Regulatory Small and Long Non-coding RNAs in Brite/Brown Adipose Tissue

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Abstract

Brite/brown adipose tissue (BAT) is a thermogenic tissue able to dissipate energy via non-shivering thermogenesis. It is naturally activated by cold and has been demonstrated to increase thermogenic capacity, elevate energy expenditure and to ultimately contribute to fat mass reduction. Thus it emerges as novel therapeutic concept for pharmacological intervention in obesity and other metabolic disorders. Therefore, the comprehensive understanding of the regulatory network in thermogenic adipocytes is in demand.

The surprising findings that (1) all human protein-coding genes make up not more than 2% of our genome, (2) organismal complexity goes well along with the percentage of non-protein coding sequences, and that (3) three quarters of our genome are pervasively transcribed, provide evidence that non-coding RNAs (ncRNAs) are not junk, but a significant and even predominant part or our transcriptome representing a treasure chest worth retrieving regulatory determinants in biological processes and diseases.

In this chapter, the impact of regulatory small and long ncRNAs, in particular microRNAs and lncRNAs on brite/brown adipose tissue formation and metabolic function and their involvement in physiological and pathological conditions has been reviewed.

Keywords

Brown adipose tissue, obesity, metabolism, brite/brown thermogenic adipocyte, regulatory RNA, non-coding RNA, microRNA, long non-coding RNA

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Introduction

The adipose organ is an important player in the regulation of whole-body energy homeostasis, including fatty acid and glucose metabolism, and contributes to many of an organism´s pivotal requirements of survival: fuel for metabolism, immune responses, lactation, and thermogenesis (Cinti 2012). The adipose organ can be divided into two distinct types of adipose tissues, white (WAT) and brown (BAT) adipose tissue: WAT is specialized for the storage and release of chemical energy (Cinti 2012; Cohen and Spiegelman 2016), while BAT is able to dissipates energy in the form of heat (thermogenesis). Interestingly, WAT and BAT do not display clear anatomical boundaries, as in rodents and humans, islands of brown-like adipocytes emerge within WAT depots after cold or β-adrenergic receptor stimulation. These adipocytes, termed "brite" (brown-in-white) or "beige" adipocytes, differ by embryonic origin from genuine brown adipocytes but are functional, i.e., thermogenically active (Petrovic et al. 2010; Wu et al. 2012). Brite/brown adipocytes are endowed with high capacity of glucose and lipid oxidation thus making the brite/brown adipose tissue a promising target for lowering plasma levels of glucose and fatty acids thus diminishing the risks of overweight, obesity and follow-up complications (Nedergaard et al., 2011). Indeed, brite/brown adipocyte formation and activation emerge as a novel therapeutic concept for pharmacological intervention in obesity and other metabolic disorders (Nedergaard and Cannon 2010), and the identification of regulatory factors and drugs able to initiate the formation and activation of thermogenic adipocytes, particularly in humans, is in demand and constitutes a highly active research field.

In this review, I tempt to summarize recent findings on a novel class of regulatory determinants in brite/brown adipose tissue biology with impact on metabolism and disease, non-coding RNAs.

Non-coding RNAs

For a long time, research on molecular mechanisms has been centered on protein-coding genes. However, efforts investigating our entire genome brought up surprising discoveries. Firstly, the Human Genome Project revealed much less protein-coding genes than previously expected, and all 20,500 protein-coding genes known in human make up not more than 2% of our genome, raising questions for the majority of 98% of our genome (Lander et al. 2001; Venter et al. 2001). Secondly, even single cell organisms such as Tetrahymena thermophila exceed the number of human protein-coding genes, indicating that this is not the determinant of organismal complexity (Taft et al. 2007). However, organismal complexity goes well along with the increasing relative amount of non-protein-coding sequences, suggesting indeed a function for the non-coding part of the genome in higher organisms (Taft et al. 2007). Thirdly, the ENCODE project intriguingly demonstrated transcriptional activity for 74.7% of the human genome, with many novel non-protein-coding transcripts of small and long non-coding RNA (ncRNA) (Birney et al. 2007; Djebali et al. 2012; Dogini et al. 2014). Altogether, these findings indicate that the non-coding part of the genome is not 'junk' DNA, but a significant and even predominant part of our genome representing a promising treasure chest worth retrieving regulatory determinants in both biological processes and diseases.

ncRNAs are defined as RNA transcripts that do not encode a protein, and are divided into two primary categories: small ncRNAs (< 200 nt) and long ncRNAs (lncRNAs; > 200 nt). Some small ncRNAs are housekeeping RNAs, such as tRNA, snRNA and snoRNA, which are crucial for cell physiology,

while others, such as microRNAs (miRNAs) and piRNAs, are associated with protein-coding gene regulation (Figure 1). Also long ncRNAs comprise housekeeping RNAs, such as ribosomal RNAs (rRNAs), and regulatory elements such as lncRNAs, including antisense RNAs (AS-RNAs) and enhancer RNAs (eRNAs) (Ponting et al. 2009; Wilusz et al. 2009; Vance and Ponting 2014; Sun and Kraus 2015; Iyer et al. 2015).

miRNAs were first discovered in 1993 and are to date the most extensively studied class of non-coding RNAs, with more than 2,500 candidates in human and 1,900 candidates in mouse (Lee et al. 1993). MiRNAs are endogenous, single-stranded, non-coding, small RNAs with a length of 21-22 nucleotides that are involved in regulating gene expression in the cytoplasm by incorporating into the RNA-induced silencing complex (RISC), and preferential binding to specific sequences in the 3'-UTR of their target mRNAs suppress translation or induce mRNA degradation (Filipowicz et al. 2008).

On the other hand, regulatory lncRNAs were already discovered in 1990, with now more than 58,000 loci found in human (Brannan et al. 1990; Iyer et al. 2015). They are found in the cytoplasm as well in the nucleus where they bind to enhancer regions, promoter sequences, 5´-UTRs, exons, introns, intragenic regions, intergenic sequences, antisense sequences and 3´-UTRs. The regulatory role of lncRNAs is directly dependent on their cellular localization. In the cytoplasm, lncRNAs can act as molecular decoys for proteins and microRNAs, while in the nucleus, lncRNAs have been shown to perform as transcriptional activators or inhibitors in *cis*, i.e. regulating neighboring genes), or in *trans*, i.e. regulating genes from other regions or chromosomes (Zhang et al. 2014). However, in contrast to miRNAs, lncRNAs are poorly conserved between species and are highly tissue-specific, which makes them specifically and tightly regulated, even though they are found at lower abundance compared to mRNAs (Babak et al. 2005; Mercer et al. 2008; Guttman et al. 2009; Ramsköld et al. 2009; Derrien et al. 2012).

Over the last decades, it has been unraveled that small and long ncRNAs govern the formation and function of tissues and organs, including the adipose organ. For the characterization of miRNAs in the adipose organ, several mouse models with adipose-specific knockout of key regulators of miRNA biogenesis were generated. Importantly, fat-selective inactivation of Dicer, an essential factor in miRNA biogenesis, resulted in mice which were almost devoid of WAT (Mudhasani et al. 2010, 2011). Moreover, adipose-specific ablation of Dicer or DGCR8 in mice, another crucial determinant in miRNA biogenesis, displayed enlarged but pale interscapular BAT, decreased expression of genes characteristic of brown fat and intolerance to cold exposure (Mori et al. 2014; Kim et al. 2014). These findings suggest a pivotal role of miRNAs in the formation of white, brite and brown adipocytes. In recent years, an explosion in the identification of ncRNAs and their functions was observed, yet one only began to understand the complexity of this new regulatory RNA world, in particular how ncRNAs control various aspects of gene expression and their involvement in diseases (Prasanth and Spector 2007; de Almeida et al. 2016). The impact of miRNAs on diseases is acknowledged by their deployment as biomarkers, drugs and/or drug targets, with first candidates in clinical trials phase 1 and 2 (Wahid et al. 2010; van Rooij et al. 2012; Hydbring and Badalian-Very 2013; Wahid et al. 2014a; Christopher et al. 2016), while the impact of lncRNAs as potential diagnostic markers and/or valuable therapeutic targets for diseases is just emerging. Here we review the regulatory impact of miRNAs and lncRNAs on brite/brown adipose tissue biology and thermogenic capacity and their involvement in metabolic disease.

MicroRNAs in brite/brown adipose tissue

Brite/brown adipocyte differentiation is tightly governed in a coordinated manner using various regulatory pathways which finally activate several transcription factors and coactivators (Xue et al. 2005; Kajimura et al. 2010), such as peroxisome proliferator-activated receptor α (PPARα) and γ (PPARγ), PPARγ-coactivators-1 (PGC-1α (Puigserver et al. 1998; Rohas et al. 2007) and PGC-1β (Villena 2015)), cAMP responsive element binding protein (CREB), CCAAT/enhancer-binding proteins (C/EBPs)(Tanaka et al. 1997; Rosen et al. 2002), PR domain containing 16 (PRDM16) (Seale et al. 2008, 2011), and activating transcription factor 2 (ATF2) (Cao et al. 2004), but can also repress transcriptional repressors, such as the corepressor receptor-interacting protein 140 (RIP140) (Kiskinis et al. 2014) in order to induce the expression of browning genes, with UCP1 as the hallmark of brite/brown adipocytes. These transcriptional factors drive the brite/brown adipogenic program, which ultimately leads to the remodeling of the adipocyte including increased mitochondrial density and size, altered mitochondrial morphology with laminar cristae, lipid droplets of smaller size but of higher number per adipocyte, and increased oxidative capacity of carbohydrates and fatty acids. The pathways which are known to be targeted by miRNAs are illustrated in Figure 2.

miRNAs targeting PPARγ and PRDM16 in brite/brown adipogenesis

In this context, miR-27 was found to be endogenously downregulated during white and brite/brown adipocyte differentiation, as well as in BAT and WAT. Moreover, miR-27 was identified as central upstream inhibitor of PPARγ in white adipocyte differentiation (Karbiener et al. 2009) and was shown to directly target and repress a number of essential factors of the brite/brown transcriptional network, e.g. PRDM16, CREB, PGC-1α/β, PPARα and PPARγ, during brite/brown adipogenesis (Figure 2) (Sun and Trajkovski 2014; Zhu et al. 2014). Under pathophysiological conditions, miR-27 was less abundant in mature adipocytes of obese compared to lean mice (Kim et al. 2010), thus probably allowing adipose tissue hyperplasia, while miR-27 was found to be more abundant in the adipose tissue of hyperglycaemic Goto-Kakizaki rats compared to normoglycaemic Brown Norway rats, which could also be corroborated by elevated miR-27 levels in 3T3-L1 adipocytes, a murine adipogenesis model, upon exposure to increased glucose concentrations (Herrera et al. 2010).

The muscle-enriched miR-133 was found to be markedly downregulated in BAT and subcutaneous WAT. This repression is a result of decreased expression of the myocyte enhancer factor 2 (MEF2), its transcriptional regulator, which is also repressed upon elevated cAMP levels after cold exposure. In line with this, inhibition of miR-133 or Mef2 promotes brite and brown adipogenesis. Mechanistically, miR-133 directly targets and represses PRDM16 (Trajkovski et al. 2012).

The targeted deletion of the RNA-binding protein KSRP, that regulates gene expression at several levels, caused a reduction in adiposity, with elevated expression of brite/brown marker genes in subcutaneous WAT, and in reduced expression of miR-150. In this context, forced expression of miR-150 indeed attenuated the browning program. Mechanistically, miR-150 directly targets and represses PRDM16 and PGC-1α (Chou et al. 2014).

miRNAs targeting the cAMP-PKA-CREB and p38-ATF2 signaling pathways in BAT

β-adrenergic receptor signaling leads to elevated levels of cyclic AMP (cAMP), followed by p38/MAPK signaling, which all play a vital role in BAT thermogenic response leading to ATF2 activation, thus promoting transcription of downstream targets such as PGC-1α, UCP1, and FGF21 (Cao et al. 2004;

Robidoux et al. 2005). Conversely, repressors of p38/MAPK signaling, such as TOB1, are able to silence the pathway under normal conditions (Sun et al. 2013; Wu et al. 2015).

In this context, miR-378/378* is a miRNA encoded within the PGC-1β gene and was the first miRNA found to increase BAT mass and is sufficient to prevent both genetic and high fat diet-induced obesity. Mechanistic studies at the molecular level revealed that miR-378/378* directly targets the phosphodiesterase (PDE) (Figure 2), which then leads to diminished degradation of cAMP to AMP, thus leading to elevated cAMP levels which activate PKA and downstream signaling pathways (Pan et al. 2014). Moreover, another study demonstrated that the ω-3 fatty acid eicosapentaenoic acid (EPA) binds and activates the free fatty acid receptor (FFAR4), a functional receptor for n-3 polyunsaturated fatty acids (PUFA), which positively modulates miR-378 leading to elevated cAMP levels and ultimately UCP1 expression (Kim et al. 2016).

Another miRNA, miR-32, was identified to be expressed selectively in BAT, and its levels were elevated by cold exposure. Mechanistically, miR-32 directly targets the p38/MAPK signaling repressor TOB1, thus diminishing the repressive effect of TOB1 on p38/MAPK signaling which leads to phosphorylation and activation of ATF2 with enhanced BAT thermogenesis (Figure 2). Interestingly, this also drives FGF21 expression and secretion from BAT, thereby also trans-activating the browning of WAT (Ng et al. 2017).

miRNAs ultimately modulating C/EBPβ activity

C/EBPβ is a critical transcription factor that activates transcription of C/EBPα and PPARγ, two important transcriptional inducers of the adipogenic brite/brown transcriptional program. C/EBPβ cooperates with PRDM16 in a complex that initates both brown adipocyte differentiation from myoblastic precursors and brite adipocyte formation in subcutaneous WAT (Kajimura et al. 2009; Seale et al. 2011; Jimenez-Preitner et al. 2011).

In this context, miR-155 has been demonstrated to be enriched in BAT, highly enriched in proliferating brown preadipocytes, and declines after induction of brown adipogenesis. Thus inhibition of miR-155 enhanced brite and brown adipogenesis and increased BAT thermogenesis and browning of WAT in mice, while mice transgenically overexpressing miR-155 exhibited reduced BAT mass and function. Interestingly, as direct target of miR-155, C/EBPβ was identified, with C/EBPβ repressing again miR-155 expression, thus forming a self-inhibitory feedback loop that tightly governs brite/brown adipogenesis (Figure 2) (Chen et al. 2013).

miR-196a was found to be specifically required for the induction of the browning program of WAT, not BAT, progenitor cells. Mechanistically, HOXC8 was identified as direct miR-196a target and was repressed post-transcriptionally (Figure 2). HOXC8 is a white-fat gene, which represses C/EBPβ and UCP1. In line with that, transgenic mice with elevated miR-196a levels exhibited enhanced energy expenditure and resistance to diet-induced obesity. Thus, these data indicate that the induced brite adipocytes in the inguinal WAT are indeed metabolically functional (Mori et al. 2012).

The first described miRNAs in murine brown adipogenesis was the miRNA cluster miR-193b-365 which was enriched in BAT. Blocking miR-193b and/or miR-365 in brown preadipocytes impaired brown adipogenesis and promoted the expression of myogenic markers, while forced expression in C2C12 myoblasts blocked the entire program of myogenesis and promoted brown adipogenesis (Sun et al. 2011). The runt-related transcription factor 1 (RUNX1T1) was identified as direct miR-193b-365

target, which is known to act as inhibitor of C/EBPβ and consequently of white adipogenesis (Figure 2) (Rochford et al. 2004). However, another study challenged these in vitro results by demonstrating that in mice with an inactivated miR-193b-365 locus the development, differentiation and function of BAT was unaffected, indicating that BAT do not require the presence of miR-193b and miR-365 (Feuermann et al. 2013).

Another miRNA, which also targets RUNX1T1, besides other direct targets such as Necdin, and promotes brown and brite adipocyte differentiation, is miR-455. This miRNA exhibited a BAT-specific expression pattern and is induced by cold and the browning inducer bone morphogenetic protein 7 (BMP7). In adipose-specific transgenic mice, elevated miR-455 levels led to marked browning of subcutaneous WAT upon cold exposure by activating the hypoxia inducible factor 1 α inhibitor (HIF1an), that further activates AMPK, which then promotes the browning program including PGC-1α expression and mitochondrial biogenesis (Zhang et al. 2015).

miRNAs modulating the transcriptional coactivator PGC-1α

The thermogenic program of BAT includes mitochondrial biogenesis, and PGC-1α is a key regulator of mitochondrial biogenesis, oxidative metabolism and UCP1 (Puigserver et al. 1998; Cannon and Nedergaard 2004). However, the transcriptional repressor RIP140 is able to block PGC-1α effects, as mice devoid of RIP140 are lean, show resistance to high fat diet (HFD)-induced obesity and have increased oxygen consumption, with a marked increase in expression of genes involved in energy dissipation and mitochondrial uncoupling, including UCP1 (Leonardsson et al. 2004).

MiRNA miR-34a has been shown to be elevated in WAT and BAT upon obesity, associated with inhibited browning of WAT and pale BAT. Mechanistically, miR-34a directly targets the fibroblast growth factor receptor 1 (FGFR1), reduces expression of βklotho and SIRT1, which results in reduced FGF21/SIRT1-dependent deacetylation of PGC-1α, finally repressing the browning program (Figure 2). Thus, lentiviral-mediated repression of miR-34a levels in adipose depots of mice with diet-induced obesity to levels which were detected in lean mice reduced adiposity and improved mitochondrial biogenesis and oxidative metabolism (Fu et al. 2014). However, global miR-34a knockout mice are again susceptible to diet-induced obesity (Lavery et al. 2016).

Members of the miR-30 family, miR-30b and miR-30c, were greatly elevated in expression levels during adipocyte differentiation and are stimulated by cold or β-adrenergic receptor stimulation. Interestingly, the corepressor RIP140 was identified as direct target of miR-30b/c (Figure 2). Consequently, overexpression of miR-30b/c induced the browning program, including UCP1 and mitochondrial respiration, in the development of white and brown adipocytes. Moreover, miR-30b/c was able to potentiate β-adrenergic receptor stimulation-induced browning, suggesting a positive feedback loop of miR-30 family members on the β-adrenergic receptor signaling and action (Hu et al. 2015).

miRNA targeting ADAM17 and PTEN

The miR-26 family members miR-26a and miR-26b have been identified to be upregulated in murine WAT upon cold exposure. So far, they are the first in-depth characterized miRNAs able to shift human adipocyte differentiation from white to brite via inducing UCP1 expression, increasing mitochondrial density, changing mitochondrial morphology towards brown adipocyte characteristics, and elevating coupled and uncoupled respiration (Karbiener et al. 2014). The identified and validated

target that at least partially mediates the miR-26 effects on both adipocyte differentiation and browning, is ADAM17, also known as TNFα converting enzyme (TACE), which upon knockdown causes a lean, hypermetabolic phenotype in mice (Gelling et al. 2008)(Figure 2). However, how ADAM17 mediates mechanistically the browning of WAT yet needs to be elucidated. On the other hand, miR-26b has been identified to directly target the phosphatase and tensin homolog (PTEN), thereby improving insulin sensitivity in human mature adipocytes (Xu et al. 2015), which is in line with results from in vivo studies where transgenic mice, which globally or liver-specifically overexpress miR-26a, also exhibited increased insulin sensitivity (Fu et al. 2015). Interestingly, in these mice HFD-induced obesity is not ameliorated upon liver-specific overexpression, but upon global miR-26a overexpression. This indicates that this obesity resistant phenotype of miR-26 action is dependent on its function in another organ than the liver.

miRNA targeting the β-secretase BACE1

miR-328 has recently been identified to promote the shift in cell commitment from muscle to BAT. Repressed miR-328 function blocked adipogenesis, and miR-328 overexpression promoted brown adipogenesis while diminishing myogenesis. Mechanistically, the β-secretase BACE1 was identified as direct target of miR-328 (Oliverio et al. 2016)(Figure 2). Reduced BACE1 levels are known to decrease body weight, to protect against diet-induced obesity, at least partially via UCP1 induction, and to enhance insulin sensitivity in mice (Meakin et al. 2012), and to control the G-protein coupled receptor 5b (GPRC5b), a known link between diet-induced obesity and type 2 diabetes (Kim et al. 2012).

miRNAs with impact on brite/brown adipocyte function and formation but with unknown direct targets

There are a number of further miRNAs with impact on brite/brown adipocyte formation and function, however, they still lack a known direct target by which the miRNA effects are mediated (Figure 2).

For example, let-7i is a repressor of brite adipocyte function, as inhibition was able to promote the conversion of adipocytes from white to brite in mouse and human, while let-7i mimic injection in murine subcutaneous WAT partially blocked β-adrenergic activation of the browning process (Giroud et al. 2016a). Another miRNA that was characterized in humans and rodents, is miR-125b, which was found to be downregulated upon β-adrenergic receptor stimulation in WAT and BAT and lower expressed in BAT than in WAT. While miR-125b overexpression led to decreased mitochondrial biogenesis and respiration, miR-125b inhibition promoted both in human adipocytes (Giroud et al. 2016b). However, a direct target has not been validated yet.

miR-19b has recently been identified to be transcriptionally upregulated by glucocorticoids (GC) which are known to inhibit the function of BAT and browning of WAT (Kong et al. 2015). While miR-19b overexpression had the same effect as GC treatment, miR-19b inhibition blocked dexamethasone-mediated suppression of the browning program, placing miR-19b as an essential target for GC-mediated control of adipose tissue browning (Lv et al. 2018).

Expression levels of the miRNA cluster miR-106b-93 were found to be elevated in BAT of HFD-fed mice compared to mice fed a low fat diet, and knockdown of miR-106b and miR-93 significantly

induced the adipogenic browning program, while ectopic expression of both miRNAs suppressed brown marker genes, such as UCP1 (Wu et al. 2013).

The miRNAs miR-182 and miR-203 were found in brown adipocytes of DGCR8 KO mice to be among the 10 most downregulated miRNAs. Inhibition of both miRNAs in brown adipogenesis led to a reduction in brown adipogenic marker genes, including UCP1, PGC-1α, CIDEA and PPARα, but not common adipogenic marker genes. Thus these two miRNAs are required for brown adipocyte differentiation (Kim et al. 2014).

miRNAs as serum biomarker

Beyond functioning as energy buffer, the adipose organ vitally cross-talks with other organs as adipocytes are endowed with secretory abilities of different bioactive compounds which can act in a paracrine, autocrine, and/or endocrine manner (Ailhaud 2000; Villarroya et al. 2017). This also includes the brown adipose depots contributing 87% of the total amount of exosomes under cold exposure (Chen et al. 2016). Profiling of miRNAs in these exosomes revealed miR-92a to be inversely correlated with human BAT activity which is usually measured by ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography coupled with computer tomography (PET/CT). Thus exosomal miR-92a represents a potential serum biomarker for BAT activity in mice and humans (Chen et al. 2016).

LncRNAs in brite/brown adipose tissue

Increasing the thermogenic capacity of adipose tissue has been proposed as a strategy for combating obesity and its associated metabolic disorders. As various small ncRNAs have been implied in the formation and function of brite/brown adipocytes, it is also worth to pay attention to long ncRNAs and their regulatory functions in thermogenic adipocytes. And indeed, lncRNAs have been demonstrated to have a regulatory impact on brite/brown adipose tissue biology, however, only a few candidates have been functionally characterized so far which we review in the following (Figure 3).

LncRNA BLNC1

PPARγ cooperates with C/EBPα to control the expression of a large number of adipogenic genes, and PRDM16, PGC-1α and the early B-cell factor 2 (EBF2) have been identified as transcription factors that work with PPARγ to selectively promote the formation of adipocytes with thermogenic capacity. In this context, the first lncRNA named brown fat lncRNA 1 (BLNC1) was identified, which has a length of 965 nucleotides, does not associate with ribosomes, is not translated into a protein and is highly conserved between mice and humans. Overexpression of BLNC1 promoted the browning program in white and brown adipocytes, including elevated UCP1 expression, mitochondrial content, total respiratory capacity, and uncoupled respiration, while BLNC1 inhibition impaired these characteristics. Mechanistically, BLNC1 has been found to be strictly dependent on EBF2, forming a ribonucleoprotein complex with EBF2, which on the one hand promotes expression of BLINC1 itself, and on the other hand facilitates binding to the UCP1 promoter leading there to higher activity (Jones and Tontonoz 2014; Zhao et al. 2014)(Figure 3). This BLNC1/EBF2 complex is formed by support of the heterogeneous nuclear ribonucleoprotein U (hnRNPU) (Mi et al. 2017). Moreover, the zinc finger and BTB domain-containing protein 7b (ZBTB7B) has been identified as potent transcription factor of brite and brown adipocyte differentiation and thermogenic capacity.

Interestingly, ZBTB7B is able to recruit the BLNC1/hnRNPU ribonucleoprotein complex to drive the browning program (Li et al. 2017).

LncRNA BATE1

Another transcriptomics study comparing three different murine adipose depots (BAT, subcutaneous WAT, visceral WAT) revealed 127 lncRNAs with an expression pattern restricted to BAT that are often targeted in their promoter region by the transcriptional regulators C/EBPα, C/EBPβ, and PPARγ. One of them is lnc-BATE1, which has been found to be enriched 10-20 fold during brown adipogenesis. Functional studies elucidated that lnc-BATE1 is required for the establishment and maintenance of BAT identity and thermogenic capacity. Interestingly, also lnc-BATE1 interacts with hnRNPU to form a functional ribonucleoprotein complex to regulate brown adipogenesis (Alvarez-Dominguez et al. 2015) (Figure 3).

LncRNA BATE10

Another BAT-enriched lncRNA is lnc-BATE10, which was found to be highly upregulated during brown adipogenesis, is higher expressed in brown compared to white adipocytes, is induced upon BAT activation in cold exposed mice as well as in subcutaneous WAT by β-adrenergic receptor stimulation. Inhibition of lnc-BATE10 depleted the response to norepinephrine and significantly impaired the expression of BAT-selective genes such as UCP1 and PGC-1α. Thus lnc-BATE10 is required for BAT-selective gene expression in white and brown adipocytes. Mechanistically, lnc-BATE10 has been shown to be regulated by the cAMP-CREB signaling pathway and interacts with the CUG-binding protein and ELAV-like family member 1 (CELF1) to finally compete with PGC-1α for CELF1 binding (Bai et al. 2017). CELF1 is known to bind the 3'-UTR of its target mRNAs to promote RNA degradation and to repress translation. By competing with CELF1, lnc-BATE10 blocked its inhibitory function on PGC-1α mRNA thus promoting brite/brown adipogenesis.

lncRNAs in circulation as potential biomarkers

Moreover, also circulating lncRNAs have been studied in lean and obese human subjects, as well as in obese patients submitted to diet for 12 weeks. It appeared that three lncRNAs, lncRNA-p5549, lncRNA-p21015, and lncRNA-p19461, are inversely correlated with body mass index (BMI), waist circumference, waist-to-hip ratio, and fasting insulin levels (Sun et al. 2016).

Outlook

The worldwide epidemic of obesity is inexorably progressing and thus demands the development of novel and more effective therapeutic approaches. Adipose tissue is the core unit in energy metabolism which can cope with a positive energy balance either by energy storage in white adipocytes or an increase in energy expenditure via non-shivering thermogenesis in brite/brown adipocytes. The latter has ameliorating impact on blood glucose and triglyceride levels as well as on insulin sensitivity. However, the comprehensive regulatory network of brite/brown adipocyte formation remains to be elucidated.

In this context, small and long ncRNAs are an emerging novel regulatory layer in energy metabolism, involved in physiological and pathological conditions. So far, numerous miRNAs have been identified

and characterized to govern brite/brown adipose tissue biology, while for lncRNAs only three candidates have been revealed. Interestingly, while miRNAs have been shown to promote or impair brite/brown adipocyte formation and function, the so far all identified lncRNAs promote brite/brown adipogenesis and thermogenic capacity (Table 1). While most endogenous miRNAs and all lncRNAs which are known so far to be involved in brite/brown adipose tissue biology are characterized in mouse models, only three miRNAs, miR-26, let-7i and miR-125b, have also been functionally characterized in human. ncRNA candidates that also have a protective role in diet-induced obesity are still rare, and will further shrink when criteria for therapeutic applications are applied, such as cross-species conserved function and a comprehensive list of validated direct targets and mediators in order to allow and extrapolate animal studies to humans and to minimize adverse side effects in the long run. Thus the list of ncRNA candidates is far from being exhaustive, with plenty of space for further research in that field.

At the moment, anti-RNA treatments are currently being developed to expand the options available to clinicians (Wahid et al. 2010, 2014b; Kole et al. 2012; Slaby et al. 2017). However, from the current perspective, lncRNAs seem to be more challenging than miRNAs, as lncRNAs can have high turnover rates, lower transcriptional expression and less cross-species conservation, and a lack of mechanistic understanding hinders further investigation into the application of targeted therapeutics. Nevertheless, miRNAs and lncRNAs as drug targets can be targeted by RNA interference technology, while both classes of ncRNAs as drugs have, in contrast to small molecules and antibodies, very similar physico-chemical properties which will emerge as advantage in targeted drug delivery. The reason is that once a targeted ncRNA delivery system has been developed for one specific cell type, it could be easily loaded with any other member of this ncRNA class, thus changing the paradigm from one delivery system per drug to one delivery system per class of drugs. Moreover, due to the substantial number of lncRNA loci in the mammalian genome, lncRNAs are a treasure chest yet to be discovered and applied for therapeutic applications. To conclude, despite the currently existing obstacles, we have reached the point where modulating ncRNA expression and function has become a viable option for the modulation of energy metabolism and metabolic diseases. Moreover, it will be interesting to determine whether miRNA/lncRNA-targeting therapeutics could be combined with other chemical or biological drugs for multidrug therapy.

References

Ailhaud G (2000) Adipose tissue as an endocrine organ. Int J Obes Relat Metab Disord 24 Suppl 2:S1-3

Alvarez-Dominguez JR, Bai Z, Xu D, et al (2015) De Novo Reconstruction of Adipose Tissue Transcriptomes Reveals Long Non-coding RNA Regulators of Brown Adipocyte Development. Cell Metab 21:764–776. doi: 10.1016/j.cmet.2015.04.003

Babak T, Blencowe BJ, Hughes TR (2005) A systematic search for new mammalian noncoding RNAs indicates little conserved intergenic transcription. BMC Genomics 6:104. doi: 10.1186/1471-2164-6-104

Bai Z, Chai X-R, Yoon MJ, et al (2017) Dynamic transcriptome changes during adipose tissue energy expenditure reveal critical roles for long noncoding RNA regulators. PLoS Biol 15:e2002176. doi: 10.1371/journal.pbio.2002176

Birney E, Stamatoyannopoulos JA, Dutta A, et al (2007) Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. Nature 447:799–816. doi: 10.1038/nature05874

Brannan CI, Dees EC, Ingram RS, Tilghman SM (1990) The product of the H19 gene may function as an RNA. Mol Cell Biol 10:28–36

Cannon B, Nedergaard J (2004) Brown adipose tissue: function and physiological significance. Physiol Rev 84:277–359. doi: 10.1152/physrev.00015.2003

Cao W, Daniel KW, Robidoux J, et al (2004) 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

Chen Y, Buyel JJ, Hanssen MJW, et al (2016) Exosomal microRNA miR-92a concentration in serum reflects human brown fat activity. Nat Commun 7:11420. doi: 10.1038/ncomms11420

Chen Y, Siegel F, Kipschull S, et al (2013) miR-155 regulates differentiation of brown and beige adipocytes via a bistable circuit. Nat Commun 4:1769. doi: 10.1038/ncomms2742

Chou C-F, Lin Y-Y, Wang H-K, et al (2014) KSRP ablation enhances brown fat gene program in white adipose tissue through reduced miR-150 expression. Diabetes 63:2949–2961. doi: 10.2337/db13-1901

Christopher AF, Kaur RP, Kaur G, et al (2016) MicroRNA therapeutics: Discovering novel targets and developing specific therapy. Perspect Clin Res 7:68–74. doi: 10.4103/2229-3485.179431

Cinti S (2012) The adipose organ at a glance. Dis Model Mech 5:588–594. doi: 10.1242/dmm.009662

Cohen P, Spiegelman BM (2016) Cell biology of fat storage. Mol Biol Cell 27:2523–2527. doi: 10.1091/mbc.E15-10-0749

de Almeida RA, Fraczek MG, Parker S, et al (2016) Non-coding RNAs and disease: the classical ncRNAs make a comeback. Biochem Soc Trans 44:1073–1078. doi: 10.1042/BST20160089

Derrien T, Johnson R, Bussotti G, et al (2012) The GENCODE v7 catalog of human long noncoding RNAs: analysis of their gene structure, evolution, and expression. Genome Res 22:1775–1789. doi: 10.1101/gr.132159.111

Djebali S, Davis CA, Merkel A, et al (2012) Landscape of transcription in human cells. Nature 489:101–108. doi: 10.1038/nature11233

Dogini DB, Pascoal VDB, Avansini SH, et al (2014) The new world of RNAs. Genet Mol Biol 37:285–293

Feuermann Y, Kang K, Gavrilova O, et al (2013) MiR-193b and miR-365-1 are not required for the development and function of brown fat in the mouse. RNA Biol 10:1807–1814. doi: 10.4161/rna.27239

Filipowicz W, Bhattacharyya SN, Sonenberg N (2008) Mechanisms of post-transcriptional regulation by microRNAs: are the answers in sight? Nat Rev Genet 9:102–114. doi: 10.1038/nrg2290

Fu T, Seok S, Choi S, et al (2014) MicroRNA 34a inhibits beige and brown fat formation in obesity in part by suppressing adipocyte fibroblast growth factor 21 signaling and SIRT1 function. Mol Cell Biol 34:4130–4142. doi: 10.1128/MCB.00596-14

Fu X, Dong B, Tian Y, et al (2015) MicroRNA-26a regulates insulin sensitivity and metabolism of glucose and lipids. Journal of Clinical Investigation 125:2497–2509. doi: 10.1172/JCI75438

Gelling RW, Yan W, Al-Noori S, et al (2008) Deficiency of TNFalpha converting enzyme (TACE/ADAM17) causes a lean, hypermetabolic phenotype in mice. Endocrinology 149:6053–6064. doi: 10.1210/en.2008-0775

Giroud M, Karbiener M, Pisani DF, et al (2016a) Let-7i-5p represses brite adipocyte function in mice and humans. Sci Rep 6:28613. doi: 10.1038/srep28613

Giroud M, Pisani DF, Karbiener M, et al (2016b) miR-125b affects mitochondrial biogenesis and impairs brite adipocyte formation and function. Molecular Metabolism 5:615–625. doi: 10.1016/j.molmet.2016.06.005

Guttman M, Amit I, Garber M, et al (2009) Chromatin signature reveals over a thousand highly conserved large non-coding RNAs in mammals. Nature 458:223–227. doi: 10.1038/nature07672

Herrera BM, Lockstone HE, Taylor JM, et al (2010) Global microRNA expression profiles in insulin target tissues in a spontaneous rat model of type 2 diabetes. Diabetologia 53:1099–1109. doi: 10.1007/s00125-010-1667-2

Hu F, Wang M, Xiao T, et al (2015) miR-30 promotes thermogenesis and the development of beige fat by targeting RIP140. Diabetes 64:2056–2068. doi: 10.2337/db14-1117

Hydbring P, Badalian-Very G (2013) Clinical applications of microRNAs. F1000Res 2:136. doi: 10.12688/f1000research.2-136.v3

Iyer MK, Niknafs YS, Malik R, et al (2015) The landscape of long noncoding RNAs in the human transcriptome. Nat Genet 47:199–208. doi: 10.1038/ng.3192

Jimenez-Preitner M, Berney X, Uldry M, et al (2011) Plac8 is an inducer of C/EBPβ required for brown fat differentiation, thermoregulation, and control of body weight. Cell Metab 14:658–670. doi: 10.1016/j.cmet.2011.08.008

Jones M, Tontonoz P (2014) Enhanced thermogenesis in the blinc of an eye. Mol Cell 55:343–344. doi: 10.1016/j.molcel.2014.07.015

Kajimura S, Seale P, Kubota K, et al (2009) Initiation of myoblast to brown fat switch by a PRDM16-C/EBP-beta transcriptional complex. Nature 460:1154–1158. doi: 10.1038/nature08262

Kajimura S, Seale P, Spiegelman BM (2010) Transcriptional control of brown fat development. Cell Metab 11:257–262. doi: 10.1016/j.cmet.2010.03.005

Karbiener M, Fischer C, Nowitsch S, et al (2009) microRNA miR-27b impairs human adipocyte differentiation and targets PPARgamma. Biochem Biophys Res Commun 390:247–251. doi: 10.1016/j.bbrc.2009.09.098

Karbiener M, Pisani DF, Frontini A, et al (2014) MicroRNA-26 Family Is Required for Human Adipogenesis and Drives Characteristics of Brown Adipocytes. Stem Cells 32:1578–1590. doi: 10.1002/stem.1603

Kim H-J, Cho H, Alexander R, et al (2014) MicroRNAs are required for the feature maintenance and differentiation of brown adipocytes. Diabetes 63:4045–4056. doi: 10.2337/db14-0466

Kim J, Okla M, Erickson A, et al (2016) Eicosapentaenoic Acid Potentiates Brown Thermogenesis through FFAR4-dependent Up-regulation of miR-30b and miR-378. J Biol Chem 291:20551–20562. doi: 10.1074/jbc.M116.721480

Kim SY, Kim AY, Lee HW, et al (2010) miR-27a is a negative regulator of adipocyte differentiation via suppressing PPARgamma expression. Biochem Biophys Res Commun 392:323–328. doi: 10.1016/j.bbrc.2010.01.012

Kim Y-J, Sano T, Nabetani T, et al (2012) GPRC5B activates obesity-associated inflammatory signaling in adipocytes. Sci Signal 5:ra85. doi: 10.1126/scisignal.2003149

Kiskinis E, Chatzeli L, Curry E, et al (2014) RIP140 represses the “brown-in-white” adipocyte program including a futile cycle of triacylglycerol breakdown and synthesis. Mol Endocrinol 28:344–356. doi: 10.1210/me.2013-1254

Kole R, Krainer AR, Altman S (2012) RNA therapeutics: beyond RNA interference and antisense oligonucleotides. Nat Rev Drug Discov 11:125–140. doi: 10.1038/nrd3625

Kong X, Yu J, Bi J, et al (2015) Glucocorticoids transcriptionally regulate miR-27b expression promoting body fat accumulation via suppressing the browning of white adipose tissue. Diabetes 64:393–404. doi: 10.2337/db14-0395

Lander ES, Linton LM, Birren B, et al (2001) Initial sequencing and analysis of the human genome. Nature 409:860–921. doi: 10.1038/35057062

Lavery CA, Kurowska-Stolarska M, Holmes WM, et al (2016) miR-34a(-/-) mice are susceptible to diet-induced obesity. Obesity (Silver Spring) 24:1741–1751. doi: 10.1002/oby.21561

Lee RC, Feinbaum RL, Ambros V (1993) The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell 75:843–854

Leonardsson G, Steel JH, Christian M, et al (2004) Nuclear receptor corepressor RIP140 regulates fat accumulation. Proc Natl Acad Sci USA 101:8437–8442. doi: 10.1073/pnas.0401013101

Li S, Mi L, Yu L, et al (2017) Zbtb7b engages the long noncoding RNA Blnc1 to drive brown and beige fat development and thermogenesis. Proc Natl Acad Sci USA 114:E7111–E7120. doi: 10.1073/pnas.1703494114

Lv Y-F, Yu J, Sheng Y-L, et al (2018) Glucocorticoids Suppress the Browning of Adipose Tissue via miR-19b in Male Mice. Endocrinology 159:310–322. doi: 10.1210/en.2017-00566

Meakin PJ, Harper AJ, Hamilton DL, et al (2012) Reduction in BACE1 decreases body weight, protects against diet-induced obesity and enhances insulin sensitivity in mice. Biochem J 441:285–296. doi: 10.1042/BJ20110512

Mercer TR, Dinger ME, Sunkin SM, et al (2008) Specific expression of long noncoding RNAs in the mouse brain. Proc Natl Acad Sci USA 105:716–721. doi: 10.1073/pnas.0706729105

Mi L, Zhao X-Y, Li S, et al (2017) Conserved function of the long noncoding RNA Blnc1 in brown adipocyte differentiation. Mol Metab 6:101–110. doi: 10.1016/j.molmet.2016.10.010

Mori M, Nakagami H, Rodriguez-Araujo G, et al (2012) Essential Role for miR-196a in Brown Adipogenesis of White Fat Progenitor Cells. PLoS Biol 10:e1001314. doi: 10.1371/journal.pbio.1001314

Mori MA, Thomou T, Boucher J, et al (2014) Altered miRNA processing disrupts brown/white adipocyte determination and associates with lipodystrophy. J Clin Invest 124:3339–3351. doi: 10.1172/JCI73468

Mudhasani R, Imbalzano AN, Jones SN (2010) An essential role for Dicer in adipocyte differentiation. J Cell Biochem 110:812–816. doi: 10.1002/jcb.22625

Mudhasani R, Puri V, Hoover K, et al (2011) Dicer is required for the formation of white but not brown adipose tissue. J Cell Physiol 226:1399–1406. doi: 10.1002/jcp.22475

Nedergaard J, Cannon B (2010) The changed metabolic world with human brown adipose tissue: therapeutic visions. Cell Metab 11:268–272. doi: 10.1016/j.cmet.2010.03.007

Ng R, Hussain NA, Zhang Q, et al (2017) miRNA-32 Drives Brown Fat Thermogenesis and Trans-activates Subcutaneous White Fat Browning in Mice. Cell Rep 19:1229–1246. doi: 10.1016/j.celrep.2017.04.035

Oliverio M, Schmidt E, Mauer J, et al (2016) Dicer1-miR-328-Bace1 signalling controls brown adipose tissue differentiation and function. Nat Cell Biol 18:328–336. doi: 10.1038/ncb3316

Pan D, Mao C, Quattrochi B, et al (2014) MicroRNA-378 controls classical brown fat expansion to counteract obesity. Nat Commun 5:4725. doi: 10.1038/ncomms5725

Petrovic N, Walden TB, Shabalina IG, et al (2010) Chronic peroxisome proliferator-activated receptor gamma (PPARgamma) 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 285:7153–7164. doi: 10.1074/jbc.M109.053942

Ponting CP, Oliver PL, Reik W (2009) Evolution and functions of long noncoding RNAs. Cell 136:629–641. doi: 10.1016/j.cell.2009.02.006

Prasanth KV, Spector DL (2007) Eukaryotic regulatory RNAs: an answer to the “genome complexity” conundrum. Genes Dev 21:11–42. doi: 10.1101/gad.1484207

Puigserver P, Wu Z, Park CW, et al (1998) A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. Cell 92:829–839

Ramsköld D, Wang ET, Burge CB, Sandberg R (2009) An abundance of ubiquitously expressed genes revealed by tissue transcriptome sequence data. PLoS Comput Biol 5:e1000598. doi: 10.1371/journal.pcbi.1000598

Robidoux J, Cao W, Quan H, et al (2005) Selective activation of mitogen-activated protein (MAP) kinase kinase 3 and p38alpha MAP kinase is essential for cyclic AMP-dependent UCP1 expression in adipocytes. Mol Cell Biol 25:5466–5479. doi: 10.1128/MCB.25.13.5466-5479.2005

Rochford JJ, Semple RK, Laudes M, et al (2004) ETO/MTG8 is an inhibitor of C/EBPbeta activity and a regulator of early adipogenesis. Mol Cell Biol 24:9863–9872. doi: 10.1128/MCB.24.22.9863-9872.2004

Rohas LM, St-Pierre J, Uldry M, et al (2007) A fundamental system of cellular energy homeostasis regulated by PGC-1alpha. Proc Natl Acad Sci USA 104:7933–7938. doi: 10.1073/pnas.0702683104

Rosen ED, Hsu C-H, Wang X, et al (2002) C/EBPalpha induces adipogenesis through PPARgamma: a unified pathway. Genes Dev 16:22–26. doi: 10.1101/gad.948702

Seale P, Bjork B, Yang W, et al (2008) PRDM16 controls a brown fat/skeletal muscle switch. Nature 454:961–967. doi: 10.1038/nature07182

Seale P, Conroe HM, Estall J, et al (2011) Prdm16 determines the thermogenic program of subcutaneous white adipose tissue in mice. J Clin Invest 121:96–105. doi: 10.1172/JCI44271

Slaby O, Laga R, Sedlacek O (2017) Therapeutic targeting of non-coding RNAs in cancer. Biochem J 474:4219–4251. doi: 10.1042/BCJ20170079

Sun J, Ruan Y, Wang M, et al (2016) Differentially expressed circulating LncRNAs and mRNA identified by microarray analysis in obese patients. Sci Rep 6:35421. doi: 10.1038/srep35421

Sun K-K, Zhong N, Yang Y, et al (2013) Enhanced radiosensitivity of NSCLC cells by transducer of erbB2.1 (TOB1) through modulation of the MAPK/ERK pathway. Oncol Rep 29:2385–2391. doi: 10.3892/or.2013.2403

Sun L, Trajkovski M (2014) MiR-27 orchestrates the transcriptional regulation of brown adipogenesis. Metab Clin Exp 63:272–282. doi: 10.1016/j.metabol.2013.10.004

Sun L, Xie H, Mori MA, et al (2011) Mir193b-365 is essential for brown fat differentiation. Nat Cell Biol 13:958–965. doi: 10.1038/ncb2286

Sun M, Kraus WL (2015) From discovery to function: the expanding roles of long noncoding RNAs in physiology and disease. Endocr Rev 36:25–64. doi: 10.1210/er.2014-1034

Taft RJ, Pheasant M, Mattick JS (2007) The relationship between non-protein-coding DNA and eukaryotic complexity. Bioessays 29:288–299. doi: 10.1002/bies.20544

Tanaka T, Yoshida N, Kishimoto T, Akira S (1997) Defective adipocyte differentiation in mice lacking the C/EBPbeta and/or C/EBPdelta gene. EMBO J 16:7432–7443. doi: 10.1093/emboj/16.24.7432

Trajkovski M, Ahmed K, Esau CC, Stoffel M (2012) MyomiR-133 regulates brown fat differentiation through Prdm16. Nat Cell Biol 14:1330–1335. doi: 10.1038/ncb2612

van Rooij E, Purcell AL, Levin AA (2012) Developing microRNA therapeutics. Circ Res 110:496–507. doi: 10.1161/CIRCRESAHA.111.247916

Vance KW, Ponting CP (2014) Transcriptional regulatory functions of nuclear long noncoding RNAs. Trends Genet 30:348–355. doi: 10.1016/j.tig.2014.06.001

Venter JC, Adams MD, Myers EW, et al (2001) The sequence of the human genome. Science 291:1304–1351. doi: 10.1126/science.1058040

Villarroya F, Cereijo R, Villarroya J, Giralt M (2017) Brown adipose tissue as a secretory organ. Nat Rev Endocrinol 13:26–35. doi: 10.1038/nrendo.2016.136

Villena JA (2015) New insights into PGC-1 coactivators: redefining their role in the regulation of mitochondrial function and beyond. FEBS J 282:647–672. doi: 10.1111/febs.13175

Wahid F, Khan T, Kim YY (2014a) MicroRNA and diseases: Therapeutic potential as new generation of drugs. Biochimie. doi: 10.1016/j.biochi.2014.05.004

Wahid F, Khan T, Kim YY (2014b) MicroRNA and diseases: therapeutic potential as new generation of drugs. Biochimie 104:12–26. doi: 10.1016/j.biochi.2014.05.004

Wahid F, Shehzad A, Khan T, Kim YY (2010) MicroRNAs: synthesis, mechanism, function, and recent clinical trials. Biochim Biophys Acta 1803:1231–1243. doi: 10.1016/j.bbamcr.2010.06.013

Wilusz JE, Sunwoo H, Spector DL (2009) Long noncoding RNAs: functional surprises from the RNA world. Genes Dev 23:1494–1504. doi: 10.1101/gad.1800909

Wu D, Zhou W, Wang S, et al (2015) Tob1 enhances radiosensitivity of breast cancer cells involving the JNK and p38 pathways. Cell Biol Int 39:1425–1430. doi: 10.1002/cbin.10545

Wu J, Boström P, Sparks LM, et al (2012) Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. Cell 150:366–376. doi: 10.1016/j.cell.2012.05.016

Wu Y, Zuo J, Zhang Y, et al (2013) Identification of miR-106b-93 as a negative regulator of brown adipocyte differentiation. Biochem Biophys Res Commun 438:575–580. doi: 10.1016/j.bbrc.2013.08.016

Xu G, Ji C, Song G, et al (2015) MiR-26b modulates insulin sensitivity in adipocytes by interrupting the PTEN/PI3K/AKT pathway. Int J Obes (Lond) 39:1523–1530. doi: 10.1038/ijo.2015.95

Xue B, Coulter A, Rim JS, et al (2005) Transcriptional synergy and the regulation of Ucp1 during brown adipocyte induction in white fat depots. Mol Cell Biol 25:8311–8322. doi: 10.1128/MCB.25.18.8311-8322.2005

Zhang H, Guan M, Townsend KL, et al (2015) MicroRNA-455 regulates brown adipogenesis via a novel HIF1an-AMPK-PGC1α signaling network. EMBO Rep 16:1378–1393. doi: 10.15252/embr.201540837

Zhang K, Shi Z-M, Chang Y-N, et al (2014) The ways of action of long non-coding RNAs in cytoplasm and nucleus. Gene 547:1–9. doi: 10.1016/j.gene.2014.06.043

Zhao X-Y, Li S, Wang G-X, et al (2014) A long noncoding RNA transcriptional regulatory circuit drives thermogenic adipocyte differentiation. Mol Cell 55:372–382. doi: 10.1016/j.molcel.2014.06.004

Zhu Y, Zhang X, Ding X, et al (2014) miR-27 inhibits adipocyte differentiation via suppressing CREB expression. Acta Biochim Biophys Sin (Shanghai) 46:590–596. doi: 10.1093/abbs/gmu036

Figures

Figure 1: Classification of non-coding RNAs: ncRNAs with less than 200 nucleotides (nt) in length are small ncRNAs, while non-coding transcripts with a length of more than 200 nt are defined as long ncRNAs. tRNAs: transfer RNAs, snRNAs: small nuclear RNAs, snoRNAs: small nucleolar RNAs, miRNAs: microRNAs, piRNAs: piwi-associated RNAs, rRNAs: ribosomal RNAs, lncRNAs: long non-coding RNAs.

Figure 2: miRNAs in brite/brown adipose tissue. miRNAs with a positive impact on brite/brown adipocyte formation and function is displayed in green, while miRNAs with a repressive role are displayed in red. miRNAs which are known to be secreted are indicated in yellow.

Figure 3: LncRNAs in brite/brown adipose tissue. LncRNAs with a positive impact on brite/brown adipocyte formation and function are displayed in green. LncRNAs which are known to be secreted are indicated in yellow.

Table

Table 1: miRNAs and lncRNAs with impact on brite/brown adipose tissue biology.

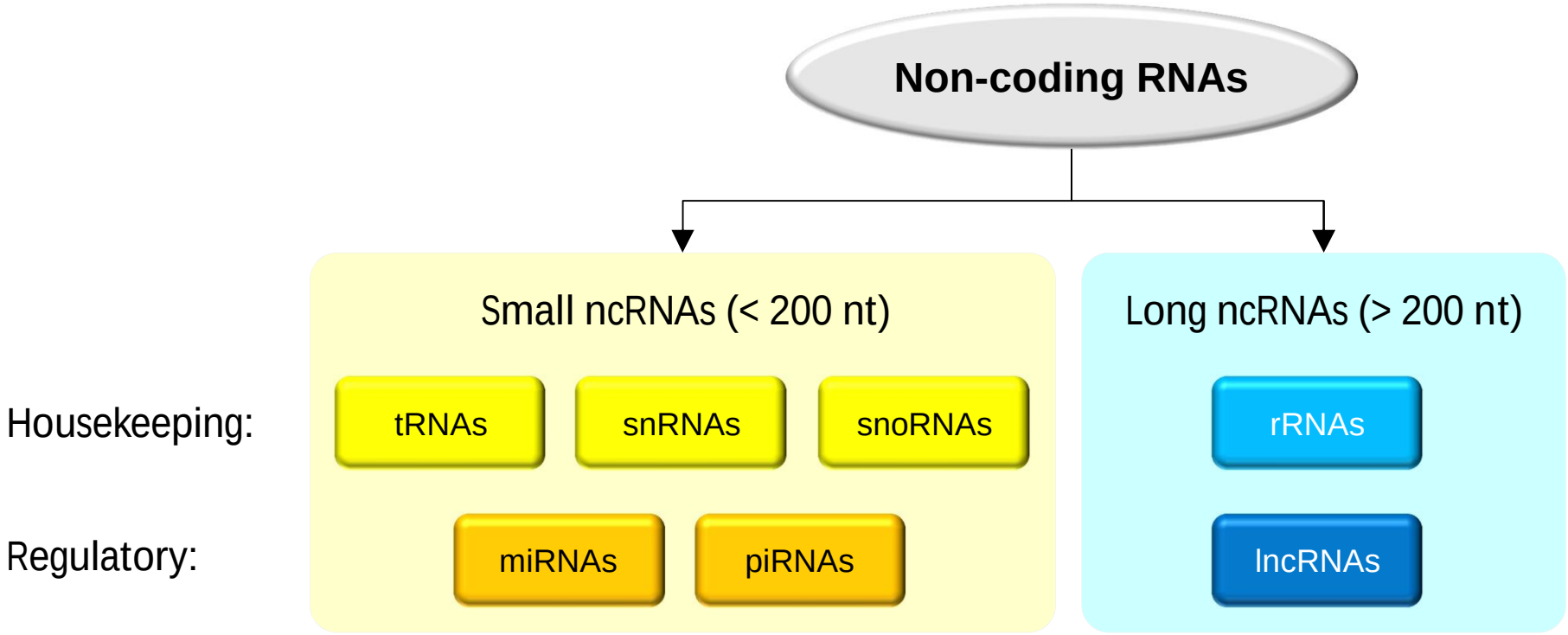

Figure 1: Classification of non-coding RNAs

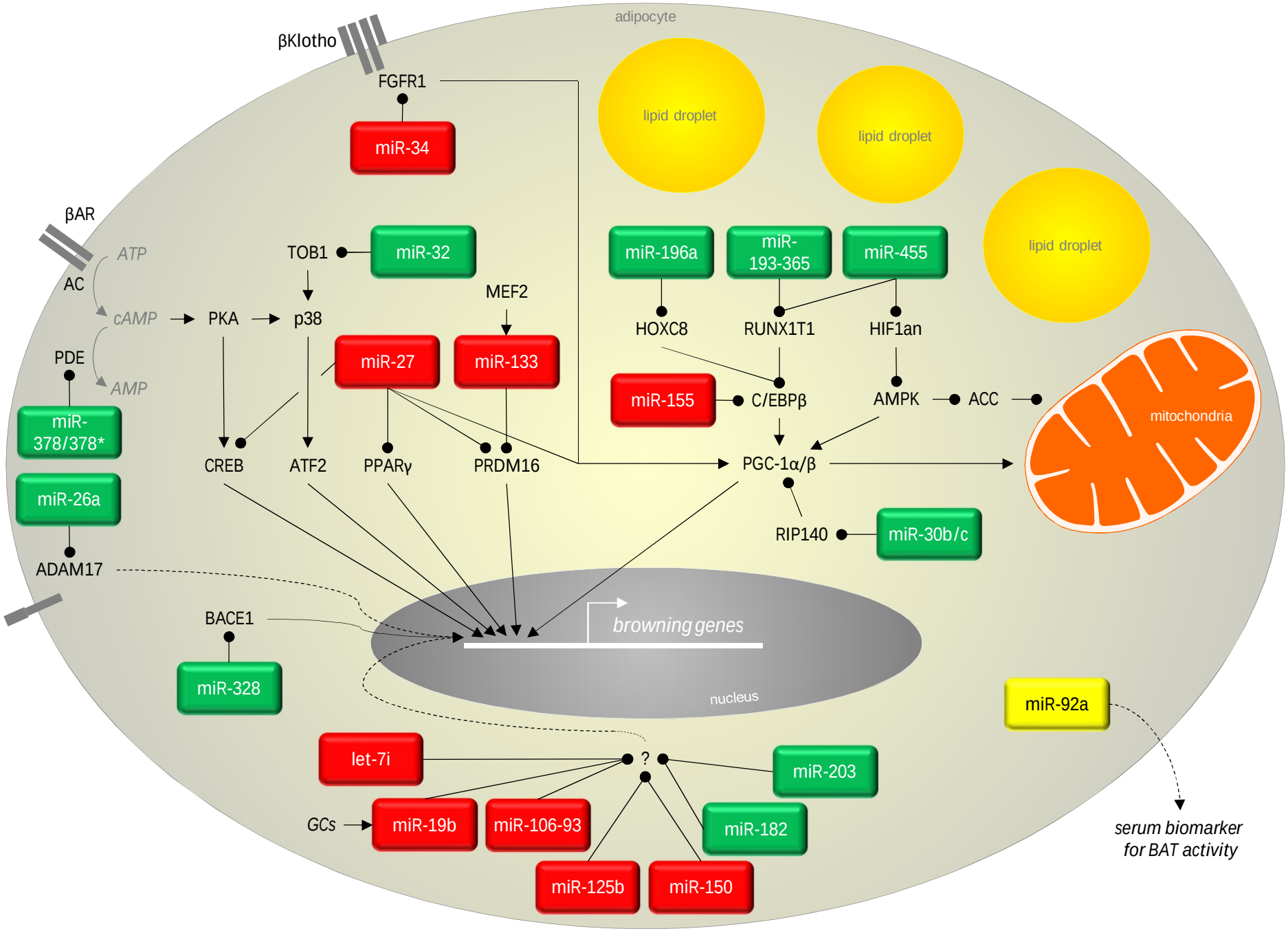

Figure 2: miRNAs in brite/brown adipose tissue

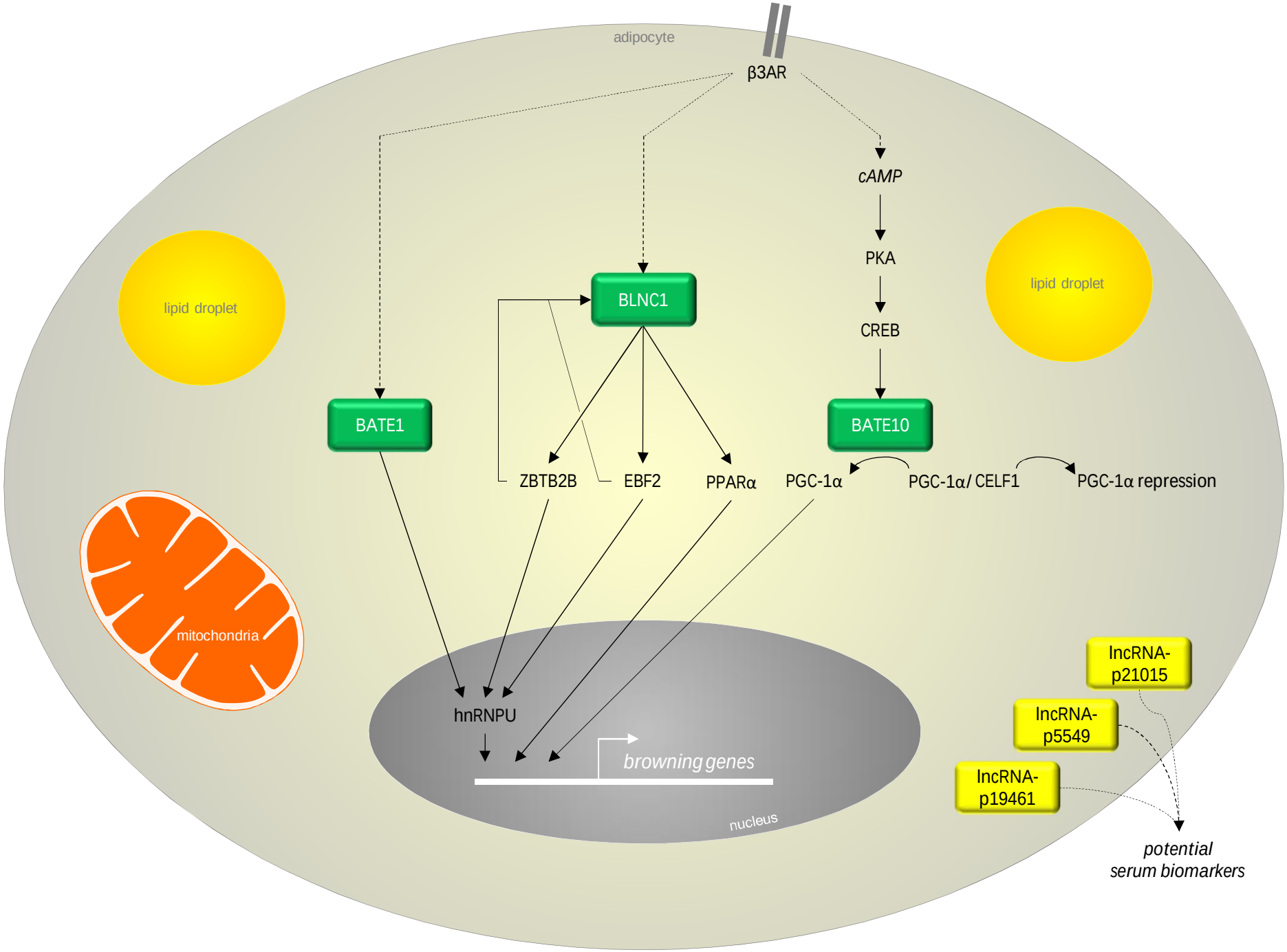

Figure 3: lncRNAs in brite/brown adipose tissue