Regulatory Role of Long Non-coding RNAs in Fat Deposition and Their Mechanisms: Postprint

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Abstract

Long non-coding RNAs (lncRNAs) are a class of non-protein-coding RNAs longer than 200 bp that possess minimal or no protein-coding capacity, and can regulate gene expression at the transcriptional or post-transcriptional level through mechanisms such as genomic imprinting and epigenetic modifications. As the global obesity problem intensifies, factors regulating lipid metabolism have become a research focus. In recent years, with continuous discoveries of lncRNA functions, numerous studies have reported that lncRNAs play crucial roles in fat deposition. This review will summarize lncRNAs that positively promote and negatively inhibit fat deposition and their mechanisms of action.

Full Text

Regulation of Fat Deposition by Long Noncoding RNAs and Their Mechanisms

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Abstract: Long noncoding RNAs (lncRNAs) are a class of noncoding RNA transcripts longer than 200 bp with very weak or no protein-coding capacity. They regulate gene expression at the transcriptional or post-transcriptional level through mechanisms such as genomic imprinting and epigenetic modifications. As the global obesity epidemic intensifies, factors regulating lipid metabolism have become a major research focus. In recent years, with the continuous discovery of lncRNA functions, numerous studies have reported that lncRNAs play crucial roles in regulating fat deposition. This review summarizes lncRNAs that

positively promote and negatively inhibit fat deposition and their underlying mechanisms.

Keywords: long noncoding RNA; fat deposition; lipid metabolism; regulation; mechanism

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Fat deposition is determined by lipid metabolism, which encompasses the processes of fat synthesis and catabolism in the body and participates in physiological functions including energy metabolism, transport of fat-soluble nutrients, and hormone synthesis. Normal lipid metabolism is essential for maintaining homeostasis, whereas abnormal lipid metabolism not only causes dyslipidemia and cardiovascular diseases but also affects fat deposition in the body. Insufficient or excessive fat deposition leads to emaciation or obesity, increasing disease risk. In livestock and poultry, fat deposition directly affects meat quality. Recent studies have revealed that long noncoding RNAs (lncRNAs) play vital roles in regulating fat deposition. This review examines the effects of lncRNAs on fat deposition and their mechanisms, with prospects for their potential applications in improving meat quality in livestock and poultry.

Overview of lncRNAs

In addition to protein-coding mRNAs, the transcriptional process in organisms produces numerous small noncoding RNAs, including microRNAs, piRNAs, and more recently discovered lncRNAs. Research has shown that these small RNA fragments can regulate gene expression through genomic imprinting, transcriptional control, and translation processes [1]. lncRNAs are defined as noncoding RNA molecules longer than 200 bp with very weak or no protein-coding capacity. Based on their genomic location relative to protein-coding genes, lncRNAs are classified into five categories: (1) long intergenic noncoding RNAs (lincRNAs), transcribed from sequences between two genes; (2) intronic lncRNAs, derived from intronic regions of another transcript; (3) antisense lncRNAs, overlapping with exons of a coding gene on the opposite strand; (4) sense lncRNAs, overlapping with exons of a coding gene on the same strand; and (5) bidirectional lncRNAs, whose transcription start sites are close to but oriented opposite from those of protein-coding genes on the opposite strand [2].

Initially, lncRNAs received little attention from researchers, and their functions were highly debated, with some even considered "transcriptional junk" of the genome [3]. However, lncRNAs have gained significant research interest in recent years. Accumulating evidence demonstrates that, similar to other noncoding RNAs, lncRNAs regulate gene expression through genomic imprinting [4], epigenetic modifications, and transcriptional and post-transcriptional mechanisms [5]. In human medicine particularly, numerous studies have reported that lncRNAs play important roles in tumor development [6,7], cardiovascular disease formation [8-13], lipid metabolism regulation [14-18], and cell development control [19-24]. Therefore, investigating lncRNAs holds great potential

for addressing cancer, cardiovascular diseases, diabetes, obesity, and improving meat quality in livestock and poultry.

2.1 Steroid Receptor RNA Activator (SRA)

SRA was initially identified as an lncRNA that promotes steroid nuclear receptor-dependent gene expression [25]. Subsequent studies by Xu et al. [18] and Liu et al. [26] demonstrated that SRA binds to peroxisome proliferator-activated receptor γ (PPARγ) to activate PPARγ-dependent transcription, inhibit adipocyte-related inflammatory gene expression, and promote insulin receptor expression, thereby facilitating preadipocyte differentiation. In adipocytes, SRA increases glucose uptake and enhances phosphorylation of protein kinase B (Akt) and forkhead box protein O1 (FoxO1) upon insulin stimulation, improving insulin sensitivity.

Liu et al. [27] further showed that SRA knockout mice (SRA(-/-)) were significantly protected against high-fat diet-induced obesity, exhibiting reduced fat deposition, increased lean mass, and improved insulin sensitivity with lower blood glucose levels. Notably, SRA(-/-) mice on a high-fat diet showed no hepatic fat deposition, reduced triglyceride content, and decreased expression of fat-related genes in the liver. This study was the first to elucidate the important role of SRA in systemic fat deposition and glucose homeostasis [27].

Chen et al. [28] compared gene expression between SRA(-/-) and normal mice under normal and high-fat diets, finding that SRA knockout directly increased expression of adipose triglyceride lipase (ATGL) in hepatocytes, thereby enhancing free fatty acid β-oxidation. Additionally, SRA inhibited the FoxO1-mediated induction of the ATGL promoter and suppressed ATGL expression. The study also revealed that SRA inhibits ATGL promoter activity activated by PPARγ and its ligand rosiglitazone, thereby reducing ATGL levels, suppressing free fatty acid β-oxidation, and increasing hepatic fat deposition. Besides these two mechanisms, insulin can also regulate ATGL expression directly through the Akt/phosphatidylinositol-3-hydroxykinase (PI3K) signaling pathway by modulating FoxO1 activity, though this mechanism differs from the FoxO1-dependent pathway mediated by SRA [29]. The mechanism of SRA action is illustrated in [Figure 1: see original paper].

2.2 Metastasis Associated in Lung Adenocarcinoma Transcript 1 (MALAT1)

MALAT1 is a highly conserved lncRNA initially associated with diseases such as cancer. Recent studies have reported that MALAT1 is involved not only in diabetes-related pathogenesis [30-32] but also in regulating hepatic lipid deposition [33]. Research has shown that both high-fat diet and fasting states represent peak periods of hepatic lipid metabolism in mice, with significantly increased intracellular triglyceride and cholesterol levels that can potentially cause hepatic fat deposition. During these states, expression of both MALAT1

and sterol regulatory element-binding protein 1c (SREBP-1c) is significantly elevated in hepatocytes. SREBP-1c is a key regulator of fatty liver and dyslipidemia [34] and serves as an essential intermediate for MALAT1-induced hepatic fat deposition [33].

Silencing MALAT1 via siRNA reversed the high-fat diet-induced increases in triglyceride and cholesterol levels, significantly reducing their expression. This knockdown also decreased nuclear SREBP-1c protein expression and transcriptional activity, while reducing expression of hydroxy-methyl-glutaryl coenzyme A (HMGCoA) reductase and gluconeogenesis-related genes. HMGCoA reductase is the rate-limiting enzyme in hepatic cholesterol synthesis, and its inhibition blocks cholesterol synthesis in hepatocytes [33]. These findings demonstrate that lncRNA MALAT1 induces hepatic fat deposition and increases insulin resistance by post-transcriptionally regulating SREBP-1c protein and its target gene expression, providing new insights for research on promoting fat metabolism and treating abnormal hepatic fat deposition and diabetic complications.

2.3 PU.1 Antisense lncRNA

In the body, preadipocytes can be induced to differentiate into mature adipocytes, a process characterized by morphological changes from fibroblast-like to round-shaped cells, increased cell volume, and the appearance of lipid droplets marking the onset of fat deposition. Studies have found that overexpression of transcription factor PU.1 in preadipocytes inhibits this differentiation process [35]; therefore, promoting PU.1 mRNA translation in preadipocytes can effectively reduce fat deposition. Ebralidze et al. [36] discovered that PU.1 AS lncRNA, an antisense transcript of the PU.1 gene, regulates PU.1 protein expression. Pang et al. [37] knocked down PU.1 AS lncRNA using siRNA and found increased PU.1 protein levels and inhibited adipogenesis in preadipocytes, consistent with results from Wei et al. [38] using PU.1 AS shRNA.

Wei et al. [38] further demonstrated that PPARγ and fatty acid synthase, positively correlated with fat deposition, were upregulated by PU.1 knockdown but downregulated by PU.1 AS lncRNA knockdown. Conversely, ATGL and hormone-sensitive lipase (HSL), positively associated with fat lipolysis, were downregulated by PU.1 knockdown. Notably, inhibiting PU.1 mRNA expression did not affect PU.1 AS lncRNA expression, and vice versa. However, Western blot analysis revealed significantly increased PU.1 protein expression when PU.1 AS lncRNA was inhibited. These results indicate that PU.1 AS lncRNA forms an mRNA/AS lncRNA complex with PU.1 mRNA, hindering mRNA translation and thereby inhibiting PU.1 protein synthesis at the post-transcriptional level to promote fat deposition [37,38].

2.4 uc.417

In 2015, Rong et al. [39] used lncRNA microarray technology to screen for differentially expressed lncRNAs between differentiated brown adipocytes and brown preadipocytes in mammals, identifying lncRNA uc.417 as highly differentially expressed. Bioinformatics analysis revealed that this lncRNA is conserved across various species, including mammals, amphibians, and birds, with the highest homology between humans and mice. This ultraconservation suggests its important function in animal life processes. The study preliminarily validated that lncRNA uc.417 expression gradually increases during brown adipocyte differentiation, indicating its crucial role in brown adipocyte development.

Adipose tissue in the body is predominantly white adipose tissue, with brown adipose tissue accounting for only about 2% of total fat. During lipolysis, white adipose tissue can be converted into brown adipose tissue, and brown fat content and activity can also increase under certain inducing factors such as cold stimulation, oxidizing fatty acids to generate heat [40]. Cui et al. [41] elucidated the mechanism by which lncRNA uc.417 regulates brown adipocyte differentiation. In vivo, brown adipose tissue decreases with age, and researchers found this may be related to abnormal uc.417 expression. As age increases, uc.417 expression also increases, impairing the thermogenic effect of brown adipose tissue. The p38 mitogen-activated protein kinase (MAPK) signaling pathway is critical for stimulating uncoupling protein 1 gene expression, but uc.417 expression reduces p38 MAPK phosphorylation without affecting total p38 MAPK protein levels, thereby blocking the positive p38 MAPK signaling pathway. This suggests that increased fat deposition and decreased thermogenic effect in brown adipose tissue with age are caused by elevated lncRNA uc.417 expression, providing a new therapeutic approach for obesity-related metabolic diseases.

2.5 GM15290

Recently, Liu et al. [42] compared lncRNA expression profiles in white adipocytes from obese and normal mice, identifying 246 differentially expressed lncRNAs. Gene Ontology (GO) and KEGG pathway analysis of the five most upregulated and downregulated lncRNAs revealed that the most upregulated lncRNA, GM15290, is associated with metabolic processes, cellular biosynthesis, and participates in insulin and PPAR signaling pathways. The study found that transfecting mouse preadipocytes with a GM15290-containing vector significantly promoted expression of adipogenesis-related genes, including PPARγ, early adipogenic marker transcription factor CCAAT/enhancer-binding protein (C/EBP)α, and late adipogenic marker adiponectin 2 (aP2). Oil Red O staining confirmed that GM15290 overexpression increased fat deposition, while specific inhibition of GM15290 via siRNA produced opposite effects. Furthermore, in vivo injection of GM15290-specific siRNA significantly reduced high-fat diet-induced obesity and decreased white fat deposition. Therefore, lncRNA GM15290 positively regulates adipogenesis and obesity development [42].

The study also found that GM15290 contains seven consecutive matching bases with the PPARγ target gene miR-27b, with the lowest free energy, suggesting that GM15290 may bind to miR-27b to regulate adipogenesis [42]. Pearson correlation analysis revealed a negative correlation between GM15290 expression levels and miR-27b in white adipose tissue of obese mice ($r^2 = 0.9635$). Overexpression of miR-27b inhibited GM15290 expression but had no effect on GM15290 mutants, while miR-27b expression was reduced in white adipose tissue of high-fat diet-fed mice. These results demonstrate that in white preadipocytes, GM15290 acts as a competing endogenous RNA that binds to miR-27b, reducing miR-27b-mediated silencing of PPARγ and thereby increasing PPARγ expression to promote adipogenesis [42]. The discovery of GM15290' s regulatory mechanism provides a new target for controlling intramuscular fat deposition and treating obesity.

2.6 HOTAIR

Abdominal obesity, also known as central obesity, carries greater risks for heart disease, fatty liver, and type II diabetes compared to gluteal obesity, making regional obesity treatment a recent research focus. Divoux et al. [43] found that transfecting lncRNA HOTAIR, which is normally expressed only in gluteal adipose tissue, into abdominal subcutaneous preadipocytes significantly increased expression of adipogenesis-related genes such as PPARγ, fatty acid-binding protein 4 (FABP4), and adipokines, ultimately promoting differentiation of abdominal preadipocytes into mature adipocytes. This study demonstrates that lncRNA HOTAIR plays an important role in regulating the distribution of fat deposition and represents a key factor causing regional adipose tissue differences, providing a theoretical basis for future research on HOTAIR and other lncRNAs as therapeutic targets for reducing visceral fat and treating regional obesity.

3.1 Adipocyte Differentiation-Associated Long Noncoding RNA (ADNCR)

In 2013, Li et al. [44] analyzed the transcriptome profiles of bovine preadipocytes and differentiated cells in vitro, identifying 16 differentially expressed lncRNAs during adipocyte differentiation, with ADNCR showing the greatest downregulation. Mechanistic investigation revealed that in preadipocytes, ADNCR acts as a competing endogenous RNA for miR-204, preventing miR-204 from silencing its target gene silent information regulator factor 2-related enzyme 1 (SIRT1). This leads to increased SIRT1 expression, which can interact with nuclear receptor corepressor (NCoR) and silencing mediator of retinoid and thyroid hormone receptor (SMRT) to inhibit adipocyte differentiation and the activity of adipogenesis-related gene PPARγ. This study was the first to propose a novel regulatory model of lncRNA-microRNA interaction.

3.2 U90926

Recent researchers used cDNA microarray technology to investigate the expression and mechanism of lncRNA U90926 in 3T3-L1 preadipocytes, differentiated adipocytes, and mouse adipose tissue. They found that lncRNA U90926 is predominantly distributed in adipose tissue, with significantly lower expression in subcutaneous and visceral adipose tissue of obese mice compared to lean mice [45]. Overexpression of lncRNA U90926 significantly inhibited preadipocyte differentiation and fat deposition, indicating a negative correlation between U90926 and preadipocyte differentiation [45].

Further mechanistic analysis revealed that U90926 overexpression significantly reduced mRNA and protein levels of adipogenesis-related genes including PPAR$ 2, $FABP4$, and adiponectin (AdipoQ), while knockdown of U90926 produced opposite effects, signifi
L1 preadipocyte differentiation and fat deposition by suppressing PPAR 2 or PPAR $
transcription.

3.3 GM13133

Fat burning can reduce body fat deposition, and brown and beige adipose tissues are important thermogenic tissues in the body. Therefore, increasing thermogenic adipose tissue and promoting white adipose tissue browning have become new strategies for reducing fat deposition and preventing obesity [46-48]. As lncRNA regulatory functions have become a research hotspot, their role in regulating fat deposition has also attracted attention. You et al. [49] identified specific expression of lncRNA GM13133 in multiple mouse tissues, particularly in adipose tissue. Further analysis revealed that GM13133 expression in brown adipose tissue was twice that in white adipose tissue, and that cold, $ $3-adrenergic, and cAMP stimulation increased GM13133 expression in white adipose tissue. This suggests that GM13133 is associated with fat deposition, particularly with thermogenesis and white adipose tissue browning.

Cold stimulation increases cAMP expression in white adipose tissue cells through the $ 3—adrenergic signaling pathway [50]. During this process, increased GM13133 expression regulate
related molecules including PPAR $ coactivator 1α (PGC1α), UCP1, and PPARα, increasing oxygen consumption rate (OCR) and promoting thermogenesis [49]. Overexpression studies showed that GM13133 had no negative effect on white preadipocyte proliferation but inhibited white adipocyte differentiation and expression of adipogenesis-related genes such as PPARγ, C/EBPβ, FABP4, and glucose transporter 4 (GLUT4). Oil Red O staining revealed significantly reduced lipid accumulation and triglyceride formation. Moreover, GM13133 overexpression in white adipocytes increased mitochondrial number and promoted expression of molecules related to white-to-brown fat conversion, including cytochrome c and bone morphogenetic protein 7 (BMP7) [49]. These results demonstrate that lncRNA GM13133 reduces fat deposition by increasing mitochondrial biogenesis to maintain thermogenesis in brown adipose tissue and by inhibiting white adipocyte differentiation while

promoting brown adipocyte-specific marker expression through the cAMP signaling pathway to induce white adipose tissue browning. This discovery has significant implications for reducing subcutaneous fat deposition in animals.

4 Summary

In recent years, the regulation of fat deposition by lncRNAs and their associated mechanisms have become a research hotspot for clinical treatment of obesity and related diseases. This review summarizes how lncRNAs regulate expression of adipocyte coding genes through different mechanisms and participate in lipid metabolism-related signaling pathways, thereby playing important roles in fat deposition. However, clinical application of lncRNAs faces significant challenges and limitations. For instance, RNA interference technology may sometimes yield unsatisfactory inhibition effects due to lncRNA secondary structures or intracellular localization, or may exhibit off-target effects due to unstable binding with lncRNAs. Currently, research on lncRNA functions and mechanisms in fat deposition remains at the basic experimental animal stage, but these findings have important reference value for improving meat quality in livestock production. Therefore, research on lncRNAs in fat deposition in livestock and poultry urgently needs to be conducted.

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