thought to exist only in hibernating mammals and human babies since it was first described in the 16th century. This opinion was text book knowledge until 2007 (Nedergaard et al., 2007) and 2009 when functional BAT was identified in adult human (Cypess et al., 2009; Saito et al., 2009; van Marken Lichtenbelt et al., 2009; Virtanen et al., 2009). It is mainly located in the supraclavicular and neck regions of human body (Nedergaard et al., 2007). BAT activation is induced by cold and results in non-shivering thermogenesis. This process is dependent on uncoupling protein 1 (UCP1)-driven uncoupling of the proton gradient generated by the respiratory chain reaction at the inner membrane of mitochondria from oxidative phosphorylation. Interestingly, slim people exhibit higher BAT activity than obese individuals (van Marken Lichtenbelt et al., 2009).

In addition to "classical" white and brown fat cells, "brown-like" adipocytes, also known as brite or beige adipocytes have been found in WAT depots — especially igWAT (Young et al., 1984; Cousin et al., 1992). Morphologically, beige/brite adipocytes are similar to brown adipocytes, containing multilocular lipid droplets and plenty of UCP1 positive mitochondria. Moreover, beige/brite adipocytes express brown fat-specific genes, including *UCP1*, cell death-inducing DNA fragmentation factor alpha-like effector A (*Cidea*), peroxisome-proliferator-activated receptor γ-coactivator 1α (*PGC-1α*), protein PR domain containing 16 (*PRDM16*) and CCAAT/enhancer-binding protein β (*C/EBPβ*). Given the fact that beige/brite adipocytes show a morphology and thermogenic gene expression very similar to brown adipocytes (Xue et al., 2007; Wu et al., 2012), and an ability to undergo thermogenesis as well, these adipocytes have also been termed inducible brown adipocytes (Hoffmann et al., 2015b).

1.2. Development of adipose tissue

During embryonic development, BAT develops earlier than WAT (Cannon & Nedergaard, 2004). Despite both adipose tissues arise from a mesodermal origin (Hausman & Campion, 1982), they originate from different mesenchymal stem cell lineages. BAT is derived from the central dermomyotome that also gives rise to muscle and dermis (Atit et al., 2006). During differentiation brown adipocytes express a myogenic signature (Timmons et al., 2007). Seale et al. (Seale et al., 2008) published that cells expressing the transcription factor myogenic factor 5 (Myf5) specifically give rise to muscle cells or brown adipocytes but not to white adipocytes. However, Guertin and colleagues clearly showed in mice that nearly all of the white adipocytes in the anterior subcutaneous and retroperitoneal visceral depots are Myf5 positive whereas all posterior subcutaneous as well as all mesenteric and perigonadal visceral white adipocytes are Myf5 negative (Sanchez-Gurmaches et al., 2012), suggesting that Myf5 expression is not per se specific for brown adipocytes but rather a marker for cell position within the body.

There is an ongoing debate about the nature and origin of beige/brite adipocytes. It was postulated that (i) they are derived from pre-existing white adipocytes by "transdifferentiation" (Vitali et al., 2012); (ii) they are masked as white adipocytes and might "de-mask" upon cold exposure (Nedergaard & Cannon, 2014); (iii) they arise "de novo" by differentiation from precursors (Wang et al., 2013). Lee et al. showed that most inducible brown adipocytes in vWAT are derived from cells expressing platelet-derived growth factor receptor alpha (PDGFRα), CD34 and Sca1 by de novo differentiation, whereas only circa 6% of UCP1-positive cells in igWAT were newly-born (Lee et al., 2012). Thus, the origin/generation of beige adipocytes apparently differs according to their location/depot (Lee et al., 2012). A recent study showed that upon cold-exposure circa 10% of beige adipocytes in igWAT actually arise from smooth muscle precursors (Long et al., 2014) indicating that the beige/inducible brown adipocyte population is more heterogeneous than previously appreciated (Long et al., 2014).

2. Transcriptional regulation of brown/beige adipocyte development

miRNAs that regulate brown and beige/brite adipocyte function often target transcription factors, therefore, we will briefly summarize major transcription factors and their role in brown and beige fat. PRDM16, a 140 kDa zinc finger protein, has been demonstrated to play a major role in brown/beige adipocyte development (Cohen et al., 2014). Although PRDM16 has been indicated to control the switch between skeletal myoblasts and brown adipocytes (Seale et al., 2008) and to stimulate brown adipogenesis by direct binding to peroxisome-proliferator-activated receptor γ (PPARγ), classical BAT is not affected by ablation of PRDM16 in mice (Cohen et al., 2014). PRDM16 has been shown to bind to many regulatory factors including PGC-1α, peroxisome-proliferator-activated receptor γ-coactivator 1β (PGC-1β), C/EBPβ (Seale et al., 2007; Kajimura et al., 2009), euchromatic histone-lysine *N*-methyltransferase 1 (EHMT1) (Ohno et al., 2013) and C-terminal-binding proteins (CtBPs) (Kajimura et al., 2008), respectively. Furthermore, another regulator, early B cell factor-2 (EBF2), has been shown to bind to PRDM16, recruiting PPARγ to BAT-selective gene targets (Rajakumari et al., 2013). Although PRDM16 is dispensable for embryonic BAT development, recent studies suggest that it is required to maintain BAT function during aging (Harms et al., 2014). Thus, PRDM16 is a main regulator of beige adipocyte differentiation and postnatal BAT, probably as a complex with many other regulatory factors.

The regulatory role of peroxisome-proliferator-activated receptor α (PPARα) in brown adipocyte differentiation is not yet clear. However, PPARα ablation decreases expression of brown adipocyte-specific genes, including *Zic1*, *Lhx8* and *PRDM16* (Walden et al., 2010), suggesting the importance of PPARα in the process of brown adipogenesis. In 2011, Marta Giralt's group has demonstrated that PPARα can induce PGC-1α expression by its binding to a PPAR-responsive element in the distal PGC-1α gene promoter (Hondares et al., 2011).

Other positive regulators of brown adipogenesis include bone morphogenetic protein 7 (BMP7) and Orexin. BMP7 can promote brown adipogenesis and thermogenesis via several mechanisms including induction of PRDM16 and PGC-1α expression, increased UCP1 expression, elevation of PPARγ and C/EPBs expression and induction of mitochondrial biogenesis (Tseng et al., 2008). Orexin can promote brown adipocyte differentiation via p38 mitogen activated protein kinase (MAPK) and bone morphogenetic protein receptor-1α (BMPR1A) dependent Smad 1/5 signaling (Sellayah et al., 2011).

In the process of "browning" of WAT, PRDM16 and PPARs play critical roles, respectively. Activation of PPARα has been shown to promote beige adipogenesis via PRDM16 and PGC-1α (Hondares et al., 2011). PPARγ activators/agonists have been widely used to induce "browning" of WAT in an efficient way throughout the years (Fukui et al., 2000; Wilson-Fritch et al., 2004; Hondares et al., 2006; Koh et al., 2009; Petrovic et al., 2010). Their "browning" effect has been related to an induction in PGC-1α expression after PPARγ agonist treatment