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REVIEW

Long noncoding RNAs in regulating adipogenesis: new RNAs shed lights on obesity

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Abstract Long noncoding RNAs (lncRNAs) are an emerging class of regulators involved in a myriad of biological processes. Recent studies have revealed that many lncRNAs play pivotal roles in regulating adipocyte development. Due to the prevalence of obesity and the serious effects of adiposity on human health and society development, it is necessary to summarize functions and recent advances of lncRNAs in adipogenesis. In this review, we highlight functional lncRNAs contributed to the regulation of adipogenesis, discussing their potential use as therapeutic targets to combat human obesity.

Keywords ncRNAs · Adipose tissue · Beige cells · SRA · HOTAIR · NEAT1 · Blnc1

Introduction

Obesity refers to a condition of abnormal or excessive fat accumulation that is harmful to human health. Over the last several decades, the population of obese individuals has rapidly increased not only in developed countries but also in developing countries [1, 2]. According to data from the World Health Organization (WHO) in 2014, the prevalence of obesity worldwide more than doubled since 1980, and over 13 % of adults in the world were obese, with the body mass index (BMI) greater than or equal to 30.0. Although there is disagreement on the obesity definition and BMI classification method [3, 4], it is clear that obesity is a high risk factor for several serious human diseases, such as type 2 diabetes, cardiovascular disease, and certain types of cancers [5, 6]. Up to now, despite great progress in our understanding of adipose biology, an effective method for preventing/treating obesity remains to be developed. Further understanding molecular mechanisms controlling adipogenesis is critical to identify new targets for combating obesity.

In general, there are two types of adipose tissue in human and other mammals, white adipose tissue (WAT) and brown adipose tissue (BAT). WAT is mainly involved in the storage and mobilization of energy in the form of triglycerides and secretes adipokines that influence systemic energy homeostasis. Differing from WAT, BAT dissipates energy and generates heat through UCP1 (uncoupling protein 1) mediated uncoupling of respiration from ATP synthesis, defending against hypothermia and obesity [7]. Moreover, BAT- and WAT- derived fat cells possess both common features as well as individual properties regarding their origins, morphologies, functions, and gene expression patterns. For example, both PPARγ (peroxisome proliferator-activated receptor gamma) and CEBPs (CCAAT/enhancer binding proteins) are the master regulators driving BAT- and WAT- adipogenesis, while UCP1, PGC1α (peroxisome proliferator-activated receptor gamma coactivator 1 alpha), EBF2 (early B cell factor 2), and PRDM16 (PR-domain containing protein 16) only function in the transcriptional cascade of brown

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adipogenesis [8–10]. Of note, except for classical white or brown adipocytes, recent data suggest that inducible brown-like adipocytes, also referred to as beige or brite adipocytes, emerge in WAT in response to various stimuli (such as cold or β-adrenergic stimulation) [11, 12]. Distinct from white or brown adipocytes, the beige cells have high mitochondrial contents but express low levels of UCP1 in the basal (unstimulated) state; upon stimulation, beige cells elevate UCP1 expression and turn on robust programs of respiration and energy expenditure that are similar to those of classic brown fat cells, contributing to thermogenesis and obesity prevention [12].

Despite important progress toward revealing molecular regulations of adipogenesis, our knowledge on the regulatory mechanism of adipose development is rudimentary. Recent investigations on adipose development suggest a significant number of long noncoding RNAs (lncRNAs) participate in the regulatory networks of adipogenesis and play a key role in regulating adipogenic commitment and differentiation [13, 14]. This review summarizes recent advances on the most prominent lncRNAs that regulate adipogenesis (Table 1), providing novel insights into possible solutions to prevent or treat obesity.

lncRNAs

An overview of lncRNAs

Traditionally, messenger RNA is considered to deliver information from DNA to protein [15]. However, the rapid development of sequencing technology has revealed RNA also plays important regulatory functions in various biological processes of cells [16]. In mammals, most of the genome is transcribed in a developmentally regulated pattern, yielding a complex network of overlapping transcripts [15, 17, 18]. The sequencing of the human genome indicated that there are only around 20,000–25,000 protein-coding genes, representing less than 2 % of the total genomic sequence; the vast majority of transcripts are non-protein coding RNAs [19, 20]. Generally, noncoding RNAs (ncRNAs) can be sorted into two classes: housekeeping ncRNAs and regulatory ncRNAs. Housekeeping ncRNAs include transfer RNAs (tRNAs), ribosomal RNAs (rRNAs), small nuclear RNAs (snRNAs), small nucleolar RNAs (snoRNAs) and are usually expressed constitutively, while regulatory RNAs consists of piwi-interacting RNAs (piRNAs), microRNAs (miRNAs), and lncRNAs [21, 22]. In

Table 1 Direct roles of lncRNAs in regulating adipogenesis

lncRNA	Characteristics	Cell type/model	Functions in adipogenesis	References
Functional white adipocyte regulators				
SRA	Polyadenylated; intergenic	3T3–L1; mouse marrow-derived ST2 cells	Promotes preadipocyte differentiation partly via coactivation of PPARγ	[14, 36]
lnc-RAP-n (n = 1–10)	Polyadenylated	Primary white adipocytes from mice	Promotes white preadipocyte differentiation; lnc-RAP-1 functions via binding to hnRNP-U	[13, 39]
slincRAD	Non-polyadenylated; intergenic; primarily in the nucleus	3T3–L1	Promotes preadipocyte differentiation with unknown mechanisms	[45]
PU.1 AS	Antisense	3T3–L1; primary porcine preadipocytes	Promotes adipogenesis through preventing PU.1 mRNA translation via binding to PU.1 mRNA	[42, 43]
HOTAIR	Antisense/intergenic	Primary preadipocytes from human	Promotes preadipocyte differentiation with unknown mechanisms	[34]
ADINR	Polyadenylated; bidirectional; exclusively in the nucleus	Human MSCs	Promotes adipogenesis by activating CEBPα	[46]
NEAT1	Exclusively in the nucleus	Primary mouse preadipocytes	Promotes adipogenesis with unknown mechanisms	[50]
Functional brown adipocyte regulators				
Blnc1 (AK038898)	Polyadenylated; intergenic; primarily in the nucleus	Primary brown and beige preadipocytes from mice	Promotes brown and beige adipocyte differentiation and function via forming the EBF2 ribonucleoprotein complex	[33]
lnc-BATE-1	Polyadenylated; intergenic; similarly abundant in the cytoplasm and nucleus	Primary brown adipocytes from mice	Promotes brown adipogenesis possibly via forming a functional ribonucleoprotein complex with hnRNP-U	[51]

addition to the better known housekeeping ncRNAs, regulatory ncRNAs especially lncRNAs have been recently established as functional regulators in many differentiation and development processes and aberrant functions of lncRNAs may lead to a wide range of human diseases, such as cancer, cardiovascular disease, neurodegenerative disease, and metabolic syndrome, etc. [15, 23, 24]. Moreover, an increasing number of lncRNAs have been identified to regulate adipose development [13, 14].

The discovery of lncRNAs

Transcribed from the genome but rarely possessing protein-coding sequences, lncRNAs are a newly discovered class of ncRNAs with greater than 200 nucleotides in length. Instead of accumulating silence in cells, an increasing number of lncRNAs were found to be closely related with human health. Actually, the first recognized lncRNA, imprinted H19, was reported in 1990 [25], which is preferentially expressed from the maternal allele and participates in embryogenesis and human carcinogenesis [26]. Shortly after the discovery of H19, the silencing X-inactive-specific transcript (XIST) was also brought to light [27]. However, the discovery of the first miRNA lin-14 and subsequent breakthroughs in the miRNA field rapidly drew the foucus of ncRNA research from lncRNAs to miRNAs [28]. lncRNA related research grew dramatically with the advent of whole transcriptome sequencing techniques. New technologies combined with the novel functional annotation of a few lncRNAs greatly accelerated lncRNA discovery and its functional exploration.

Characterization and roles of lncRNAs

Generally, lncRNAs possess heterogeneous structures, may or may not be polyadenylated (polyA+ or polyA−; the polyA+ phenotype consists of multiple adenosine monophosphates at the 3′ end), and are located within the nuclear or cytosolic fractions. In addition, lncRNAs tend to be expressed at lower levels compared with mRNAs [29–31], and a high proportion of lncRNAs are preferentially expressed in specific tissues or cell lines [30, 32]. The expression of adipose lncRNAs is low and depot-specific [33, 34]. According to its position with respect to protein coding genes, a lncRNA can be classified into one or more of five categories [21]: sense, antisense, bidirectional, intronic, and intergenic (Fig. 1).

Heterogeneity in both sequences and genomic location determine the diversity and complexity of lncRNA functions. Up to now, lncRNAs have been implicated in a wide range of biological processes, including epigenetic regulation, small RNA processing, pattern formation and development, transcriptional/post-transcriptional regulation, protein metabolism, and tumorigenesis [22, 35], as well as a recent discovery that lncRNA possess the ability to regulate adipogenesis [13]. Considering functions of lncRNAs in adipogenesis are poorly characterized, this review focused on the recent advances of lncRNA in adipogenesis, including their discovery, functions, and clinical value, in order to facilitate research in this emerging field.

lncRNAs in white adipogenesis

SRA

SRA (steroid receptor RNA activator) was initially identified as a lncRNA that functioned as a transcriptional coactivator of steroid receptors [36], and was subsequently found to interact directly with a large variety of proteins including non-steroid receptors [37]. A recent study revealed that adipose-enriched SRA was capable of binding to PPARγ and enhancing PPARγ transcriptional activity to promote 3T3–L1 preadipocyte differentiation [14], for the first time showing the involvement of lncRNAs in adipogenesis (Fig. 2). During 3T3–L1 preadipocyte differentiation, SRA expression was induced by around twofold; overexpression of SRA in ST2 mesenchymal precursor cells with differentiation induction media (DMI) promoted adipogenesis, with enhanced

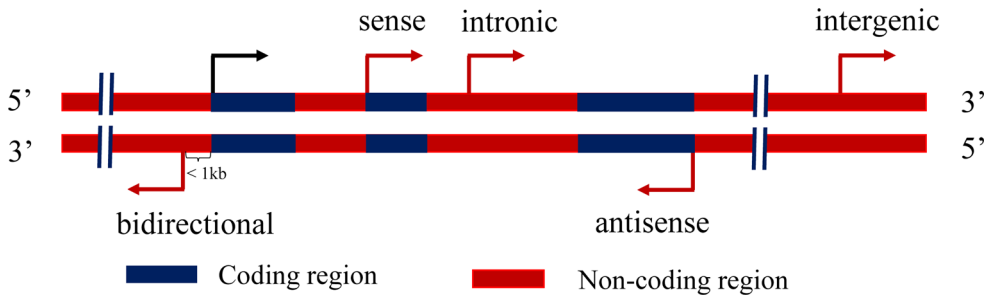

Fig. 1 Categories of lncRNAs classified on the basis of their relatively locations to protein coding region. *Black arrow* represents the transcription initiation site and direction of a protein coding gene; *red arrows* represent positions and directions of five types of lncRNAs, including sense, antisense, bidirectional, intronic, and intergenic

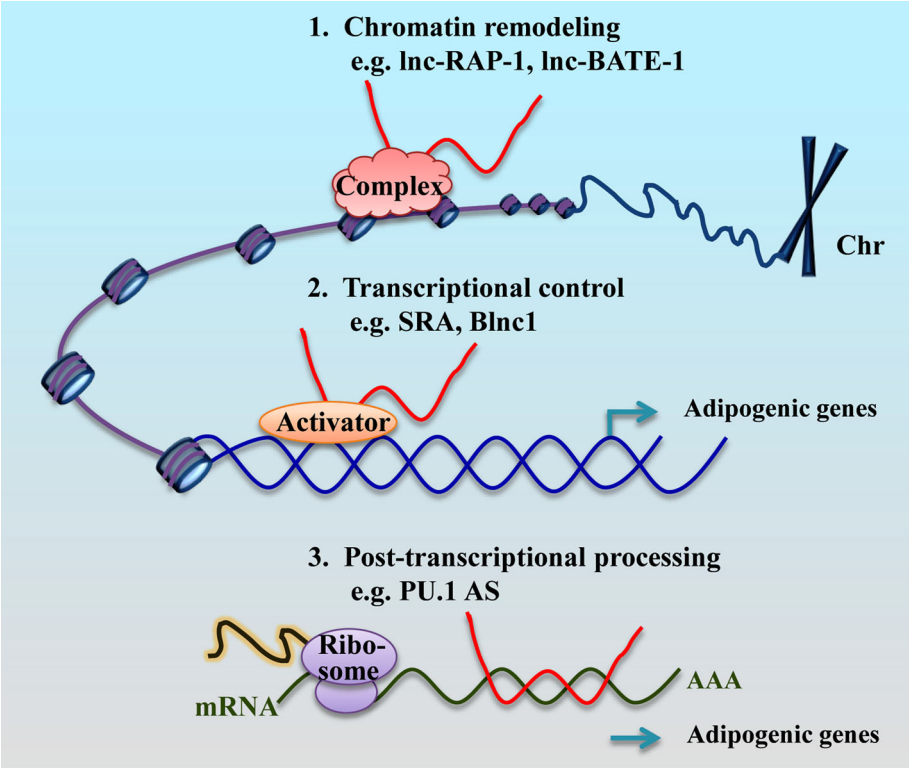

Fig. 2 Functions of lncRNAs in adipogenesis. lncRNAs participate in chromatin remodeling, transcriptional control, and post-transcriptional processing in cells to regulate adipogenesis. For example, lnc-RAP-1 or lnc-BATE-1 participates in chromatin remodeling via binding hnRNP-U; SRA acts as a coactivator of adipogenic transcriptional factors to enhance PPARγ transcriptional activity; PU.1 AS inhibits PU.1 mRNA translation by forming an mRNA/AS lncRNA duplex to enhance expressions of adipogenic genes

expressions of adipocyte master regulators PPARγ and CEBPα, as well as FABP4 (fatty acid binding protein 4) and AdipoQ (adiponectin) [14]. RNAi-mediated SRA loss-of-function showed opposite effects on 3T3–L1 cells, illustrating SRA as an essential pro-adipogenic regulator. Microarray analysis revealed that SRA regulated various cellular processes in adipocytes, including cell cycle and insulin-related signal transduction pathways, suggesting SRA might enhance adipogenesis and adipocyte function through multiple pathways [14].

Consistently, SRA expression was induced in WAT of HFD (high fat diet) induced obese mice [38]. To directly investigate SRA function in vivo, a whole SRA gene knockout mice was generated. Consistent with the previous data in vitro, SRA knockout mice were resistant to HFD-induced obesity, with reduced fat mass, decreased expression of a cluster of adipocyte marker genes and inflammation genes, lower plasma TNFα (tumour necrosis factor α) levels, and improved insulin sensitivity [38]. These data clearly indicate an important role of SRA in adipose tissue development, providing a potential target to control obesity and metabolic syndrome.

lnc-RAP-n

Research on lncRNAs as functional adipogenic regulators was largely promoted by large-scale genomic studies. Transcriptome profiling was used to examine the systematic implication of polyadenylated lncRNAs during adipogenesis, 175 poly-A tailed lncRNAs were significantly up- or down-regulated during differentiation of both white and brown mouse adipocytes; a substantial fraction of these lncRNAs were adipose-enriched and were tightly controlled by key transcription factors involved in adipogenesis (such as PPARγ and CEBPα) [13]. Several of these lncRNAs were strongly induced during differentiation, and siRNA-mediated loss of function demonstrated ten specific lncRNAs that could independently impair white pre-adipocyte differentiation, with reduced lipid accumulation as well as lower expressions of the majority of adipocyte markers (including PPARγ, CEBPα, FABP4, and AdipoQ), implicating that these lncRNAs were required for maturation of preadipocytes [13]. These 10 lncRNAs were therefore termed lnc-RAP-n (lncRNAs regulated in adipogenesis; $n = 1$–10). Among them, lnc-RAP-1, also known as FIRRE (functional intergenic repeating RNA element) or 6720401G13Rik, is an intergenic lncRNA that localized across a ~5 Mb domain on the X-chromosome which is in spatial proximity to five distinct trans-chromosomal loci within the nucleus, interfacing with and modulating nuclear architecture across chromosomes [39]. Furthermore, FIRRE binds hnRNP-U (heterogeneous nuclear ribonucleoprotein U, which is required for adipogenesis) to mediate the expression of adipogenic factors [39], providing a potential mechanism for the regulation of adipogenesis.

HOTAIR

HOTAIR, HOX antisense intergenic RNA, is located in the HOXC locus, and has been demonstrated to be involved in metastasis [40, 41]. Recently, a study has shown that HOTAIR participated in human subcutaneous preadipocyte differentiation [34]. HOTAIR was expressed in human gluteal fat but not in abdominal subcutaneous adipose tissue, and HOTAIR expression increased by twofold during gluteal preadipocyte differentiation in vitro [34]. Ectopic expression of HOTAIR in abdominal preadipocytes enhanced the percentage of differentiated cells and increased expressions of functional adipogenic markers including PPARγ, LPL (lipoprotein lipase), FABP4, and AdipoQ, with no effect on preadipocyte proliferation rate [34], suggesting an underlying transcriptional mechanism for HOTAIR to modulate preadipocyte differentiation. However, further study is required to decipher the molecular mechanism by which HOTAIR acts to regulate adipogenesis.

PU.1 AS

AS lncRNA (antisense long non-coding RNA) is a class of lncRNAs that are transcribed from the opposite DNA strand and overlap in part with its sense mRNA. Recent studies indicated that PU.1 AS lncRNA regulated adipogenesis through preventing PU.1 mRNA translation by forming an mRNA/AS lncRNA duplex [42, 43]. PU.1 is a transcription factor with inhibitory effects on preadipocyte differentiation [44]. Through attenuating PU.1 AS lncRNA binding to its mRNA, PU.1 AS lncRNA knockdown in 3T3–L1 preadipocytes promoted PU.1 protein expression and inhibited adipogenesis, as reflected by decreased lipid accumulation and reduced master gene expressions of PPARγ and CEBPα [42], indicating PU.1 AS lncRNA also plays a role in regulating adipogenesis.

slincRAD

A dynamic expressional profiling was performed in the induced differentiation of 3T3–L1 cells to examine potential functions of non-polyadenylated lncRNAs in adipogenesis; a super-long intergenic RNA transcript with a calculated size of 136 kb was shown to play a critical role in adipogenesis [45]. This gene was therefore named slincRAD (super-long intergenic non-coding RNA functioning in adipocyte differentiation) [45]. Quantitative analysis indicated that slincRAD inhibition in 3T3–L1 cell cultures reduced lipid accumulation and PPARγ expression, while the proliferation of the cells was not affected [45], demonstrating that slincRAD is a contributing factor in adipogenesis. Further investigation is needed to understand the underlying mechanism of slincRAD on fat cell development.

ADINR

Using mRNA-lncRNA-combined microarray technology, a recent study revealed 1423 differentially expressed lncRNAs on days 0, 3, and 6 of adipogenic differentiation of human mesenchymal stem cells (hMSCs) [46]. One of the highly induced lncRNAs, named ADINR (adipogenic differentiation induced noncoding RNA), was divergently transcribed from a position ~450 bp upstream of the CEBPα gene and was shown to be co-expressed with CEBPα during adipogenic differentiation [46]. Depletion of ADINR led to a dramatic adipogenic defect, as shown by decreased lipid accumulation and reduced adipogenic transcripts CEBPα, PPARγ, FABP4, and LPL. In addition, lentivirus-mediated ectopic expression of CEBPα enhanced expression of CEBPα as well as other adipogenic markers, and restored the severe adipogenic defects caused by the depletion of endogenous ADINR [46]. Mechanistically, ADINR RNA specifically binds to PA1 and recruits MLL3/4 histone methyl-transferase complexes to increase H3K4me3 and decrease H3K27me3 histone modification in the CEBPα locus, resulting in CEBPα activation as well as enhanced adipogenesis [46]. This data demonstrates that ADINR plays important roles in regulating the differentiation of hMSCs into adipocytes by modulating CEBPα in *cis*, demonstrating a mechanism of lncRNAs regulation of nearby gene expressions.

NEAT1

NEAT1 (nuclear enriched abundant transcript 1, also known as nuclear paraspeckle assembly transcript 1, MENε/β) is a nuclear lncRNA that is necessary for the formation of paraspeckles [47–49]. A recent study showed that miR-140 physically interacted with NEAT1 and increased NEAT1 expression [50]. In primary mouse preadipocytes, miR-140 knockout resulted in downregulation of NEAT1 as well as remarkable decreased lipid accumulation and the expression levels of PPARγ and CEBPα; re-expression of NEAT1 rescued the adipogenic phenotype, showing NEAT1 participates in miR-140 induced adipogenesis [50]. More functional essays are required to further understand NEAT1 roles in adipogenesis.

lncRNAs in brown/beige adipocyte development

Blnc1

It was recently illustrated that Blnc1 (brown fat lncRNA 1; AK038898), which was identified through global profiling of lncRNA expression during mouse thermogenic adipocyte formation, functioned as a driver of thermogenesis in brown and beige adipocytes, bringing a new layer of BAT developmental regulation. During adipogenesis, Blnc1

expression was highly induced by transcription factor EBF2; in addition, Blnc1 formed a ribonucleoprotein complex with EBF2 to enhance EBF2 expression, which promoted mouse brown and beige adipocyte differentiation and function by modulating the thermogenic gene program [33]. Overexpression of Blnc1 in brown preadipocytes significantly increased mRNA expressions of a subset of genes functioning in mitochondria that included UCP1 and PRDM1, with enhanced mitochondrial mass and DNA content and modest effect on lipid accumulation [33]. Further, mRNA expression of key thermogenic markers, including UCP1, was higher in Blnc1-expressing beige adipocytes [33]. In fat pads formed from transplanted Blnc1-transduced preadipocytes, UCP1 mRNA and protein levels reached approximately 30–40 % of that of endogenous brown fat [33], indicating Blnc1 as an effective activator of brown adipogenesis and brown fat formation. On the contrary, RNAi knockdown of Blnc1 severely impaired adipogenesis in cultured cells and in vivo [33].

lnc-BATE1

lnc-BATE1 is another BAT-specific lncRNA required for proper development and maintenance of mature, thermogenic brown adipocytes in mice. A recent study found that lnc-BATE1 was dramatically upregulated during brown adipogenesis or cold-induced beige adipocyte expansion [51]. lnc-BATE1 inhibition in brown preadipocytes resulted in decreased expression of brown fat markers (such as UCP1, PRDM16, and PGC1α), mitochondrial markers and, to a lesser extent, common adipogenic markers (PPARγ, CEBPα, FABP4, and AdipoQ), with limited effects on lipid accumulation and cell morphology; similar effects of lnc-BATE1 knockdown in beige adipocytes were also found [51]. Moreover, depletion of lnc-BATE1 in mouse mature brown adipocytes reduced BAT, mitochondrial, and common adipogenic markers, indicating lnc-BATE1 was essential for development and maintenance of mature brown adipocytes [51]. Indeed, lnc-BATE1 acts in *trans* to selectively sustain the core BAT gene program and repress WAT-selective genes through binding hnRNP-U, and both lnc-BATE1 and hnRNP-U were required for brown adipogenesis [51]. These data demonstrate that lnc-BATE1 is an essential factor during brown adipogenesis for induction of multiple mitochondrial proteins and for thermogenesis in brown adipocytes.

Potential lncRNAs that involved in adipogenesis

ecCEBPA

Recently, a functional lncRNA arising from the CEBPα locus, ecCEBPA (extra-coding CEBPα), was shown to bind directly to DNMT1 (DNA methyltransferase 1) and prevent CEBPα gene methylation, resulting in elevated expression of the CEBPα mRNA [52]. Loss and gain-of function experiments in HL-60, U937, and K562 cell lines suggested that CEBPα gene locus methylation levels were inversely correlated with ecCEBPA levels [52]. As CEBPα is a key driver of adipogenesis, epigenetic regulation of ecCEBPA on CEBPα expression might play an important role in adipogenesis. However, whether ecCEBPA is expressed in fat cells is unclear and further experiments are needed to evaluate ecCEBPA effects on adipogenesis.

AK142386 and AK133540

Via lncRNA microarray technology, Chen et al. evaluated differences in the lncRNA expression profiles of WAT and BAT [53]. In this study, hundreds of lncRNAs were identified to be differentially expressed between the two adipose depots [53]. GO (gene ontology) and pathway analyses of the differentially expressed lncRNAs showed that AK142386 and AK133540 might be involved in BAT and WAT development through their target genes Hoxa3 and Acad10 to regulate adipogenesis and metabolism [53]. Therefore, AK142386 and AK133540 might potentially serve as the required components for proper adipogenesis, but confirmation and elucidation of this assumption warrants further study.

Gm15051, Tmem189, and Cebpd

Additionally, differential expressions of lncRNAs on day 0 and day 8 during brown adipocyte differentiation were also profiled by microarray technology, providing a comprehensive analysis of lncRNA transcripts during classical brown adipocyte differentiation [54]. Among 1064 differentially expressed lncRNAs, lncRNA Gm15051, Tmem189, and Cebpd were identified to be important in the adipogenesis pathway via potential targets (Hoxa1, CEBPβ and CEBPδ) and might contribute to brown adipogenesis [54]. Further investigation of the molecular and biological functions of these candidate lncRNAs is required.

Clinical significance of lncRNAs for fighting against obesity

The worldwide prevalence of obesity has created heightened interest in understanding the detailed mechanisms regulating adipogenesis. Over the past several decades, great progress has been made in revealing master genes (such as PPARγ) and signal pathways in the complex transcriptional networks regulating fat development.

Recent research on lncRNAs allow us further understanding factors that regulate adipogenesis and expand our traditional knowledge about fat development. Although lncRNAs are among the least well-understood transcripts, studies on adipose tissue have identified the lncRNAs as a novel class of adipogenic regulators, which play an essential role in regulating both white and brown/beige adipogenesis.

Clear evidences indicate that SRA knockout mice are resistant to HFD-induced obesity, with reduced expression of inflammation genes [14, 38], showing its potential clinical value since obesity is usually associated with a state of low-grade inflammation. Interestingly, improved insulin sensitivity is also detected in $SRA^{-/-}$ mice [38], which might partly be due to reduced inflammatory signaling observed in the experiment. Furthermore, as these mice have a global loss of SRA, other tissues, such as liver, in addition to fat tissue, may contribute to the whole body insulin sensitivity. It should be noted, however, that the primary SRA transcript can be alternatively spliced to generate a lncRNA (SRA) and a protein (SRAP) [55, 56]. Although the previous in vitro study indicates that SRA exerts the major adipogenic effects observed in SRA gene knockout mice [14], a possible role of SRAP in adipocytes cannot be completely excluded, as the knockout abolishes expressions of both SRA and SRAP, and the function of SRAP remains largely unclear; similar situation may exist in cell culture knockdown experiments of SRA. Nevertheless, the role of SRA on obesity and the metabolic syndrome deserves further attention. Followed to SRA, lnc-RAP-n, slincRAD, PU.1 AS, HOTAIR, ADINR, and NEAT1 are also found to be involved in white preadipocyte differentiation [13, 34, 42, 45, 46, 50]. Furthermore, Blnc1 and lnc-BATE-1 positively regulate brown or beige adipogenesis via forming a ribonucleoprotein complex with distinct transcriptional factors [33, 51].

Unlike microRNAs, a familiar class of ncRNAs modulating adipogenesis, diverse mechanisms for lncRNAs in regulating adipogenesis have been revealed, indicating their complexity and diversity. Although lncRNAs have been indicated to impact genetic output at almost every step of a gene's life cycle [22, 35], the current functions of adipogenic lncRNAs focus on chromatin remodeling, transcriptional control (coactivator of transcriptional factors), and post-transcriptional processing (inhibition of translation) in cells to regulate adipogenesis (Fig. 2). In short, emerging lncRNAs function as important contributors to the intricate regulation network of fat cell development, and studies are further needed to elucidate their detailed mechanisms regulating fat accumulation.

As reviewed by Sun and Kraus, lncRNAs have been implicated in metabolism, endocrinology, reproduction, immunology, neurobiology, muscle biology, and cancer [57], and many of them possess tremendous clinical values [57, 58]. Recently, lncRNAs have been increasingly recognized as viable biomarkers for a number of diseases. For example, PCA3 lncRNA in urine samples has been developed into a clinical test for detecting human prostate cancer [59]. In addition to lncRNA-based diagnostics, lncRNA also serves as targets for lncRNA-based therapies, though many of which have focused on the treatment of cancers [57]. For combating human obesity, several possible lncRNA-based approaches might include developing pharmacological compounds that specifically activate/suppress lncRNA expressions to regulate white adipocyte differentiation. Notably, a new discovered drug ribocil is a synthetic small molecule selectively targeting riboswitches (the specific non-coding RNA structures) in mRNAs, indicating that non-coding RNA structural elements may successfully be targeted by synthetic small molecules [60]. As some adipogenic related lncRNAs have been uncovered functional structural elements (e.g. HOTAIR and NEAT1) or the complete secondary structure (e.g. SRA) with potential functions [37, 61], developing small molecule targeting specific lncRNA structures may be an effective therapeutic approach for combating metabolic related diseases. Additionally, overexpression or suppression of targeted lncRNAs regulating white adipogenesis through gene therapy provides a possibility to treat adiposity; one of the promising targets is SRA [38], though lncRNA-based gene therapies still have a long way to go before entering clinical trials in obese patients. Alternatively, lncRNA NEAT1 suggests that certain lncRNAs interact with miRNAs during fat cell differentiation [50], thus regulating lncRNA levels or activity via miRNAs may also prove useful. Another possible way for the development of possible approaches against obesity might involve the brown/beige adipogenesis, as some lncRNAs (such as Blnc1) can increase energy expenditure of brown fat to physiologically protect against obesity [33]. Strategies for stimulating brown/beige adipocyte abundance or function via lncRNAs have unique advantages as lncRNAs possess strong tissue specificity.

Collectively, similar with other modulators identified in adipogenesis, a few lncRNAs, not all, that regulating adipogenesis may have profound implications and clinical potential in obesity, although functions and mechanisms need to be explored in much more detail.

Conclusions

lncRNAs are a newly discovered class of regulatory RNAs that participate in a variety of cellular activities. Emerging evidence from both gain- and loss-of-function studies strongly indicates that lncRNAs are involved in the regulation of adipogenesis and play an important role in both

white and brown/beige adipose tissue development and function. lncRNA functions in adipocytes are gradually being revealed, serving as a theoretical basis for understanding fat biology. Although this area warrants further investigation, the identification of lncRNA molecules with adipogenic activity may open up new possibilities of potential therapeutic targets and strategies for combating human obesity.

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Compliance with ethical standards

Conflict of interest The authors have declared that no conflicts of interest exist.

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