

Progress and prospects of long noncoding RNAs in lipid homeostasis



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ABSTRACT

Background: Long noncoding RNAs (lncRNAs) are a novel group of universally present, non-coding RNAs (>200 nt) that are increasingly recognized as key regulators of many physiological and pathological processes.

Scope of review: Recent publications have shown that lncRNAs influence lipid homeostasis by controlling lipid metabolism in the liver and by regulating adipogenesis. lncRNAs control lipid metabolism-related gene expression by either base-pairing with RNA and DNA or by binding to proteins.

Major conclusions: The recent advances and future prospects in understanding the roles of lncRNAs in lipid homeostasis are discussed.

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Keywords lncRNA; Liver; Lipid metabolism; Adipose tissue; Adipogenesis

1. INTRODUCTION

Obesity and type 2 diabetes (T2D) are epidemic health problems that affect millions of people worldwide. Fat accumulation is determined by the balance between anabolic (adipogenesis and lipogenesis) and catabolic (lipolysis, fatty acid β -oxidation, and thermogenesis) processes. Adipogenesis is the process by which preadipocytes develop into mature white or brown adipocytes, contributing to energy balance [1]. Lipogenesis is the process of fatty acid synthesis and subsequent triglyceride synthesis in both white adipose tissue (WAT) and liver. Lipogenesis is triggered by circulating insulin and ingestion of nutrients [2]. Conversely, other hormones and exercise induce lipolysis, the breakdown of triglycerides into glycerol and free fatty acids, in both WAT and muscle [3,4]. Free fatty acids released into the circulation during lipolysis are subsequently taken up by liver, muscle, and brown adipose tissue (BAT) as an energy source for β -oxidation [4]. Lastly, adaptive thermogenesis in BAT is a catabolic process in which oxidative phosphorylation and fatty acid β -oxidation are uncoupled to generate heat [5,6]. All of these processes are initiated and regulated by hormones, nutrients, and/or environmental stress, transduced by signal pathways, and controlled by transcription factors [2,4,6]. The balance of these processes is critical for maintaining normal adiposity and regulating systemic lipid metabolism. All too often, however, dysregulation of these processes leads to increased adiposity, dyslipidemia, and metabolic perturbations that can accelerate diabetes, cardiovascular diseases, and nonalcoholic fatty liver disease (NAFLD). Emerging studies now suggest that non-coding RNAs are also key regulators of lipid homeostasis. More than 90% of the human genome is likely to be transcribed; yet less than 2% of the genome encodes approximately 20,000 proteins (International Human Genome Sequencing Consortium 2004). This leaves the balance of the human

genome (~98%) to be transcribed into thousands of non-coding RNAs (ncRNAs). ncRNAs are classified into two main subgroups: short ncRNAs (<200 nt) and long ncRNAs (>200 nt). Short ncRNAs include microRNAs (miRNAs), which regulate many biological processes by inducing mRNA degradation via the RNA interference pathway. miRNAs are well studied and have been implicated in human diseases including cancer [7], cardiovascular disease [8], diabetes [9], and neurodegenerative disorders [10]. Furthermore, miRNAs regulate lipid metabolism and adipogenesis [11,12]. By contrast, long non-coding RNAs (lncRNAs) are less well-studied. The most recent release from Gen-Code (version 22) has annotated ~15,900 lncRNA genes in humans. lncRNAs are categorized based on genome location into intergenic, intronic, antisense and enhancer lncRNAs [13]. Multiple studies have shown that many lncRNAs are regulated during development, exhibit cell type-specific expression patterns, localize to specific subcellular compartments, and are associated with human diseases such as cancer [14] and diabetes [15–20]. As summarized in Table 1, there is now accumulating evidence that lncRNAs are important regulators of lipid metabolism and adipogenesis [21–26]. Recent studies that implicate lncRNAs in the regulation of lipid metabolism in the liver and adipogenesis are reviewed here.

1.1. Tissue specific lncRNAs

Unlike mRNAs, lncRNAs are poorly conserved. lncRNAs are expressed in a species-, cell-, tissue-, and developmental stage-specific manner. There are approximately 11,000 primate-specific lncRNAs but only about 425 highly conserved lncRNAs. Conserved lncRNAs appear to predominantly regulate embryonic development [27]. Notably, each tissue generates unique lncRNAs during development [27]. For example, in mice, about 1109 polyadenylated lncRNAs are expressed in erythroblasts, megakaryocytes, and megakaryocyte-erythroid

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Table 1 — Functional lncRNAs involved in lipid metabolism and adipogenesis.

Name	Tissue/cell type	Loss-of-function phenotype	Gain-of-function phenotype	Assays	References
<i>lncLSTR</i>	Liver	Reduce plasma TG level		Knockdown	[23]
<i>HULC</i>	Hepatoma cell		Increase triglyceride and cholesterol levels	Overexpression	[30]
<i>APOA1-AS</i>	Liver	Increase APOA1 expression both <i>in vitro</i> and <i>in vivo</i>		Knockdown	[31]
<i>DYNLRB2-2</i>	Macrophage		Decrease cellular cholesterol level, increase APOA1 mediated cholesterol efflux	Overexpression	[34]
<i>SRA</i>	Fat	Reduce adipose size and liver TG level		Knockout	[37–39]
<i>ADINR</i>	3T3-L1 cell	Reduce adipogenesis		Knockdown	[41]
<i>NEAT1</i>	3T3-L1 cell		Increase adipogenesis	Overexpression	[42,43]
<i>HOTAIR</i>	Gluteal adipose tissue		Increase adipogenesis	Overexpression	[44]
<i>lnc-BATE1</i>	Brown adipose tissue	Reduce BAT activation		knockdown	[35]
<i>Blnc1</i>	Brown adipose tissue/epididymal white adipose tissue	Reduce brown adipogenesis	Stimulate brown adipogenesis	Knockdown/overexpression	[26]

precursors, whereas 594 lncRNAs are expressed in human erythroblasts [28]. Collectively, 53.6% of lncRNAs in megakaryocyte-erythroid precursors are conserved between mouse and human, whereas only 15% of mouse erythroid lncRNAs are expressed in human erythroblasts [28], indicating that the conservation of lncRNAs is highly dependent on both species and development stage. Each tissue has its own catalog of specific lncRNAs, which may contribute to the unique function of each tissue. Liver, skeletal muscle, and adipose tissue are three major metabolic tissues controlling lipid metabolism. An analysis of a dataset of multi-tissue gene expression profiles identified 30 lncRNAs that are enriched in liver, muscle, or adipose tissues [23]. These lncRNAs may regulate lipid metabolism in these tissues.

1.2. lncRNAs regulate lipid metabolism in the liver

Analysis of liver-enriched lncRNAs identifies *lncLSTR* as a putative regulator of plasma triglyceride (TG) levels [23]. Liver-specific knockdown of *lncLSTR* increases ApoC2 expression and LPL activities, enhances plasma TG clearance, and ultimately results in decreased plasma TG [23]. However, knockdown of *lncLSTR* in primary hepatocytes fails to increase ApoC2 expression, suggesting that another mediator exists in the liver cells. Liver-specific knockdown of *lncLSTR* decreases the expression of Cyp8b1, increases the ratio of muricholic acid (MA) and cholic acid (CA) in bile acid, and enhances FXR activity, leading to increased ApoC2 expression [23]. Mechanistically, *lncLSTR* is shown to directly bind to TDP43 and inhibit Cyp8b1 expression [23]. Another lncRNA, *HULC*, which is abnormally overexpressed in hepatocellular carcinoma (HCC) [29], has been shown to increase triglyceride and cholesterol levels by activating PPAR α and ACSL1 in hepatoma cells [30]. Together, these studies demonstrate that liver-enriched lncRNAs regulate lipid metabolism in the liver.

Another potential group of lncRNAs that regulates lipid metabolism is natural antisense transcripts (NATs). About 70% of lncRNAs are NATs, which regulate sense gene expression in a positive or negative manner [31]. *APOA1-AS* has been shown to negatively regulate *APOA1* expression both *in vitro* and *in vivo* [31]. Moreover, *APOA1-AS* regulates different histone methylation patterns that activate or suppress gene expression. Knockdown of *APOA1-AS* increases the level of H3K4-me3, decreases the level of H3K27-me3, but does not alter the level of H3K9-me3 at *APO* gene cluster, leading to increased expression of *APOA1*, *APOA4* and *APOC3* [31]. APOA1 is a major

component of high-density lipoprotein (HDL), protecting against cardiovascular disease [32], making *APOA1-AS* a potential therapeutic target for treating cardiovascular disease.

The expression of many lncRNAs can be induced by hormones [33], ligands [26], or lipoprotein [34], and these lncRNAs could regulate lipid metabolism. For example, oxidized LDL (Ox-LDL) significantly induces long intervening noncoding RNA (lincRNA)-*DYNLRB2-2* expression, resulting in the upregulation of GPR119 and ABCA1 expression through the glucagon-like peptide 1 receptor signaling pathway in THP-1 macrophage-derived foam cells [34]. As a negative feedback, GPR119 significantly decreases cellular cholesterol content and increases APOA1-mediated cholesterol efflux in the liver, reducing atherosclerosis in *APOE* knockout mice [34]. This study shows that inducible lncRNAs regulate lipid metabolism.

1.3. lncRNAs regulate adipogenesis

Adipocytes, including white, brown, and beige, play important roles in lipid storage or clearance. White adipocytes are the major constituent of white adipose tissue (WAT), controlling the storage of triacylglycerol [1]. Brown adipose tissue (BAT) and beige fat are responsible for thermogenesis. BAT is an important tissue controlling plasma lipid clearance in response to cold stimulation [5]. Both white and brown adipogenesis are tightly controlled by signal pathways, transcription factors, miRNA, and lncRNAs [1,11,26,35,36].

The first evidence of a potential role for lncRNAs in adipogenesis was reported by Xu et al [37]. The non-coding RNA, steroid receptor RNA activator (*SRA*), promotes adipogenesis *in vitro* through regulation of PPAR γ and P38/JNK phosphorylation [37,38]. Genetic deletion of *SRA* protects high fat diet induced obesity and fatty liver disease, reduces the size of adipocytes, and improves glucose tolerance [39].

To identify adipogenesis associated lncRNAs, transcriptomic analyses of primary brown and white adipocytes, preadipocytes, and cultured adipocytes have been performed [24,26,35,40]. A total of 175 lncRNAs were found to be significantly up- or down-regulated, by more than two-fold, during differentiation of both brown and white adipocytes [40]. Many lncRNAs are adipose-enriched and strongly induced during adipogenesis. Key transcription factors such as PPAR γ and C/EBP α not only control mRNA expression related to adipogenesis but also regulate lncRNA expression during adipogenesis [40]. PPAR γ is physically bound within the promoter region of 23 (13%) of the 175 lncRNAs while C/EBP α is bound upstream of 34 up-regulated lncRNAs (19%) during adipogenesis [40].

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