Molecular and Cellular Endocrinology 456 (2017) 87–94

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

Small non coding RNAs in adipocyte biology and obesity

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ARTICLE INFO

Article history:
Received 6 January 2017
Received in revised form
10 April 2017
Accepted 10 April 2017
Available online 12 April 2017

Keywords:
Small non-coding RNA
microRNA
snoRNA
tRNA
Obesity
Adipocyte

ABSTRACT

Obesity has reached epidemic proportions world-wide and constitutes a substantial risk factor for hypertension, type 2 diabetes, cardiovascular diseases and certain cancers. So far, regulation of energy intake by dietary and pharmacological treatments has met limited success. The main interest of current research is focused on understanding the role of different pathways involved in adipose tissue function and modulation of its mass. Whole-genome sequencing studies revealed that the majority of the human genome is transcribed, with thousands of non-protein-coding RNAs (ncRNA), which comprise small and long ncRNAs. ncRNAs regulate gene expression at the transcriptional and post-transcriptional level. Numerous studies described the involvement of ncRNAs in the pathogenesis of many diseases including obesity and associated metabolic disorders. ncRNAs represent potential diagnostic biomarkers and promising therapeutic targets. In this review, we focused on small ncRNAs involved in the formation and function of adipocytes and obesity.

Contents

1. Introduction

Obesity has reached epidemic proportions globally, with more than 1.9 billion adults overweight and at least 600 million of them clinically obese. The obesity epidemic is not restricted to industrialized countries; this increase is often even faster in developing countries (Hossain et al., 2007). Obesity constitutes a substantial risk factor for hypertension, type 2 diabetes, cardiovascular disease

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http://dx.doi.org/10.1016/j.mce.2017.04.009
0303-7207/

and certain cancers and corresponds to increased adiposity. Body weight gain results from a sustained imbalance of energy intake over energy expenditure leading to overweight and obesity, *i.e.* an increased mass of white adipose tissue (WAT). Pharmacological remedies or lifestyle interventions normalizing overweight or obesity with significant long-term success are not available. Moreover, disequilibrium in the amount and/or localisation of fat mass leads to the development of diseases related to metabolic syndrome.

The adipose organ plays an important role in regulating whole-body energy and glucose homeostasis through cross-talk with other organs as adipose tissues are endowed with secretory abilities of different bioactive compounds (paracrine/autocrine/endocrine) (Ailhaud, 2000; Wang and Yang, 2016; Villarroya et al., 2017). The adipose organ can be divided into two distinct types of adipose tissues, white and brown: WAT is specialized for the storage and release of chemical energy (Giordano et al., 2008; Cohen and Spiegelman, 2016). In contrast, brown adipose tissue (BAT) dissipates energy in the form of heat (thermogenesis) by uncoupling the mitochondrial electron transport chain activity from ATP formation through the specific expression of uncoupling protein 1 (UCP-1) (Ricquier, 1990; Nedergaard et al., 2001; Frontini and Cinti, 2010). BAT is characterized by a high mitochondrial content and endowed with high capacity of glucose and lipid oxidation thus making this tissue a promising target for lowering plasma levels of glucose and fatty acids thus diminishing the risks of overweight and obesity (Nedergaard et al., 2011).

BAT has long been known in rodents and is now also known to be present and active in various regions of healthy adult individuals (Nedergaard et al., 2007; Cypess et al., 2009; Saito et al., 2009; van Marken Lichtenbelt et al., 2009; Virtanen et al., 2009; Zingaretti et al., 2009). Recent data indicate that the lack of thermogenic adipocyte activity may be sufficient to cause obesity in mice and humans (Feldmann et al., 2009; van Marken Lichtenbelt et al., 2009). BAT activity is negatively associated with adiposity, insulin resistance and aging (Pfannenberg et al., 2010; Ouellet et al., 2011). Furthermore, in rodents and humans, islands of brown-like adipocytes emerge within WAT depots after cold or β3-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). Therefore, the identification of factors increasing mass/activity of human BAT would be of great interest for the treatment of overweight/obesity and associated diseases such as type 2 diabetes. Recent studies showed that BAT was involved in diet-induced thermogenesis and functions as an anti-diabetic tissue in humans (Chondronikola et al., 2014; Hibi et al., 2016). The identification of regulatory factors and drugs able to initiate the formation and activation of brite/beige adipocytes in humans constitutes an active research field.

Mechanisms related to increased adiposity and its associated metabolic disorders focused on gene regulation and secretion of bioactive compounds (adipokines) including non-peptidic effectors such as fatty acid metabolites (Pisani et al., 2014; Yore et al., 2014). In addition, it has been unraveled over the last decades that long and small non-coding RNAs (ncRNA) control the formation and function of tissues and organs. For the identification of novel regulators in general, it should be considered i) that today some 20,500 protein-coding genes are known in human whose sequences make up ‘only’ less than 2% of our genome, ii) that the human genome is pervasively transcribed, such iii) that the majority consists of many novel non-protein-coding transcripts of long and small ncRNA, among these later one have microRNAs, tRNA, snoRNA, piRNAs, circRNAs, telomeric RNAs etc (Birney et al., 2007; Dogini et al., 2014). 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 govern various aspects of gene expression and their involvement in diseases (Prasanth and Spector, 2007; Cech and Steitz, 2014; de Almeida et al., 2016). Of note, long ncRNAs (lncRNAs) are reported to play an important role in the control of adipogenesis and obesity (Wei et al., 2016). So far, small ncRNAs are thoroughly studied and the best characterized class are microRNAs (miRNAs). Their impact on diseases is acknowledged by their deployment as drugs and/or drug targets, with few 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., 2014; Christopher et al., 2016). Interestingly, miRNAs have been shown to be involved in human adipocyte differentiation, lipid metabolism, and obesity (Kim et al., 2009; Xie et al., 2009; Karbiener et al., 2014a,b; Son et al., 2014; Arner and Kulyte, 2015; Scheideler, 2016). Small ncRNAs are divided into distinct subclasses with a length of less than 200 nucleotides. In this review, we tempt to summarize recent findings on small ncRNAs involved in the control of adipose tissue biology and with focus on miRNAs as they represent the major target of reported data with more than 56,000 published papers.

2. snoRNA and adipose tissue

The short ncRNAs called small nucleolar RNAs (snoRNA), 60–300 nucleotides in length, are well-conserved molecules and are localized in the nucleolus (Jorjani et al., 2016). Their biosynthesis and processing are well described (see for review (Falaleeva and Stamm, 2013). Most snoRNA host genes encode for proteins or transcripts essential for ribosome biogenesis or function. snoRNAs represent cellular housekeeping molecules that maintain proper ribosomal maturation and protein translation. These post-transcriptional modifications of rRNA take place in the nucleolus and facilitate rRNA folding and stability. Based on defined sequence motifs and secondary structure elements, snoRNAs are classified as either C/D box or H/ACA box. However, small RNA species derived from snoRNAs have been identified and called sdRNAs with miRNA-similar roles (Taft et al., 2009; Falaleeva and Stamm, 2013; Martens-Uzunova et al., 2013). This gene cluster is imprinted and paternally expressed in both humans and mice. Few snoRNAs have also been reported to be expressed by adipose tissue (Parts et al., 2012).

SnoRNAs play an important role in the control of food intake and body weight, well described in patients with Prader-Willi syndrome (PWS). PWS is a multisystem disorder that leads to developmental delay and morbid obesity (Cassidy et al., 2012). The critical region for PWS is located on paternal chromosome 15 (q11.2–13) which contains several known protein coding genes (MKRN3, MAGEL2, NECDIN, C15ORF2, and SNURF-SNRPN (small nuclear ribonucleoprotein N)) as well as ncRNAs located downstream in clusters as C/D box-containing snoRNAs (mainly Snord115 and Snord116) (Cassidy et al., 2012; Butler et al., 2015).

Snord116 and 115 knockout mice develop some characteristics of the human PWS phenotype. There is evidence supporting the fact that selective loss of expression of SNORD116 contributes to the phenotype of PWS, as several case reports in PWS patients do (Bervini and Herzog, 2013; Hassan and Butler, 2016). Furthermore, recently, it has been shown that Snord115 negatively controls the alternative splicing of serotonin 2C receptor (5-HT2CR) pre-RNA, which is observed in almost all patients with PWS (Garfield et al., 2016). Indeed, loss of SNORD115 expression influenced 5-HT2CR regulated appetite and contributed to hyperphagia in PWS through accumulation of truncated variant Htr2c. Mice harboring a defect in the Snord116 mice displayed functional defects in prohormone processing of proinsulin, pro-GH-releasing hormone, and