Archives of Biochemistry and Biophysics xxx (2015) 1–12

Contents lists available at ScienceDirect

Archives of Biochemistry and Biophysics

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

Review article

MicroRNAs in obesity-associated disorders

Eugenio J. Abente [a, b, 1], Murugan Subramanian [a, b], Vimal Ramachandran [a, b], S.Hani Najafi-Shoushtari [a, b, *]

[a] Department of Cell and Developmental Biology, Weill Cornell Medical College, Cornell University, New York 10021, NY, USA
[b] Weill Cornell Medical College-Qatar, Qatar Foundation, Education City, P.O. Box 24144, Doha, Qatar

ARTICLE INFO

Article history:
Received 30 July 2015
Received in revised form
17 September 2015
Accepted 18 September 2015
Available online xxx

Keywords:
Obesity
MicroRNAs
Lipid/fat metabolism
Metabolic syndrome
Insulin resistance
RNA therapeutics

ABSTRACT

The emergence of a worldwide obesity epidemic has dramatically increased the prevalence of insulin resistance and metabolic syndrome, predisposing individuals to a greater risk for the development of non-alcoholic fatty liver disease, type II diabetes and atherosclerotic cardiovascular diseases. Current available pharmacological interventions combined with diet and exercise-based managements are still poorly effective for weight management, likely in part due to an incomplete understanding of regulatory mechanisms and pathways contributing to the systemic metabolic abnormalities under disturbed energy homeostasis. MicroRNAs, small non-coding RNAs that regulate posttranscriptional gene expression, have been increasingly described to influence shifts in metabolic pathways under various obesity-related disease settings. Here we review recent discoveries of the mechanistic role that microRNAs play in regulating metabolic functions in liver and adipose tissues involved in obesity associated disorders, and briefly discusses the potential candidates that are being pursued as viable therapeutic targets.

Contents

1. Introduction

Abdominal obesity, genetic or of acquired origin, is a serious health issue that has been classified as a global epidemic [1–4]. In contrast to pathogenic pandemics such as AIDS or the influenza virus, where there is an etiological agent, obesity has been mostly linked to behavior, specifically the quantity and quality of food intake in addition to a sedentary lifestyle [1]. The worldwide

* Corresponding author. Weill Cornell Medical College-Qatar, Cornell University, P.O. Box 24144, Room C007, Doha, Qatar.
E-mail address: han2005@med.cornell.edu (S.Hani Najafi-Shoushtari).
[1] Present address: Virus and Prion Research Unit, National Animal Disease Center, Agricultural Research Service, US Department of Agriculture, 1920 Dayton Ave, 50010 Ames IA, USA.

http://dx.doi.org/10.1016/j.abb.2015.09.018
0003-9861/

prevalence of obesity nearly doubled between 1980 and 2008, with an estimated ~500 million cases reported in 2008 [5]. The WHO reports that approximately 347 million people have diabetes worldwide, and that by 2030, diabetes will be the 7th leading cause of death. Obesity is a major disorder of adipose tissue that together with the development of primary insulin resistance leads to the metabolic syndrome, a condition largely reflected in atherogenic dyslipideamia [6,7], elevated blood pressure (hypertension), increased glucose output, abnormal regulation of adipose tissue [8,9], thrombogenesis and increased inflammation. This cluster of metabolic abnormalities serve as a prelude to the development of disorders of increasing severity such as Type 2 diabetes (T2DM), atherosclerotic micro-and macro-vascular diseases (MVDs) and hepatic steatosis [10].

Eukaryotic cells of higher organisms possess a plethora of mechanisms for regulating the balance between obtaining cholesterol and fatty acids through dietary consumption or cellular biosynthesis. At the molecular level, lipid associated metabolic pathways are tightly regulated and extremely sensitive to metabolic ligands in order to facilitate rapid fine-tuning for homeostatic maintenance [11]. Within the hepatocytes, lipid/cholesterol levels are primarily regulated by two main transcription factors: sterol-regulatory element binding protein (SREBP), governed by insulin and dietary fatty acids, and carbohydrate response element binding protein (CREBP), governed by ambient glucose levels. The SREBPs (SREBP-1a/SREBP-1c and SREBP-2), were reported and characterized in a series of seminal studies [12–18] and have been identified as master regulators of two arms of lipid metabolism: SREBP-1 stimulates nuclear transcription of the enzymes responsible for fatty acid synthesis and uptake, and SREBP-2 preferentially acts on cholesterol biosynthesis [19–21].

Similarly, adipose tissues play an integral role in lipid and glucose metabolism and serves two important roles: they store and release free fatty acids (FFAs) from consumption and during fasting, respectively, and serve as an immune and endocrine organ, responsible for the synthesis of adipokines such as leptin and adiponectin. Adipokines exert auto-, para, as well as endocrine functions on local and peripheral tissues such as the liver. Thereby, plasma levels of FFAs are detrimental and positively correlate with fat mass and insulin resistance, whereas leptin and adiponectin have beneficial cardiometabolic effects [22,23]. The differentiation and proliferation of pre-adipocytes is highly regulated. Adipose tissues are categorized into two different types: white adipose tissue (WAT; further divided into subcutaneous and visceral adipose tissue, SAT and VAT, respectively), and brown adipose tissue (BAT; which includes “beige” and “brite” adipose tissue that arise from *de novo* differentiation of WAT precursors or pre-existing white adipocytes). WAT mainly functions to secrete adipokines and store fatty acids/triglycerides, while BAT primarily functions in energy expenditure and non-shivering thermogenesis [24]. At the molecular level, C/EBPα and C/EBPβ were identified as master regulators of WAT and BAT differentiation, respectively [25,26].

The discovery of functional non-coding RNAs as specific gene expression regulators heralded the advent of a new field of research and also provided novel targets for drug development. Since microRNAs (miRs) were first described [14], other non-coding RNAs that function in gene regulation have been reported such as piwi RNAs and long non-coding RNAs, highlighting the complexity of gene regulation. MiRs regulate gene translation by specifically binding to the 3′-UTR of mRNAs and blocking translation or targeting the transcript for degradation [27]. Therapeutic drugs altering miR levels are being explored as novel strategies for clinical use in various diseases, where the level of a regulatory miR is either suppressed or elevated using oligonucleotide antisense strategies or mimics, respectively [28]. In this review we will highlight recent discoveries of how miRs play a crucial role in regulating metabolic pathways in the liver and adipose tissue, and discuss the therapeutic potential of modulating miR levels to treat obesity-associated diseases.

2. MicroRNAs in non-alcoholic fatty liver disease (NAFLD)

The liver is the major metabolic organ that serves many functions, including drug and lipid metabolism, and bile acid production. Lipid accumulation in the liver results from a homeostatic defect in overall calorie intake and systemic calorie utilization. Non-alcoholic fatty liver disease (NAFLD) is the accumulation of fat, mostly as triglycerides, cholesterol and phospholipids, in the absence of significant ethanol exposure [29]. The disease manifestation includes a spectrum of symptoms that includes non-alcoholic steatohepatitis (NASH) and liver injury characterized by hepatocyte ballooning, focal necrosis, inflammation and fibrosis [30]. The observed hepatic steatosis is a result of lipid accumulation and is an indicator of disrupted homeostasis of lipid metabolism, which can be both a cause and consequence of obesity and insulin resistance [31].

Dysregulated activities of several transcription factors have been shown to be involved in developing NAFLD [32]. Some of the key transcription factors that play a role in the development of NAFLD include the Pregnane X Receptor (PXR), Farnesoid X Receptor (FXR), the Liver X Receptor (LXR), Retinoid X Receptor (RXR), and Peroxisome Proliferator Activated Receptor alpha (PPARα). Early studies found that PXR forms a dimer with RXR and induces steroid-inducible genes [33]. It was also reported that the activation of PXR in transgenic mice led to the development of hepatic steatosis [34], indicating a direct role in lipogenesis. The mechanistic activity of PXR is complex, however PXR can act as a co-repressor of transcription factors involved in fatty acid oxidation and gluconeogenesis such as FOXA2, FOXO1 [35,36], and also up-regulate genes involved in fatty acid uptake [34].

Previously it was reported that levels of miR-148a inversely correlated with PXR in 25 human liver samples, and that miR-148a could specifically target the PXR 3′-UTR (Table 1) [37]. In contrast to most studies that use the full length 3′-UTR, a luciferase reporter assay was employed that only contained the predicted target site of the PXR 3′-UTR. Nevertheless, they showed that miR-148a was able to regulate PXR mRNA and protein levels in a hepatic cell line (Fig. 1). A recent study found no correlation between miR-148a and PXR levels in liver samples from a Chinese Han population [38]. One possibility is that inherent SNPs within populations can affect the predicted targeting of miRs, as has been shown in other cases [39,40]. It is also possible that the detectable levels of miR-148a could differ due to the presence of isomiRs, which most likely can affect the efficiency of cDNA synthesis depending on the enzymatic assay used to generate miR cDNA, and therefore underestimate the actual miR levels [41,42].

FXR, like PXR, also forms a dimer with RXR [43]. FXR functions in triglyceride clearance, fatty acid oxidation, and down-regulation of lipogenic genes [44]. Transgenic mice lacking the FXR gene suffer from hyperlipidemia and hepatic steatosis [45,46]. FXR agonists are being explored for clinical use [47,48], although reduced non-hepatic FXR activity may be beneficial for obesity [49]. Further elucidation of the FXR pathway may provide additional therapeutic targets that can avoid potentially negative side effects observed with FXR agonists. Using a potent FXR agonist, Q. de Aguiar Vallim et al. found that miR-144 was induced by FXR activity [50]. Through in vitro and in vivo mouse studies they identified ABCA1, a high-density lipoprotein (HDL) cholesterol transporter involved in reverse-cholesterol transport (RCT) that drives cholesterol efflux in order to protect against cholesterol overload, as a functional target

Please cite this article in press as: E.J. Abente, et al., MicroRNAs in obesity-associated disorders, Archives of Biochemistry and Biophysics (2015), http://dx.doi.org/10.1016/j.abb.2015.09.018