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Review

Posttranscriptional regulation of lipid metabolism by non-coding RNAs and RNA binding proteins

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ABSTRACT

Alterations in lipoprotein metabolism enhance the risk of cardiometabolic disorders including type-2 diabetes and atherosclerosis, the leading cause of death in Western societies. While the transcriptional regulation of lipid metabolism has been well characterized, recent studies have uncovered the importance of microRNAs (miRNAs), long-non-coding RNAs (lncRNAs) and RNA binding proteins (RBP) in regulating the expression of lipid-related genes at the posttranscriptional level. Work from several groups has identified a number of miRNAs, including miR-33, miR-122 and miR-148a, that play a prominent role in controlling cholesterol homeostasis and lipoprotein metabolism. Importantly, dysregulation of miRNA expression has been associated with dyslipidemia, suggesting that manipulating the expression of these miRNAs could be a useful therapeutic approach to ameliorate cardiovascular disease (CVD). The role of lncRNAs in regulating lipid metabolism has recently emerged and several groups have demonstrated their regulation of lipoprotein metabolism. However, given the high abundance of lncRNAs and the poor genetic conservation between species, much work will be needed to elucidate the specific role of lncRNAs in controlling lipoprotein metabolism. In this review article, we summarize recent findings in the field and highlight the specific contribution of lncRNAs and RBPs in regulating lipid metabolism.

Contents

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1. Introduction

Work done over the last fifteen years has identified numerous classes of non-coding RNA molecules as critical regulators of gene expression [1,2]. Among these, microRNAs (miRNAs) are the best characterized. Originally identified by the Ambros and Ruvkun laboratories [3,4], these small non-coding RNAs control the expression of genes associated with numerous biological processes including development and metabolism [1,2]. miRNAs primarily regulate the expression of genes by directly binding to the 3′ untranslated region of mRNAs [2]. The interaction between miRNAs and mRNA targets is mediated by the RNA-silencing complex (mRISCs) via miRNA/mRNA target sequence complementarity [2]. A single miRNA can regulate the expression of numerous mRNAs, often associated with the same physiological process [2,5]. Similarly, the expression of a single mRNA can be controlled by several miRNAs, making the regulation of gene expression by miRNAs remarkably complex. Dysregulation of miRNA expression or genetic variants associated with miRNAs or miRNA binding site loci have been associated with cardiometabolic diseases such as obesity, insulin resistance and atherosclerosis [6,7]. miRNAs have recently emerged as significant regulators of lipid metabolism and promising therapeutic targets for the treatment of cardiovascular diseases [7–10]. Their conservation between species suggests that miRNA mediated regulation of biological pathways is evolutionarily advantageous, however many miRNAs have been shown to be dysregulated under different disease states. For that reason, miRNAs have a unique therapeutic potential, and different approaches have been undertaken to examine this possibility.

While the role of miRNAs in regulation of lipid and glucose metabolism has been a topic of much research over the last few years [7–10], the role of lncRNAs in controlling lipid homeostasis has just started to emerge. lncRNAs are a heterogeneous group of transcribed RNA molecules ranging from 200 to 100,000 nucleotides in length [11,12]. Depending on their genomic location relative to established protein coding genes, lncRNAs can be classified as long intergenic ncRNAs (lincRNAs), natural antisense transcripts (NATs), enhancer-like ncRNAs (eRNAs), transcribed ultra-conserved regions (T-UCRs) and circular RNAs (circRNAs) [12,13]. lincRNAs are distinct transcriptional units located in sequence spaces that do not overlap protein-coding genes. NATs are RNA molecules transcribed opposite to the sense DNA strand of annotated transcription units, while eRNAs are short bidirectional products from enhancers that are not processed. T-UCRs are transcripts from genomic regions evolutionarily conserved among mammalian species. CircRNAs are generated from non-colinear splicing of otherwise protein coding exons. Since they form covalently closed continuous loop and do not have 5′ or 3′ ends, cirRNAs are resistant to exonuclease-mediated degradation and are mostly more stable compared to linear RNAs in cells [14]. LncRNAs can regulate gene expression through a variety of mechanisms, including epigenetic modification of DNA, alternative splicing, and post-transcriptional regulation of mRNA stability and translation [15]. Multiple studies have shown that numerous lncRNAs are regulated during development, exhibit cell type-specific expression patterns, localize to specific subcellular compartments, and are associated with physiological functions such as cholesterol metabolism and disease pathogenesis [15].

In addition to miRNAs and lncRNAs, RNA binding proteins (RBPs), especially turnover- and translation-regulatory RBPs, are known to regulate all aspects of mRNA metabolism including processing, transport, translation, and turnover via different RNA interaction motifs generally present in the 3′UTR of the target mRNA [16]. Recent studies have identified a number of RBPs that are associated with the regulation of cellular lipid metabolism. In this review, we summarize the most important and novel roles of miRNAs, lncRNAs and RBPs in regulating cholesterol homeostasis and lipoprotein metabolism.

2. miRNA regulation of cellular cholesterol metabolism

2.1. miRNA regulation of cholesterol biosynthesis

Intracellular cholesterol levels are tightly regulated by feedback mechanisms controlling the *de novo* cholesterol biosynthesis, transport, uptake, and efflux [17,18]. Cholesterol biosynthesis is regulated by a multi-enzyme pathway that includes the 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR), the rate-limiting enzyme in cholesterol biosynthesis [19]. Most of the cholesterol biosynthetic enzymes are regulated transcriptionally by the sterol regulatory element-binding protein 2 (SREBP-2) transcription factor [20]. There are three SREBP proteins, among which SREBP-2 primarily activates cholesterol synthesis genes involved in a negative feedback regulation of cellular cholesterol level, whereas SREBP-1a and SREBP-1c have greater effects on genes involved in fatty acid synthesis [20]. Under conditions of high cellular cholesterol, SREBP-2 binds to a SREBP cleavage-activating protein (SCAP)-insulin induced gene (INSIG) complex, leading to a retention of SREBP-2 in the ER. Alternatively, low cellular cholesterol levels result in the disassociation of SCAP from INSIG and promote the translocation of SREBP-2 from the ER to the Golgi [20]. In the Golgi, SREBP-2 is proteolytically cleaved by site-1 protease and site-2 protease. Then, the mature form of SREBP-2 translocates to the nucleus, where it binds to sterol response elements (SREs) present in the promoters of sterol-responsive genes, includ-

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