Review

Role of long non-coding RNAs in adipose tissue metabolism and associated pathologies

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A B S T R A C T

The incidence of obesity and its related disorders has increased dramatically in recent years and has become a pandemic. Adipose tissue is a crucial regulator of these diseases due to its endocrine capacity. Thus, understanding adipose tissue metabolism is essential to finding new effective therapeutic approaches. The "omic" revolution has identified new concepts about the complexity of the signaling pathways involved in the pathophysiology of adipose tissue-associated disorders. Specifically, advances in transcriptomics have allowed its application in clinical practice and primary or secondary prevention. Long non-coding RNAs (lncRNAs) have emerged as critical regulators of adipose tissue since they can modulate gene expression at the epigenetic, transcriptional, and post-transcriptional levels. They interact with DNA, RNA, protein complexes, other non-coding RNAs, and microRNAs to regulate a wide range of physiological and pathological processes. Here, we review the emerging field of lncRNAs, including how they regulate adipose tissue biology, and discuss circulating lncRNAs, which may represent a turning point in the diagnosis and treatment of adipose tissue-associated disorders. We also highlight potential biomarkers of obesity and diabetes that could be considered as therapeutic targets.

1. Introduction

1.1. Overweight and obesity

Overweight and obesity have become significant public health issues worldwide and are defined by the World Health Organization (WHO) as excessive and abnormal accumulation of body fat that is related to adverse health effects [1]. Epidemiological studies have identified obesity and overweight as risk factors for the development of several diseases that affect multiple body systems, such as musculoskeletal complications, metabolic inflexibility, diabetes mellitus, cardiovascular risk, several types of cancer, chronic respiratory diseases, and mental health problems [2–4]. Chronic excessive body fat has been associated with increased mortality, with over 4 million related deaths worldwide [5,6]. The life expectancy of those living with obesity is five years less than those with a normal weight [7,8].

Recent data from the WHO European Region showed that overweight and obesity affect almost 60 % of adults (>1.9 billion) and is the fourth most common risk factor for noncommunicable diseases. However, both overweight and obesity continue to grow in adults as well as children, affecting one in three children (~30 %) [9,10]. This percentage has been increasing since the COVID19 pandemic [11,12]. The prevalence of obesity increases with age and is highest in people aged over 40 years. The prevalence is lower among females (54 %) than males (63 %) across the WHO European Region, but is close to or exceeding 70 % for males in most countries [9]. Mediterranean and eastern European countries present the highest levels of both overweight and obesity, where it predominantly affects people with lower educational attainment [13]. Despite the relative stabilization of the trend in overweight and obesity in developing countries, current interventions to combat the overweight epidemic need to be maintained and strengthened since the prevalence of overweight and obesity in these regions remains very high.

Obesity and overweight are associated with changes in the structure and function of the adipose tissue (AT). Hence, robust, and healthy AT homeostasis is required for proper metabolic control, as will be discussed in the following sections. Therefore, understanding AT physiology at the molecular level is vital to preventing and controlling obesity and overweight.

1.2. White and brown AT

1.2.1. AT and its multiple functions

AT is the largest organ in the body, representing 10 %–15 % of the total body weight in healthy men and 20 %–25 % in healthy women. In addition to buffering the daily influx of dietary nutrients and maintaining energy homeostasis, AT is also the safest place for the long-term storage of lipids [14]. AT was long considered to be a simple, static, lipid-storage tissue. Today, AT is known to be an active endocrine and secretory organ with multiple functions crucial for survival, including thermoregulation, lactation, immune responses, reproduction, and satiety [15,16]. There are two main types of AT in mammals, white adipose tissue (WAT) and brown adipose tissue (BAT), which have completely opposite functions, morphology, and developmental lineages [17].

WAT is characterized by adipocytes that contain large unilocular lipid droplets that store excess energy in the form of triacylglycerides [14]. In contrast, BAT contains multilocular lipid droplets and a large number of mitochondria, which actively consume energy and produce heat via uncoupling protein 1 (UCP1) in a process called thermogenesis. Historically, BAT was only considered to be present in rodents and human fetuses and newborns and it was regarded to be absent in human adults. However, the presence of metabolically active BAT in adult humans was revealed just over a decade ago. The activity of BAT was found to be inversely correlated with age, glucose levels, and body mass index (BMI) [18].

Recent studies have identified yet another type of thermogenic adipocytes called beige adipocytes [19]. Beige or "brite" (brown-in-white) adipocytes can be found scattered in WAT and have the potential to generate heat in response to cold exposure or pharmacological stimuli in a process known as browning, which involves an increase in *Ucp1* messenger RNA (mRNA) expression [20]. Interestingly, these cells show great level of plasticity, where the white fat-like phenotype switches to a brown fat-like phenotype in response to stimuli, such as cold, nutrients, and exercise [20,21]. Both brown and beige adipocytes have gained great interest as a potential target to treat obesity and associated metabolic disorders.

Women have another type of AT known as pink AT. Pink adipocytes are milk-secreting alveolar cells that develop from subcutaneous white adipocytes during pregnancy and lactation. After the lactation period concludes, they transdifferentiate to white or brown adipocytes again. In addition to being involved in milk production, pink adipocytes are able to secrete molecules that regulate metabolism similar to WAT or BAT. These include leptin, a key hormone in obesity. For this reason it is also considered as an endocrine regulator and may be involved in metabolic syndrome [22,23].

1.2.2. Adipose tissue distribution: Does location matter?

Human BAT is predominantly located in the supraclavicular depots in the neck region. A small percentage of brown adipocytes can also be found in the axillary, paravertebral, and kidney areas [24]. On the other hand, in mice, BAT is mostly distributed on the back, between the shoulder blades, and a small amount is present in the perirenal and perivascular regions (Fig. 1).

In mammals, WAT is distributed throughout the body and is classified according to its location into two depots: visceral adipose tissue (VAT; including omental, mesenteric, retroperitoneal, gonadal, and
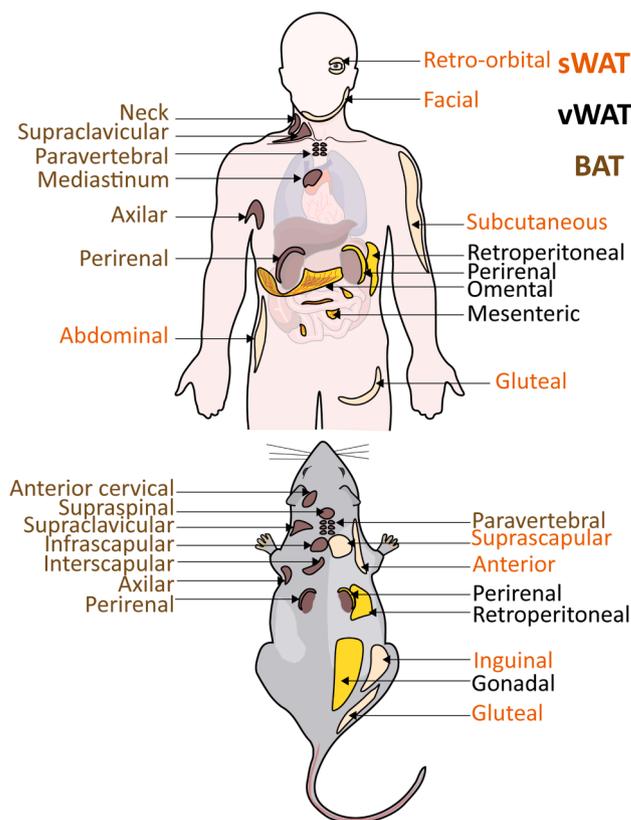

Fig. 1. Adipose tissue distribution in humans and rodents. The adipose tissue depots are grouped in sWAT (subcutaneous white adipose tissue, colored light brown), gWAT (gonadal white adipose tissue, colored yellow) and BAT (brown adipose tissue, colored dark brown).

pericardial WAT) and subcutaneous adipose tissue (SAT) (Fig. 1). SAT is further subdivided into gluteofemoral subcutaneous adipose tissue (GSAT; lower body regions in the thighs, hips, and buttocks), upper body SAT (arms, trunk, and abdomen), and abdominal subcutaneous adipose tissue (ASAT) [25]. Each depot has different metabolic functions as well as different, molecular, and physiological features, although the mechanisms that drive these differences are not fully understood.

Compared with SAT, an excess of lipid accumulation in VAT is associated with a greater risk of metabolic comorbidities, including glucose intolerance, hyperinsulinemia, and hypertriglyceridemia, which can lead to cardiovascular disease and type 2 diabetes mellitus (T2D) [26,27]. Several possible explanations for these differences have been extensively discussed in the literature. One explanation is that VAT is more metabolically active and has a greater capacity for lipolysis, which generates free fatty acids (FFAs) [28]. This, together with the anatomical location of VAT and its close proximity to the liver, leads to a greater exposure of insulin-sensitive hepatocytes to both FFA and adipokines [28,29].

Another major difference between VAT and SAT is their cellularity and adipogenic capacity. The development of preadipocytes from mesenchymal stem cells (MSCs) to adipocytes varies according to their location [30,31]. The percentage of other cells in AT, including stem cells, macrophages, neutrophils, lymphocytes, and endothelial cells, varies greatly based on their location and could also be responsible for the differences seen between AT types [32]. Karpe and Pinnick (2015) reported that the majority of functional differences seen between upper and lower-body AT are controlled by different sets of developmental genes that are under epigenetic control [33]. All these factors play a very important role in AT dysfunction, as will be discussed in the following section.

1.3. Mechanisms involved in obesity-induced derangement of adipose tissue

Ectopic fat deposition and WAT dysfunction are caused by different mechanisms implicated in obesity-related metabolic diseases. AT expansion could be achieved by recruiting new adipocytes (hyperplasia) or expanding (hypertrophy) existing adipocytes. The former mechanism is less harmful as hypertrophy and ectopic fat lead to inflammation and disease development [34]. The expansion of AT in obesity is related to increases in both adipocyte progenitor differentiation and mature adipocyte cell size [35].

In addition to storing fatty acids, AT also releases FFAs as an energy source for cells in other tissues, such as the heart, skeletal muscles, and liver. In disorders such as T2D or obesity, an increase in fat deposition causes the release of FFAs, which is associated with decreased glucose uptake, increased hepatic glucose production, insulin resistance, and metabolic disease development [36–38]. Moreover, AT secretes hormones, also known as adipokines, making it an endocrine organ [39,40]. Hence, AT regulates a wide range of metabolic processes, highlighting the importance of maintaining a healthy AT. Obesity-associated WAT dysfunction is related to increased hypertrophy, hypoxia, impaired angiogenesis, inflammation, fibrosis, mitochondrial dysfunction, and oxidative damage due to endoplasmic reticulum (ER) stress and oxidative stress.

1.3.1. Hyperplasia, hypertrophy, and impaired adipogenesis

AT expansion has a limit, and when it is exceeded, adipocytes suffer from hypertrophy. Hypertrophy leads to the tissue becoming inflamed and dysregulated, and fat begins to accumulate in the visceral and peri-epicardial areas as well as ectopic sites, including liver, heart, and skeletal muscle [41–45]. Hence, both hyperplasia and hypertrophy are mechanisms involved in AT remodeling. However, the consequences of each are quite different. Hyperplasia plays a protective role since it has been associated with improved glucose metabolism and insulin sensitivity [41]. Instead, hypertrophy is related to different disorders,

including insulin resistance, even in normal-weight individuals, and has become a marker of T2D [46].

ASAT shows a hypertrophic response with limited capacity to recruit new adipocytes, whereas GSAT demonstrates a proliferative response to weight gain [30,31,47,48]. Thus, GSAT is considered protective against metabolic-related diseases, while the opposite has been described for ASAT [33]. A greater accumulation of ASAT increases the risk of cardiovascular disease and T2D, similar to that of VAT [49,50]. The mechanisms underlying these depot-specific differences are complex and not fully understood. Several factors, including hormones, transcription factors, and cell signaling molecules, that could influence these differences have been proposed [47].

Furthermore, hypertrophic adipocytes showed reduced expression of adipogenic markers and alterations in the profile of secreted adipokines. Increased infiltration of proinflammatory macrophages has been observed in expanded VAT [51,52]. Consequently, adipocytes release inflammatory cytokines, which diminish the production of protective molecules such as adiponectin (Adipoq). Thus, normal adipogenesis and differentiation are compromised, leading to dysfunctional AT [39,42,46].

1.3.2. Hypoxia and impaired angiogenesis

The expansion of AT requires a larger number of blood vessels to supply oxygen, nutrients, and other molecules for new and/or hypertrophic adipocytes. AT expansion and angiogenesis, which is the growth of blood vessels from the existing vasculature, go hand in hand. However, it remains unclear whether adipogenesis is under the control of angiogenesis or *vice versa*. Various processes regulate angiogenesis, including adipocyte expansion [53], inflammation [54], and hypoxia [54].

During hyperplasia, tissue grows healthily and develops new blood vessels to avoid hypoxia. However, this does not occur during hypertrophy, and severe hypoxia begins to emerge. The development of hypoxia in adipocytes has been closely related to changes in the cell secretome [54–57]. Angiogenesis depends on numerous factors and although, hypoxia itself does not seem to be sufficient to enhance angiogenesis it is one of its triggering mediators both *in vitro* and *in vivo* [41].

1.3.3. Inflammation and fibrosis

Various cytokines are released in response to normal AT expansion. However, in obesity, hypertrophic adipocytes trigger signals that activate inflammation-related metabolic pathways. Inflammation causes adaptive responses in adipocytes in order to attenuate its adverse effects. Nevertheless, when inflammation becomes chronic, maladaptive responses emerge, leading to a pathological state. Some mechanisms that lead to downstream inflammatory signaling include hypoxia, FFA accumulation, and mechanical stress caused by expansion through the extracellular matrix [58].

The secretome of hypertrophic adipocytes is altered and adipocytes begin to release proinflammatory cytokines that promote immune cell infiltration, including macrophages, T cells, and mast cells [59]. The cytokines secreted by adipocytes include tumor necrosis factor alpha (TNFα), interleukin (IL) 6, IL8, monocyte chemotactic protein 1, inducible nitric oxide synthase, transforming growth factor beta 1, C-reactive protein, and soluble intercellular adhesion molecule 1 [60,61]. An increase in adipocyte size is closely related to macrophage infiltration into AT and adipocyte death. During obesity, macrophages constitute up to 40 % of all AT cells [61]. The proinflammatory molecules released by macrophages and other molecules produced by different immune cells have direct effects on cellular metabolism and block insulin action to limit energy accumulation and promote angiogenesis to prevent hypoxia [58,62–64].

Chronic inflammation is usually related to tissue remodeling and fibrosis, especially in pathological states. During fibrosis there is an excessive deposition of extracellular matrix components which

negatively affects tissue function [65]. The relationship between fibrosis and obesity is unclear. Some studies have shown a positive correlation between fibrosis and metabolic disease in murine models and humans [66–68]. However, other studies have not supported this correlation and have reported the involvement of other factors, such as BMI and hyperplastic expansion, and proposed that fibrosis limits hypertrophy expansion and acts as an adaptative feature to preserve adipocyte function [69–72]. In parallel, unresolved inflammation triggers adipocyte fibrosis, metabolic inflexibility, dysregulation of adipocyte function, and cell death [58].

1.3.4. Mitochondrial dysfunction

Mitochondria play a crucial role in fatty acid metabolism and, therefore, in adipogenesis [73,74]. A sequence of disorders leads to mitochondrial dysfunction, which has severe consequences, including insulin resistance and inflammation [75]. Obesity is strongly related to ER stress and reactive oxygen species production, which are two closely mitochondrial dysfunction-related processes. When fatty acid oxidation and mitochondrial biogenesis rates are diminished, mitochondrial DNA is reduced, triggering fibrosis, inflammation, and apoptosis [66,76]. Similar results have been found in humans [77–81] and obese patients with T2D [82].

These mechanisms, including hypertrophy, hypoxia, inflammation, fibrosis, and mitochondrial dysfunction, are some of the main drivers of the development of AT-related disorders.

2. Non-coding RNA (ncRNA)

2.1. Types and functions

Large-scale projects for systematic annotation, such as functional annotation of the Mammalian Genome (FANTOM) and the Encyclopedia of DNA Elements (ENCODE), have described widespread transcription. While most of the DNA is transcribed into RNA, only 1.5 % of that RNA is translated into protein [83–88]. Although transcriptomic studies have focused on the 1.5 % of coding transcripts or mRNA content, the appearance of ncRNAs, which are molecules that are not translated to proteins, has emerged and gained interest over the past two decades. The concept of ncRNAs has improved since they were initially dismissed as junk/black matter in gene regulatory networks [89]. The discovery of regulatory ncRNAs has completely changed our understanding of these molecules since they have been proposed to play crucial roles in multiple biological processes, regulating physiological and pathophysiological mechanisms [90–94]. Consequently, it is essential to differentiate and identify the different types of ncRNA to fully understand the mechanisms involved in these disorders and propose highly effective treatments to improve AT-related disorders (Fig. 2).

Our understating of the different types of ncRNAs is increasing exponentially with the development of next-generation sequencing techniques and bioinformatics analysis. ncRNAs are classified as small ncRNAs (length < 200 nucleotides), including ribosomal RNA, transfer RNA, microRNA (miRNA), small nuclear RNA, small interfering RNA, PIWI-interacting RNA, and long ncRNAs (length > 200 nucleotides) [95], which are further subdivided into circular (circRNA) and linear RNAs. Among these, the main groups of ncRNAs involved in AT metabolism and associated pathologies are miRNA and lncRNAs. The miRNAs are by far the most studied family of ncRNAs in this context. These molecules are small RNAs (18–22 nucleotides) that act as negative regulators of gene expression by binding to short complementary regions of target mRNAs [96–98]. All mRNAs are predicted to have more than 60 % of their 3′ untranslated region (UTR) target sites for miRNAs, indicating tight control and participation in both normal cell
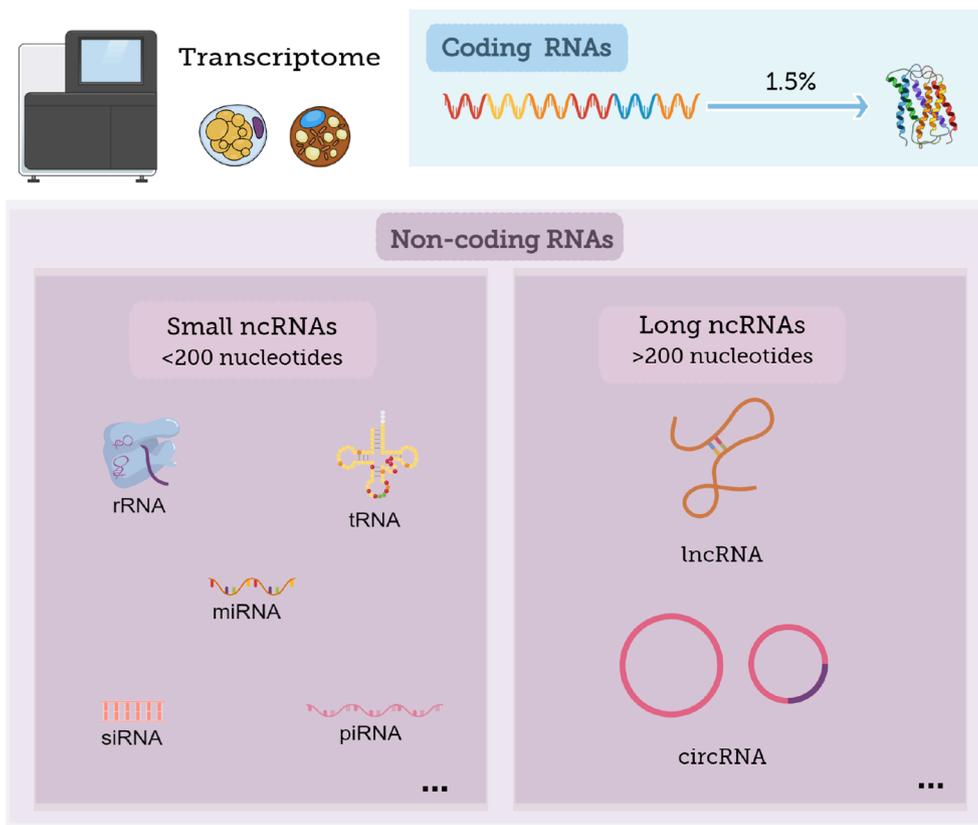
Fig. 2. Transcriptome classification. The top blue box represents that only 1.5% of the RNA is translated into protein. The purple boxes show the main types of non-coding RNA (ncRNAs) based on the transcript length (small and long ncRNAs). Abbreviations: Circular RNA (circRNA), linear RNA (lncRNA), microRNA (miRNA), non-coding RNA (ncRNA), PIWI-interacting RNA (piRNA), ribosomal RNA (rRNA), small interfering RNA (siRNA), transfer RNA (tRNA).

homeostasis and illness [99]. The circRNAs are another example of lncRNAs recently studied in AT. They are produced by alternative splicing of RNAs, act as miRNA sponges and contain RNA-binding protein (RBP) binding sites, regulating alternative splicing and gene expression. The roles of linear RNAs (from now on referred as lncRNAs) will be explained in depth in the next section in which we describe the recent findings in the field of lncRNAs, and their association with AT.

2.2. LncRNAs

In the 1990 s, the pioneering discovery of the uncharacterized ncRNAs, H19 and X-inactive specific transcript (Xist) l, led to the early belief that lncRNAs were transcriptional noise with little or no functional significance [100,101]. Although lncRNAs were discovered in the early 2000 s, later studies showed that they were critical for a wide range of biological functions [86,102]. As mentioned previously, lncRNAs are a heterogeneous group of ncRNA that range in size from 200 nucleotides to 20 kb. The nucleotide chains have the remarkable capacity to acquire various complex secondary and tertiary structures, enabling them to fulfill specialized roles required for survival [103]. Due to their structural diversity, lncRNAs can interact with DNA, RNA, and proteins and perform several regulatory activities, as we will describe. A systematic integration of annotations of existing databases revealed that there are almost 270,000 lncRNA transcripts annotated in humans [104–110]. Their nomenclature and symbols haven been certified by the HUGO Gene Nomenclature Committee [111].

Knowledge of the biosynthesis of lncRNAs is necessary to decode their functional significance, relevance, and distinction from other types of RNAs. DNA elements, such as enhancers, promoters, and intergenic regions, are responsible for the transcription of a wide range of lncRNAs. Like mRNAs, lncRNAs are transcribed by RNA polymerase II, which requires the assembly of similar preinitiation complex and transcription factors [112]. Overall, lncRNAs also present 5′ ends with a 7-methyl guanosine cap and 3′ ends with a polyadenylated tail [113]. While, several lncRNA loci have been shown to use non-canonical 3′ end processing that results in non-polyadenylated RNAs [114,115], this method of lncRNA stability involves ribonuclease P, which cleaves and generates a mature 3′ end [113].

In general, lncRNAs are intracellular (and could be released into the circulation) and stable with expression patterns that are unique to each cell type, tissue, and stage in the development and function of each cell. They are expressed at a lower rate than mRNAs in a given cell type [116,117]. Therefore, identifying the evolutionary conservation of functional sequences in the genome is one of the most solid and accurate characteristics, highlighting their involvement as potential regulatory elements in essential biological processes [118]. The skepticism concerning the evolutionary conservation of lncRNAs extends to controversy about their functionality and biological relevance [119–123]. In 2015, a study on the non-coding transcriptomes of 17 diverse species revealed that the bodies of the non-coding genes are not conserved [124]. However, their 5′ ends contained short conserved sequences [123], which revealed a higher level of expression patterns in diverse tissues, particularly those involved in development [125].

The structure, function, localization, and interaction with other biomolecules are applied to classify the wide diversity of lncRNAs [126]. The wide functions of lncRNAs are reviewed elsewhere [127–130]. Regarding their location within the genome, lncRNAs are categorized into various types, including sense lncRNAs, antisense lncRNAs, bidirectional lncRNAs, intronic lncRNAs, intergenic lncRNAs, promoter-associated lncRNAs, and UTR-associated lncRNAs [116,131]. In addition, lncRNA classification according to the intracellular location could be used to predict their mechanism of action. Whereas mature mRNAs are only found in the cytoplasm, most lncRNAs are mainly located in the nucleus [116,132] and are likely exported to the cytoplasm. Numerous RNA polymerase II-transcribed lncRNAs are processed inefficiently and remain in the nucleus. Furthermore, analysis of subcellular lncRNAs

revealed nuclear retention elements or sequence motifs in *cis*-elements and *trans*-factors, indicating that their export involves a default mechanism [133,134]. In the absence of an active *cis*-element, it is probable that capped and polyadenylated stable RNA serves as a nuclear export substrate [135]. Thus, the location of lncRNAs in the nucleus is coordinated at multiple levels (reviewed in [130]), from transcription and processing to nuclear export, using multiple sequence motifs. The functions of these lncRNAs have been linked to a variety of nuclear activities, including the assembly of nuclear domains, directing chromatin architecture and remodeling, resetting epigenetic marks, and regulating mRNA transcription (reviewed in [129,130,136]). In addition, nuclear functional lncRNAs can perform in both *cis* (when their actions are limited to the chromosome from which they are transcribed) and *trans* (when they influence genes on other chromosomes) directions [137].

A considerable proportion of lncRNAs are exported to the cytosol and are thought to use analogous processing and export pathways, similar to mRNAs [138]. When lncRNAs reach the cytoplasm, they undergo a sorting procedure that either sends them to different organelles (e.g., mitochondria, ER, ribosomes, exosomes) or spreads them out in the cytoplasm where they bind to different RBPs. LncRNAs regulate signal transduction pathways, translational programs, and posttranscriptional gene expression in the cytoplasm. For example, some lncRNAs can regulate mRNA translation and stability [139], protein activity [140], and levels through protein post-translational modifications [140,141]. Additionally, lncRNAs act as miRNA sponges by binding to complementary sites and influence gene expression by competing with endogenous RNAs [142,143].

Analysis of the human mitochondria transcriptome revealed that various lncRNAs are recruited into the mitochondria, indicating other subcellular localizations [144]. The molecular mechanisms underlying mitochondrial lncRNAs remain unclear, although they may play an essential role in regulating mitochondrial function and dynamics in the coordinated signaling system to maintain homeostasis of entire cells (extensively reviewed in [145,146]). Some other lncRNAs are sublocalized in exosomes by binding specific motifs via RBPs [147]. This sublocation may be related to their function as possible biomarkers, as described in section 4 "LncRNAs as biomarkers" of this review. In addition, high-throughput sequencing of ribosome-protected fragments (ribo-seq) analysis demonstrated that lncRNAs interact with ribosomes [148–150]. Although this is controversial (reviewed in [130,151]), some studies have demonstrated that lncRNAs may encode small polypeptides (also known as micropeptides) in certain circumstances [152], which raises the question whether lncRNAs are non-coding molecules. However, other studies have revealed that lncRNA association with ribosomes does not always indicate that they are actively translated [153].

In summary, lncRNAs can regulate gene expression at the epigenetic (e.g., DNA methylation, histone modification), transcriptional (e.g., recruitment of transcription factors), and post-transcriptional (e.g., modulation of miRNA and mRNA integrity) level (Fig. 3). Furthermore, lncRNAs may interact with DNA, RNA, miRNA, and protein complexes in order to perform their role and control a variety of physiological and pathological processes.

3. LncRNAs in AT

In the last few years, it has been postulated that lncRNAs act as coregulators in a wide range of processes, including AT development and function. As mentioned, numerous mechanisms are responsible for proper adipogenesis and functioning of WAT. BAT has is a myriad of activators, co-activators, transcription factors, and even miRNAs that have been described to play pivotal roles in the generation of adipocyte precursors (engrailed-1, myogenic factor 5), adipogenesis leading to mature brown adipocytes [PR domain containing 16 (PRDM16), peroxisome proliferator-activated receptor gamma (PPARγ), and
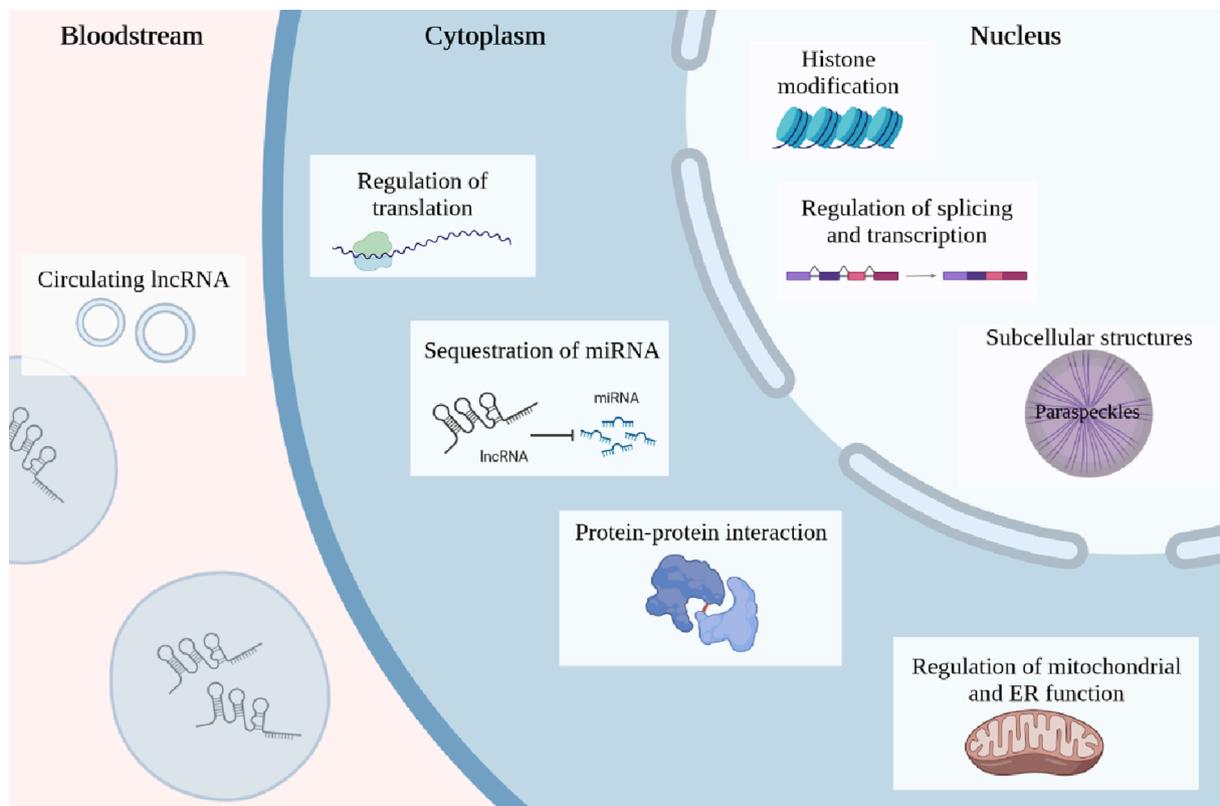
Fig. 3. LncRNA functions based on their location. In the nucleus, DNA-related interactions are highlighted. In the cytoplasm, lncRNAs interact primarily with RNA and proteins and regulate metabolism at the post-translational and post-transcriptional levels. Finally, lncRNAs can be excreted into the bloodstream to target other tissues or organs, emerging as excellent candidates for being used as biomarkers.

peroxisome proliferator-activated receptor gamma coactivator 1 (PGC1γ)], and transdifferentiation from white to beige adipocytes (irisin, meteorin-like protein) [154]. Thus, promoting the thermogenic potential is a tightly regulated process in which new regulators are constantly being discovered. Although these pathways have been studied extensively, it remains unclear how they are regulated by lncRNAs. Since most of these pathways have been described in animal models, it is crucial to unequivocally identify those related to human lncRNAs in terms of genomic or splicing signal sequence conservation, similar secondary structures, or syntenic transcription [155]. This would provide a strong background for the potential use of ncRNAs as therapeutic tools to treat metabolic diseases. The following section describes some of the lncRNAs responsible for regulating AT expansion and function that have been shown to be important in recent studies. The lncRNAs described in this section are summarized in Tables 1 and 2. The subcellular localization of each lncRNA has been collected from the databases LncATLAS [156] and BioGPS [157] and the tissue expression of these lncRNAs is shown in Fig. 4.

3.1. LncRNAs involved in AT in animal models

3.1.1. Steroid receptor RNA activator (SRA)

The steroid receptor RNA activator 1 (*Sra1)* gene encodes lncRNAs of different lengths and mRNA by alternative splicing [158]. SRA lncRNA is involved in numerous metabolic processes, including mammary gland development and muscle differentiation, and is related to the development of cancers, such as ovarian cancer [159]. Furthermore, SRA was the first lncRNA reported to be present in adipocytes [160].

SRA is highly expressed in WAT and BAT [158] and increases twofold during adipocyte differentiation. Its overexpression in the stromal cell line, ST2, induces differentiation of adipocytes *in vitro*, whereas knockdown showed the opposite effects in 3 T3-L1 white

adipocytes [161]. In addition, SRA promotes glucose uptake and reduces insulin resistance and *Sra* knockdown in mature 3 T3-L1 adipocytes led to a reduced number of insulin receptors [162]. Furthermore, *Sra* knockout in the WAT of mice led to resistance to high-fat diet (HFD)-induced obesity and a healthier phenotype with increased glucose tolerance, decreased fatty liver, decreased adipogenesis, reduced expression of inflammation-related genes, reduced plasma TNF-α levels, and improved insulin sensitivity [158]. Regarding its molecular mechanism, SRA binds to and coactivates *Pparγ*, which is the master transcriptional regulator of adipogenesis [161]. These results indicate that SRA is an essential regulator of obesity, fatty liver, and glucose homeostasis *in vivo* and may be a potential therapeutic target.

3.1.2. Adiponectin antisense (Adipoq-AS)

Within the *Adipoq* locus, Adipoq-AS is transcribed from the opposite strand to the *Adipoq* mRNA in mice and humans, presenting an overlapping sequence [163]. Like *Adipoq* mRNA, Adipoq-AS is expressed in AT and increases during differentiation of 3 T3-L1 white adipocytes. Although the expression levels of Adipoq-AS are lower than those of *Adipoq* mRNA, the half-life of Adipoq-AS is more than double that of *Adipoq* mRNA [163].

Adipoq is a hormone secreted by adipocytes that plays a complex but significant role in adipogenesis. It regulates glucose and lipid metabolism, and its overexpression was shown to increase insulin sensitivity in 3 T3-L1 cells and enhance cell proliferation. [164]. *Ob/ob* mice (genetically obese mouse model) overexpressing the *Adipoq* gene were shown to have a metabolically healthy phenotype but were predisposed to fat deposition [165]. In 2018, Cai *et al.* found that Adipoq-AS lncRNA delivered via adenovirus injection in HFD-fed animals prevented weight gain, reduced fat mass, and reduced the adipocytes size in both the WAT and BAT depots. Conversely, expression of *Ucp1*, *Pgc1α*, and *Prdm16* was increased in the epidydimal and inguinal WAT and in BAT. Circulating

Table 1
LncRNAs involved in AT function with evidence in animal models.

LncRNA	Tissue	Adipogenesis regulation	Sample's origin	Mechanisms	Localization	References
SRA	WAT, BAT	Positive	Stromal cells ST2, 3 T3-L1 adipocytes	Binds and coactivates Pparγ	Nucleus, cytoplasm	[157,158,161,300]
Adipoq-AS	WAT, BAT	Negative	3 T3-L1 adipocytes	Binds to Adipoq mRNA and inhibits its translation	Unknown	[163,166]
AK079912	WAT, BAT	Positive	Primary BAT and WAT stromal vascular fraction cells	Promoter of mitochondrial biogenesis mediated by Pgc1a and inducer of transcription of thermogenic genes mediated by Pparγ	Unknown	[168]
Xist	BAT	Positive	3 T3-L1 adipocytes	Binds C/ebpα to regulate brown differentiation	Nucleus	[156,157,169]
LncRNA-BATE1	BAT	Positive	Primary BAT stromal vascular fraction cells, 3 T3-L1 adipocytes	Interacts with hnRNPU	Nucleus, cytoplasm	[157,171]
LncRNA-BATE10	WAT, BAT	Positive	Primary BAT and WAT stromal vascular fraction cells, 3 T3-L1 adipocytes	Avoids Pgc1α degradation by sequestering Celf1	Nucleus, cytoplasm	[157,171,172]
Ctcflos	WAT, BAT	Positive	Primary BAT and WAT stromal vascular fraction cells, 3 T3-L1 adipocytes	Regulates transcription and alternative splicing of BAT key genes	Unknown	[173]
ADNCR	WAT	Negative	3 T3-L1 adipocytes, ADSCs	Sponges miR-204, leaving free SIRT1, a repressor of Pparγ	Unknown	[177]
PU.1-AS	WAT	Positive	Primary WAT stromal vascular fraction cells, 3 T3-L1 adipocytes	Binds and blocks PU.1, an inhibitor of adipogenesis	Unknown	[180,181]
SlincRAD	WAT	Positive	3 T3-L1 adipocytes	Epigenetic regulation of adipogenesis via DNMT1	Unknown	[183,184]
Lnc-U90926	WAT	Negative	3 T3-L1 adipocytes	Inhibits the transactivation of PPARγ2 or PPARγ.	Unknown	[185]
GM13133	WAT, BAT	Unknown	Primary BAT and WAT stromal vascular fraction cells	Involved in regulation of thermogenesis	Unknown	[186]
NEAT1	WAT	Positive	3 T3-L1 adipocytes, ADSCs	Associates with SRp40 to regulates *Pparγ* splicing	Nucleus	[77,156,157,187]
Paral1	WAT	Positive	3 T3-L1 and 3 T3-442A adipocytes	Co-activates and upregulates Pparγ transcriptional activity	Unknown	[188]
Lnc-leptin	WAT	Positive	Primary WAT stromal vascular fraction cells	Mediates loop formation between genomic loci of lep and lnc-leptin	Unknown	[189]
Lnc-RAP-1 (FIRRE)	WAT, BAT	Positive	Primary BAT and WAT stromal vascular fraction cells	Interacts with hnRNPU	Nucleus	[156,157,190]
Plnc1	WAT	Positive	3 T3-L1 adipocytes, C3H10T1/2 cells, stromal cells ST2, BMSCs	Reduces methylation *Pparγ2* promoter, enhancing its expression	Unknown	[193]
AK142386	WAT, BAT	Unknown	Primary BAT and WAT stromal vascular fraction cells	Targets Hoxa3 and regulates its transcription and expression	Unknown	[194]
AK133540	WAT, BAT	Unknown	Primary BAT and WAT stromal vascular fraction cells	Targets Acad10 and regulates its transcription and expression	Unknown	[194]
TCONS_00041960	WAT	Negative	Rat BMSCs	Inhibits adipogenesis by kidnapping miR-125a-3p, a regulator of GILZ, an inhibitor of PPARγ	Unknown	[195]
Gm15051	BAT	Unknown	Primary BAT adipocytes	Targets Hoxa1	Unknown	[196]
Tmem189	BAT	Unknown	Primary BAT adipocytes	Targets CEBPβ	Cytoplasm	[157,196]
Cebpd	BAT	Unknown	Primary BAT adipocytes	Targets CEBPδ	Nucleus	[157,196]
LncRNA 2310069B03Rik	WAT, BAT	Unknown	Primary BAT, WAT stromal vascular fraction cells	Unknown	Unknown	[197]

levels of Adipoq were also reduced in these animals, suggesting that the formation of a Adipoq-AS lncRNA/*Adipoq* mRNA duplex inhibited its translation resulting in the impairment of adipogenesis [163]. These results are consistent with the findings of a recent study by Spracklen *et al.* who analyzed data from over 9,000 patients and revealed an inverse relationship between Adipoq-AS1 expression and Adipoq plasma levels [166].

3.1.3. Ak079912

Uc009csb.1, also known as AK079912, is a lncRNA that was initially related to white adipogenesis [167]. Xiong *et al.* observed a 10-fold increase in expression of AK079912 in BAT compared with inguinal WAT and a 100-fold increase compared with epididymal WAT. Interestingly, there was a time-dependent decreased in lncRNA levels in BAT, which was potentially related to the gradual loss of thermogenic activity [168].

Based on this observation, the authors analyzed the expression of AK079912 lncRNA during brown adipocyte differentiation and in cold-stimulated white adipocytes and observed increased levels. Knockdown of AK079912 inhibited brown adipocyte differentiation and suppressed the expression of BAT-specific genes, whereas its overexpression promoted a thermogenic phenotype [168]. Overexpression of AK079912 also induced browning of WAT both *in vivo* and *in vitro*. Although a mechanistic approach is still needed, the authors proposed that AK079912 may play a role in the regulation of mitochondrial biogenesis via PGC1α and as a mediator of PPARγ-induced transcriptional activation of thermogenic genes [168].

3.1.4. Xist

Wu *et al.* recently proposed Xist as a potential regulator of BAT differentiation [169]. This lncRNA has been widely related to pathological

Table 2
LncRNAs involved in AT function with evidence in humans.

LncRNA	Tissue	Adipogenesis regulation	Sample origin	Mechanism	Localization	References
H19	WAT, BAT	Unknown	Human primary WAT adipocytes, primary BMSC lines	Binds the methylated binding factor (MBD1), downregulating the expression of paternally inherited genes that reduce mitochondrial biogenesis in BAT. Sponges miR-188, a positive regulator of WAT adipogenesis.	Cytoplasm	[156,157,200,202–204]
Blnc1	BAT	Positive	C3H10T1/2 cells, Primary BAT adipocytes	Stabilizes the Blnc1/ Zbtb7b/hnRNPU/EBF2 ribonucleoprotein complex	Plasma membrane	[157,206–208,210]
Lnc-dPrdm16	WAT, BAT	Positive	Human fetal BAT	Prdm16 stabilization in WAT browning; unknown in BAT	Unknown	[211]
HOTAIR	WAT	Unknown	Primary WAT adipocytes, ASDCs, immortalized multipotent adipose-derived (iMAD) cells, 3 T3-L1 cells	Acts via DNA methylation and has been associated with transcriptional regulation of adipogenic genes	Nucleus	[156,212,214–217]
UC.417	BAT	Negative	Primary BAT stromal vascular fraction cells	Reduces p38 MAPK phosphorylation	Unknown	[196,218]
Dio3os	BAT	Positive	Primary BAT stromal vascular fraction cells	Directly inhibits Dio3 expression. Potential inhibition of miRNA-122	Nucleus	[156,221]
LINC00473	BAT	Positive	Human primary adipocytes from stromal vascular fraction	cAMP/CREB-dependent activation of UCP1 promoter. Lipolysis activator and potential role sequestering miRNA-15a	Nucleus	[156,157,225]
HoxA-AS3	WAT	Positive	Human ADSCs, mouse ADSCs	Acts via EZH2, a switch for adipogenesis and osteogenic differentiation, promoting transcription of osteogenic genes	Cytoplasm	[156,229]
MIR31HG	WAT	Positive	Human ADSCs	Acts on the FABP4 gene, triggering histone methylation and acetylation, enhancing its expression	Cytoplasm	[156,232]
FoxC2-AS1	WAT	Unknown	Human primary WAT adipocytes	Unknown	Unknown	[234]
HOXA11-AS1	WAT	Positive	Human primary WAT adipocytes	Regulates adipogenesis by upregulating adipogenic-related genes	Nucleus	[157,235]
ADINR	WAT	Positive	Human ADSCs	ADINR induces C/EBPα gene expression during adipogenesis via MLL3/4	Unknown	[236]
MEG3	WAT	Unknown	Human ADSCs, 3 T3-L1 adipocytes, rat primary BMSC lines	Inhibits adipogenesis via miR-140-5p in hADSCs and rat BMSCs. Promotes adipogenesis in 3 T3-L1 via the miR-217/Dkk3 axis	Nuclear	[156,238,239,301]
ecCEBPA	Unknown	Positive	Leukemic cell lines HL-60 and U937	Avoids methylation of promoter C/EBPα and leads to its overexpression	Unknown	[240]
ASMER	WAT	Positive	Human primary WAT adipocytes	Unknown	Unknown	[241]
Gm15290	WAT	Positive	hMADS-2, hMADS-3	Sponges miR-27b, an inhibitor of PPARc and C/EBPα	Unknown	[242,243]
LncRNA RP11-20G13.3	WAT	Positive	Human primary WAT adipocytes	Unknown	Unknown	[244]
LINC00968	WAT	Unknown	Human primary WAT adipocytes	Unknown	Nucleus	[156,244]
AC011891.5	WAT	Unknown	Human primary WAT adipocytes	Unknown	Unknown	[244]
GYG2P1	WAT	Unknown	Human primary WAT adipocytes	Unknown	Unknown	[244]
RP11-529H2.1	WAT	Unknown	Human primary WAT adipocytes	Unknown	Unknown	[244]
OLMALINC	WAT	Unknown	Human primary WAT adipocytes	Unknown	Nucleus	[156,244]

conditions, such as cancer, fibrosis, and inflammation [170]. The authors reported that Xist levels increased during brown adipocyte differentiation *in vitro*. Overexpression of Xist during differentiation increased the expression of BAT marker genes, such as *Ucp1*, CCAAT enhancer binding protein (*C/ebp*) α, and *Pparγ* [169]. Conversely, the expression of these genes was reduced after Xist silencing during differentiation. However, by *Xist* silencing in mature brown adipocytes showed no effects. Moreover, RNA immunoprecipitation assays demonstrated that Xist may directly bind *C/ebpα* to regulate brown differentiation [169]. Although there is no evidence of a potential adipogenic role in human BAT, if confirmed, this could provide new insight into the biological differences of BAT between men and women beyond hormonal control.

3.1.5. LncRNA-BATE1 and LncRNA-BATE10

In 2015, murine transcriptome profiling analysis revealed that 40 lncRNAs were upregulated during BAT adipogenesis [171]. Both lnc-BATE1 and lnc-BATE10 were found to be specifically highly expressed in murine brown adipocytes both *in vivo* and *in vitro*. Knockdown of these lncRNAs did not cause a significant impact on lipid accumulation during brown adipogenesis but reduced the expression of common BAT marker genes, such as *Ucp1* and *Pgc1α*. Furthermore, ablation of these regulatory RNAs reduced the expression of *Ucp1* and *Pgc1α* during the transdifferentiation of white adipocytes into beige adipocytes, suggesting a pivotal role of lnc-BATE1 and lnc-BATE10 in browning [171,172]. Knockdown of *lnc-BATE1* resulted in lower mitochondrial oxygen consumption [171], whereas suppression of *lnc-BATE10* hindered norepinephrine-mediated thermogenesis in brown adipocytes [172].

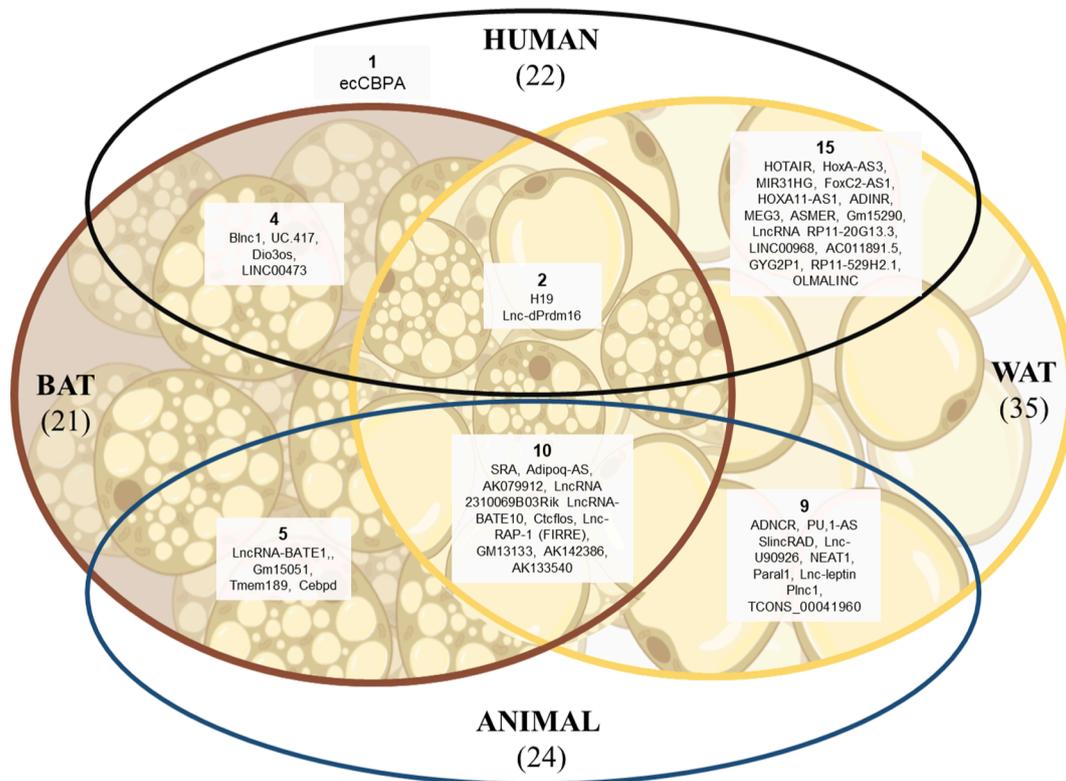It was shown that lnc-BATE1 can act in *trans* to regulate brown

Fig. 4. Venn diagram showing the localization and distribution of lncRNAs in AT. Values in brackets represent the number of lncRNAs belonging to animals and humans or BAT and WAT. Common areas contain the numbers and names of the exclusive lncRNAs within the overlapping groups. The diagram includes all of the lncRNAs summarized in this review. The diagram is structured using the following groups: exclusive to human WAT (15 lncRNAs); exclusive to human BAT (4 lncRNAs) and human WAT and BAT (2 lncRNAs); exclusive to animal WAT (9 lncRNAs) and exclusive to animal BAT (5 lncRNAs) and animal WAT and BAT (10 lncRNAs).

adipogenesis by controlling the expression of BAT-specific genes (including *Dio2*, *Ucp1*, and *Pparα*) and adipogenic genes (such as *C/ebpα* and *Pparγ*). RNA immunoprecipitation analysis revealed that lnc-BATE1 interacts with heterogeneous nuclear ribonucleoprotein U (hnRNPU) to form a functional ribonucleoprotein [171]. Meanwhile, lnc-BATE10 competitively binds Celf1, which is an RNA-binding protein that targets *Pgc1α* mRNA, causing its degradation [172].

3.1.6. CCCTC-binding factor (zinc finger protein)-like, opposite strand (Ctcflos)

Bast-Habersbrunner *et al.* used whole-transcriptome analysis of primary beige preadipocytes from different mouse strains to identify 198 lncRNAs [173] that were correlated with UCP1 expression, significantly regulated during white-to-brown differentiation, and responded to rosiglitazone *in vitro*. In parallel, they analyzed lncRNA expression in cold-induced BAT from BL/6J mice. These *in vitro* and *in vivo* approaches to examining browning and thermogenesis control identified seven common regulatory lncRNAs, among which the top three were isoforms of Ctcflos lncRNA [173].

Knockdown of Ctcflos variants during browning *in vitro* reduced *Ucp1* mRNA levels without affecting lipid accumulation. Similarly, lack of Ctcflos impaired brown adipocyte differentiation and function; however, this was not seen in white adipocytes, suggesting a selective role in thermogenic adipocytes [174]. Besides the regulation of the thermogenic gene expression, the authors demonstrated that Ctcflos regulates alternative splicing of target genes, such as *Prdm16*, suggesting that this lncRNA is capable of regulating gene expression to select more active isoforms [174].

3.1.7. ADNCR

ADNCR is a competing endogenous RNA for miR-204, which is involved in adipocyte differentiation and inhibits the expression of Sirtuin 1 (SIRT1; a repressor of the *Pparγ* gene) to promote adipogenesis [175,176]. ADNCR sponges miR-204, leaving free SIRT1 to bind to its cofactors, nuclear receptor co-repressor and silencing mediator of retinoid and thyroid hormone receptors. This leads to inhibition of *Pparγ* expression and adipocyte differentiation in 3 T3-L1 cells [177–179]. SIRT1 overexpression decreased adipogenesis in 3 T3-L1 cells, whereas silencing of SIRT1 via RNA interference enhanced adipogenesis [178]. ADNCR was the most downregulated lncRNA during differentiation of bovine adipocyte-derived stem cells (ADSCs). Li *et al.* reported that ADNCR overexpression impaired adipogenesis, decreased the number of mature adipocytes, increased SIRT1 levels, and significantly decreased the expression of PPARγ, C/EBPα, and fatty acid binding protein 4 (FABP4), whereas ADNCR knockdown increased PPARγ and FABP4 expression [177].

3.1.8. PU.1 antisense (PU.1-AS) lncRNA

PU.1 regulates a wide range of pathways, including adipogenesis. *PU.1* is strongly related to insulin resistance and inhibition of adipocyte differentiation in 3 T3-L1 cells. PU.1-AS lncRNA is transcribed from the opposite DNA strand and overlaps with sense *PU.1* mRNA [180]. Several studies have confirmed the inhibitory role of PU.1-AS in different animal models, including murine [181] and porcine [182] adipocytes. PU.1-AS knockdown inhibits adipogenesis and promotes the expression of PU.1 protein in both preadipocytes and adipocytes. Furthermore, repression of PU.1-AS led to decreased *Adipoq* expression and secretion in mature adipocytes of C57BL/6 male mice [181]. These results indicate that PU.1 is an inhibitor of preadipocyte differentiation and is blocked by PU.1-AS to promote adipogenesis.

3.1.9. Super-long intergenic ncRNA functioning in adipocyte differentiation (slincRAD)

SlincRAD is an essential lncRNA for AT expansion. Its expression is upregulated in the early stages of 3 T3-L1 differentiation and decreases to remain stable during the later stages [183]. Zhang *et al.* demonstrated that slincRAD knockdown in 3 T3-L1 cells led to impaired expression of adipogenic markers and an imbalanced AT development, with smaller adipocytes, decreased lipid accumulation, and decreased *Pparγ* and *Fabp4* expression. Furthermore, these adipocytes showed unregulated glucose and lipid metabolism, defective epigenetic regulation, and impaired adipogenesis [184]. Although the mechanisms of slincRAD remain unclear, it appears to be involved in clonal expansion together with DNA methyltransferase 1 (DNMT1), regulating adipogenesis via epigenetic processes [183].

3.1.10. Lnc-U90926

Lnc-U90926 is an adipogenesis regulator whose expression is negatively correlated with adipocyte differentiation in 3 T3-L1 cells [185]. It is mainly expressed in WAT and its levels are lower in obese mice. Overexpression of lnc-U90926 impaired adipogenesis, decreased lipid accumulation, decreased mRNA levels of *Pparγ2*, *Fabp4*, and *Adipoq* (but not *C/ebpα*), and reduced protein levels of PPARγ2 and FABP4. In contrast, knockdown of lnc-U90926 showed the opposite effects and enhanced adipogenesis, with significant increases in *Pparγ2*, *C/ebpα*, *Fabp4*, and *Adipoq* mRNA levels, PPARγ and FABP4 protein levels, and lipid accumulation [185]. These results suggest that lnc-U90926 inhibits *Pparγ2* promoter transactivation. However, further studies are needed to determine its mechanism of action since lnc-U90926 is located in the cytoplasm and it does not seem to interact directly with the *Pparγ2* promoter [185].

3.1.11. GM13133

You *et al.* published novel data about GM13133, a 736-bp lncRNA transcribed in the opposite direction from the first intron of PRDM16 in mice; however, no homology or synteny has been observed in humans. It was found to be predominantly expressed in BAT, although its expression is not modified by cold or β3-adrenergic agonist treatment [186]. Overexpression of GM13133 *in vitro* increased the expression of BAT markers and mitochondrial DNA, although there is not enough evidence to show whether it impacts thermogenic activity. Although oxygen consumption rates were measured, the results showed no differences in basal respiration or proton leak compared with control cells and the lack of a normalization method may invalidate these results. In addition, no evidence of *Gm13133* ablation *in vitro* was presented [186]; therefore, further *in vivo* studies should be carried out to evaluate the potential of this lncRNA.

3.1.12. Nuclear enriched abundant transcript 1 (NEAT1)

NEAT1 is a lncRNA that is highly abundant in nuclei, essential for paraspeckles, and involved in adipogenesis [187]. NEAT1 expression presents a variable profile during adipocyte differentiation and regulates *Pparγ2* splicing during adipogenic differentiation of 3 T3-L1 cells. Furthermore, downregulation of NEAT1 decreases lipid accumulation and reduces the expression of *C/ebpα* and *Pparγ* but re-expression of NEAT1 rescues the adipogenic phenotype [77,187]. The published information on its mechanism of action is minimal. It appears that NEAT1 regulates *Pparγ* splicing during adipogenesis via SRp40, which is a protein responsible for regulating the alternative splicing of pre-mRNA [187].

3.1.13. PPARG activating RBM14 associated lncRNA 1 (Paral1)

Paral1 is exclusive to mature adipocytes. Its expression is positively correlated with PPARγ expression and a decrease in diet-induced obesity or genetic mouse models of obesity [188]. Little is known about its mechanism, except that Paral1 acts by co-activating and upregulating *Pparγ* transcriptional activity. In 3 T3-L1 cells, Paral1 downregulation significantly decreased lipid accumulation and adipogenic gene expression *in vitro*. Surprisingly, overexpression of Paral1 did not reverse this effect, demonstrating that Paral1 is necessary but not sufficient for adipogenesis [188].

3.1.14. Lnc-leptin

Lnc-leptin plays a regulatory role in *leptin* expression and is necessary to maintain *leptin* levels. Its expression is closely correlated with *leptin* expression in adipocytes from mouse inguinal and epididymal WAT [189]. Moreover, knockdown of lnc-leptin showed impaired adipogenesis, whereas overexpression of lnc-leptin did not affect *leptin* or other adipocyte markers. These results provide evidence that lnc-leptin is necessary but not sufficient to regulate *leptin* expression and its effects on adipogenesis [189]. Although its mechanisms remain unclear, the authors proposed that lnc-leptin forms a loop with the lep loci to enhance its expression.

3.1.15. Polyadenylated lncRNA

Polyadenylated lncRNA (lnc-RAP-n) is a group of 10 lnc-RNAs that are required for the differentiation and maturation of adipocytes and were identified in a study on primary adipocytes from mouse WAT and BAT. Twenty lnc-RAPs were upregulated during adipocyte differentiation and knockdown using RNA interference impaired white pre-adipocyte differentiation and reduced the expression of *Adipoq, C/ebpα, Fabp4*, and *Pparγ* [190]. Among the 20 lnc-RAPs, lnc-RAP-1, also known as Functional Intergenic Repeating RNA Element (Firre), was localized on the X-chromosome. Firre mediates the expression of indispensable adipogenic factors binding to hnRNPU in *trans* [191,192].

3.1.16. Plnc1

Zhu *et al.* identified Plnc1 as a regulator of adipogenesis as it is transcribed −25,000 bp upstream of the *Pparγ2* gene. They reported that Plnc1 was upregulated in obese mice and its knockdown inhibited adipocyte differentiation in ST2 cells and bone marrow stem cells (BMSCs) and diminished the expression of adipocytes markers, such as *Pparγ2, C/Ebpα*, and adipocyte protein 2 (*Ap2*), whereas Plnc1 overexpression showed the opposite results [193].

Plnc1 decreases *Pparγ* promoter methylation of the CpG region and promotes its expression, enhancing adipocyte differentiation and, consequently, adipogenesis [193].

3.1.17. AK142386 and AK133540

AK142386 and AK133540 were both described by Chet *et al.* after performing lncRNA microarray analysis to evaluate the expression profiles of WAT and BAT from C57BL/6 J mice. AK142386 and AK133540 target Hoxa3 and Acad10 to regulate WAT and BAT adipogenesis and metabolism. Unfortunately, information about their role is limited and further studies are required to understand their mechanisms [194].

3.1.18. TCONS_00041960

TCONS_00041960 was shown to be involved in adipogenic and osteogenic differentiation in glucocorticoid-treated BMSCs from Sprague–Dawley rats. TCONS_00041960 enhances osteogenic differentiation and inhibits adipogenesis by targeting miR-125a-3p, which is a regulator of glucocorticoid induced leucine zipper, that inhibits PPARγ [195]. However, there is insufficient information on this lncRNA and further studies are required.

3.1.19. Gm15051, Tmem189, and Cebpd

Microarray technology identified Gm15051, Tmem189, and Cebpd as potential regulators of brown adipogenesis in C57BL/6 J mice. These lncRNAs were selected among 1,064 lncRNAs due to their proximity to *Hoxa1, C/ebpβ*, and *C/ebpδ* genes, which play a crucial role in adipogenesis [196].

3.1.20. LncRNA 2310069B03Rik

RNA sequencing (RNA-seq) analysis of BAT and inguinal WAT of cold-stimulated mice revealed 2310069B03Rik as the only lncRNA that was upregulated in both tissues [197]. This lncRNA was also upregulated in both tissues after β3-adrenergic stimulation and PPARγ agonist treatment. However, subsequent experiments were not able to clearly demonstrate a cause and effect relationship to consider this lncRNA as a potential candidate at this stage [197].

3.2. LncRNAs involved in adipose tissue in humans

In this section we have listed some lncRNAs that have been identified in human AT. Although the vast majority of lncRNAs have been studied in animal models, in recent years homologous lncRNAs have been found in humans. However, their implementation in human therapy still has many limitations due to the little available information of lncRNAs in humans, and due to the fact that obtaining human samples is sometimes complicated, especially for BAT. Because of this, many of these lncRNAs have been more extensively studied in animals than in humans. In this section we focus specifically on those that have been isolated from human samples.

3.2.1. H19

LncRNA H19 is a maternal imprinted gene located on human chromosome 11 whose regulatory roles in diseases, such as cancer [198] and diabetes [199], have been widely described. In addition to this myriad of roles, Schmidt *et al.* reported that its expression changed in BAT from mice exposed to cold or fed an HFD. The authors used gain and loss-of-function approaches in primary brown preadipocytes to describe a regulatory role of H19 in brown adipogenesis and oxidative metabolism [200]. *In vivo*, the ubiquitous overexpression of H19 in HFD-fed mice prevented weight gain by increasing energy expenditure, whereas selective knockdown of H19 in fat made HFD-fed mice more prone to obesity. In lean and obese humans, H19 expression was shown to be inversely correlated with BMI in subcutaneous and visceral WAT and positively related to *UCP1* mRNA levels [200].

Concerning gene expression, H19 acts as a *trans* regulator to bind the methylated binding factor, downregulate the expression of paternally inherited genes that predispose to obesity, and reduce mitochondrial biogenesis exclusively in BAT [200]. Although Schmidt *et al.* showed no impact of H19 on WAT, Huang *et al.* proposed a different mechanism. H19 has been shown to drive the fate of BMSCs toward an osteogenic program [201]. It appears to play an inhibitory role in adipogenic differentiation of BMSCs via epigenetic modification along with miR-675, which targets histone deacetylases (essential molecules in adipogenesis). H19 and miR-675 are downregulated during adipogenic differentiation and knockdown of H19 increases the expression of PPARγ, C/EBPα, and FABP4, whereas overexpression of H19 and miR-675 compromises adipogenesis [202,203]. Furthermore, the expression levels of H19 are negatively correlated with miR-188. Downregulation of H19 leads to overexpression of miR-188, inhibits the effect of ligand-dependent corepressor, and promotes adipogenesis in WAT [204,205]. Thus, the observations by Schmidt *et al.* who found that H19 had no impact on white adipogenesis may be explained by the early role of H19 selecting an osteogenic fate of precursor cells to the detriment of preadipocytes.

3.2.2. Brown fat lncRNA 1 (Blnc1)

Zhao *et al.* used transcriptional profiling arrays to identify 21 lncRNAs that were overexpressed in BAT and β3 adrenergic-stimulated WAT, and during brown adipocyte differentiation. Among these, three were highly conserved intergenic lncRNAs, but only one affected adipogenesis when silenced. This lncRNA, identified as AK038898, was then renamed Blnc1 [206].

In vitro gain and loss-of-function studies revealed Blnc1 as a key factor during thermogenic adipocyte development in brown and beige adipocytes. A full-length human transcript of Blnc1 was created and different truncated mutants were transfected into mouse brown pre-adipocytes [207]. This allowed identification of the conserved region that is required to promote the thermogenic program by stabilizing the Blnc1/Zbtb7b/hnRNPU/EBF2 ribonucleoprotein complex [207,208]. Early B-cell factor 2 (EBF2) collaborates with PPARγ to enhance the expression of crucial BAT markers, such as PRDM16, which are critical for the development of the thermogenic phenotype [209].

Finally, an *in vivo* approach in which fat-specific Blnc1 transgenic mouse and conditional knockouts were fed an HFD demonstrated that Blnc1 is also critical for maintaining adaptive thermogenesis [210].

3.2.3. Lnc-dPrdm16

In 2018, a *de novo* reconstruction of the transcriptome of human fetal BAT, subcutaneous WAT, and omental WAT using deep RNA-seq yielded two main improvements to the preexisting lncRNA database, GENCODE. First, it revealed more than 2,000 new unannotated lncRNAs and second, it showed that lncRNAs are almost 25 times more tissue-specific than mRNAs [211]. This *in silico* analysis also revealed 54 pairs of conserved lncRNA–mRNA between mice and humans related to canonical pathways in AT. Among these, the authors focused on lnc-dPrdm16, which is located divergently from Prdm16. *In vitro*, knockdown of lnc-dPrdm16 reduced lipid accumulation and expression of BAT markers during differentiation of white and brown adipocytes [211].

In addition, lnc-dPrdm16 silencing via shRNA-associated adenovirus reduced the expression of BAT markers when injected into WAT and BAT after browning and cold-induced thermogenesis, respectively [211]. Although the regulatory mechanisms have not yet been elucidated, it is interesting to highlight that lnc-dPrdm16 silencing reduced *PRDM16* mRNA levels in WAT but not BAT, which raises the question whether the regulatory mechanism of this lncRNA could be depot-specific or related to PRDM16.

3.2.4. HOX antisense intergenic RNA (HOTAIR)

Further studies are required to understand the role of HOTAIR, which remains controversial. HOTAIR was initially shown to be exclusively related to subcutaneous preadipocyte differentiation in human gluteal fat. Its ectopic expression upregulated the adipogenic markers *PPARγ*, lipoprotein lipase, and *FABP4* but did not increase the proliferation rate [212,213]. Later studies corroborated the importance of HOTAIR in adipogenesis. Silencing HOTAIR diminished the expression of adipogenic markers and led to defects in adipogenesis in mice [214,215]. Furthermore, the results in human cells were similar. HOTAIR knockout in AT resulted in gluteal–femoral fat defects [216] evidencing its indispensable role in the development of adipocytes. However, Kuo *et al.* recent demonstrated that HOTAIR overexpression in human abdominal preadipocytes showed anti-adipogenic effects along with significant changes in both DNA methylation and gene expression during abdominal adipogenesis [217]. These findings indicate that HOTAIR may play an important role in the epigenetic regulation of adipogenesis, although further studies are required.

3.2.5. UC.417

You *et al.* identified 1,064 lncRNAs that were differentially expressed during brown adipocyte differentiation in mice. Among these, the ultra-conserved lncRNA UC.417 was highly upregulated in mature brown adipocytes compared with brown preadipocytes [196]. UC.417 exhibits high homology within species, including 100 % sequence homology between mice and humans. However, unlike lnc-BATE, UC.417 is postulated to be a negative regulator of brown adipogenesis and thermogenesis since its overexpression caused a reduction in fat accumulation in BAT, limited expression of thermogenic markers, and reduced mitochondrial size, number, and respiration [218]. In parallel, cold and chemical-induced thermogenesis caused a reduction of UC.417 levels; however, knockdown of *UC.417* in brown preadipocytes did not exert any effects during differentiation. Gene chip analysis of preadipocytes

overexpressing UC.417 suggested its role in the p38 MAPK pathway [218]; however, further studies are required since different isoforms of p38 may exhibit opposite roles in brown fat differentiation [219].

3.2.6. DIO3 opposite strand upstream RNA (DIO3OS)

DIO3 encodes type 3 iodothyronine deiodinase (D3), which inactivates the thyroid hormones, T4 and T3, converting them into inactive metabolites. T3 has been shown to play a crucial role in brown adipocyte differentiation during embryogenesis [220]. Knockout of BAT-specific *Dio3* triggered early exposure of embryonic BAT to T3, resulting in a long-term upregulation of thermogenic genes [220].

Mouse and human DIO3OS, which show around 25 % homology, overlap with the DIO3 gene, although they are transcribed in opposite directions. *In vitro*, CRISPR–Cas9 knockdown of *Dio3os* in mouse embryonic fibroblasts activated DIO3 expression, which reduced T3 levels and PRDM16 expression and thus, inhibited brown adipogenesis. Conversely, *Dio3os* overexpression promoted brown adipogenesis and thermogenesis, although this was ablated when *Dio3* was also overexpressed, suggesting *Dio3* inhibition as the primary mechanism involved in DIO3OS-induced adipogenesis. These results were also reproduced *in vivo* by injecting a *Dio3os* adeno-associated virus into the interscapular BAT of mice neonates. Five weeks later, lower body weight gain, increased BAT mass, and reduced D3 content were observed [221].

In addition to direct inhibition of Dio3 expression, other mechanisms may explain the regulatory roles of Dio3os lncRNA. Specifically, Dio3os binds and inhibits miRNA-328 in hepatocellular carcinoma [222] and miRNA-122, which suppresses cell proliferation in pancreatic cancer cells [223]. It is attractive to speculate that the latter mechanism may also be involved in Dio3os-mediated adipogenesis since miRNA-122 has been negatively associated with BAT activity in humans [224].

3.2.7. LINC00473

In 2020, Tran *et al.* investigated the potential role of LINC00473 as a regulator of thermogenesis in human adipocytes [225]. LINC00473 is located on chromosome 6 and has been classified as an oncogenic lncRNA as it has been shown to promote cell proliferation, migration, and invasion in several types of cancer cells [226,227].

RNA-seq analysis of norepinephrine-stimulated adipocytes from abdominal subcutaneous fat and supraclavicular AT revealed that LINC00473 was among the most upregulated genes following thermogenic induction and adipogenesis [225]. Although initially there is a low abundance of this lncRNA in the nuclei of the cells, it may regulate thermogenesis via activation of the Ucp1 promoter in a cAMP/CREB-dependent mechanism. After norepinephrine or forskolin-mediated induction, LINC00473 translocates to the cytoplasm where it participates in the stabilization between lipid droplets and mitochondria, coordinating lipolysis [225]. Finally, a regulatory mechanism as a competitive endogenous lncRNA cannot be ruled out, although this has not been empirically demonstrated. In cancer cells, LINC00473 sequesters miR-15a, which acts as a tumor suppressor and has been demonstrated to participate in human adipocyte differentiation [228].

3.2.8. HoxA-AS3

HoxA-AS3 lncRNA is encoded by the *HoxA* loci and plays a regulatory role in MSC differentiation. Its expression is upregulated during adipogenesis of human and mouse BMSCs, whereas it is downregulated in osteogenic differentiation [229]. Furthermore, *in vitro*, knockdown of *HoxA-AS3* showed impaired adipogenesis and decreased the expression of adipogenic markers PPARγ, C/EBPα, ADIPOQ, and FABP4 in hBMCs while promoting the expression of osteogenic markers, calcium deposition and bone formation. *In vivo*, *HoxA-AS3* knockdown enhanced bone formation 2.6-fold and 2.2-fold in the HoxA-AS3-sh1 and HoxA-AS3-sh2 human MSC groups, respectively [229].

Hox is believed to act via EZH2, which is a component of the polycomb repressive complex that works as a switch for adipogenesis and osteogenesis, repressing transcription of osteogenic genes by catalyzing

the methylation of histone 3 lysine 27 [229]. These results demonstrate that HoxA-AS3 is required to inhibit osteogenic differentiation and promote adipogenesis.

3.2.9. MIR31HG

The *MIR31* gene is located on chromosome 9 and encodes MIR31HG (also known as LOC554202). Initially, MIR31HG was exclusively related to cancer and cell proliferation [174,230,231] but it was later identified as a regulator of osteogenic and adipogenic differentiation. MIR31HG is involved in adipocyte differentiation *in vitro* and *in vivo* in primary ADSCs from healthy humans and shows a variable expression profile during adipocyte differentiation. Moreover, knockdown of *MIR31HG* inhibited adipocyte differentiation and enhanced osteogenic differentiation, whereas *MIR31HG* overexpression promoted adipogenesis [232].

MIR31HG acts directly on the *FABP4* gene, triggering histone methylation and acetylation, enhancing its expression. Depletion of MIR31HG by gene silencing compromises adipogenesis [232]. In addition, MIR31HG promotes inflammation via nuclear factor-κB (NF-κB), which promotes osteogenic differentiation of human ADSCs [233].

3.2.10. Forkhead box protein C2 antisense (FoxC2-AS1)

Wang *et al.* investigated the potential mechanism of lncRNA FoxC2-AS1 as a regulator of white adipocyte differentiation and browning in human subcutaneous adipocytes [234]. FoxC2-AS1 is located on chromosome 16 and transcribed from the negative strand of FOXC2 [234]. *FOXC2-AS1* is downregulated during white adipogenesis but its transcription is increased after browning stimulation. Gain and loss-of-function studies showed no effect on white adipogenesis but it may promote the browning process of white adipocytes. To support this theory, the authors presented protein levels of key markers measured by Western Blot and oxygen consumption rates measured by Seahorse [234]. Unfortunately, the quantification of the Western Blot did not match the blots shown in the figures and the Seahorse analysis lacked biological replicates; therefore, in our opinion, more robust evidence should be presented to consider this antisense lncRNA as a potential regulator of thermogenesis.

3.2.11. HOXA11-AS1

Nuermaimaiti *et al.* demonstrated that HoxA11-AS1 is involved in adipocyte differentiation. The expression levels of HOXA11-AS1 were higher in differentiated human ADSCs compared with control undifferentiated ADSCs and was positively correlated with the expression levels of adipogenic genes, such as *C/EBPα, CIDEC, Perilipin,* and *Diacylglycerol acyltransferase 2* [235]. Furthermore, *HOXA11-AS1* knockdown impaired adipocyte differentiation, decreased lipid accumulation, and reduced the expression of adipogenic genes. Finally, expression levels of HOXA11-AS1 and adipogenic markers were higher in obese individuals compared with non-obese individuals. These results demonstrate the role of HOXA11-AS1 in adipogenesis [235].

3.2.12. Adipogenic differentiation-induced noncoding RNA (ADINR)

ADINR is located ~ 450 bp upstream of the *C/EBPα* gene and is co-expressed with *C/EBPα* during adipogenic differentiation. In human MSCs, ADINR is drastically upregulated 20 to 30-fold during differentiation. Moreover, *ADINR* knockdown is related to a decrease in *C/EBPα* and *PPARγ* expression and leads to defects in adipogenesis that is not reversible through the expression of ADINR in *trans* [236]. Although its mechanism of action remains unclear, the authors propose a model in which ADINIR promotes *C/EBPα* transcription activity in *cis* through PA1, which is a subunit of the histone methylation complex MLL3/4, although further studies are needed to corroborate this hypothesis [236].

3.2.13. Maternally expressed gene 3 (MEG3)

MEG3 is an imprinted gene located on chromosome 14 in humans and chromosome 12 in mice [237]. This lncRNA is involved in the

adipogenic and osteogenic differentiation of human ADSCs [195]. Numerous studies have identified the effect of MEG3 on adipogenesis but there is controversy concerning its mechanism. MEG3 inhibits adipogenic differentiation sponging miR-140-5p, which promotes adipogenesis, and its expression is downregulated during adipogenic differentiation in rat BMSCs [238] and human ADSCs [239].

3.2.14. *Extra-coding C/EBPα (ecCEBPA)*

EcCEBPA was discovered by Di Ruscio *et al.* in the HL-60 and U937 leukemic cell lines. It is encoded from the upstream *C/EBPα* gene on chromosome 19 and interacts with DNMT1. Consequently, the *C/EBPα* promoter is prevented from being methylated, leading to its overexpression. This mechanism could promote adipogenesis epigenetically but there is still very little information about its role in AT [240].

3.2.15. *Adipocyte-specific metabolic related lncRNA (ASMER)*

Gao *et al.* found that adipocyte-specific metabolic-related lncRNAs (ASMER) 1 and 2 were upregulated in the AT of obese humans and mice, suggesting that they play a significant role in adipogenesis, lipolysis, and obesity. Knockdown of both ASMERs led to a significant decrease in Adipoq release, PPARγ expression, and lipid accumulation [241].

3.2.16. *Gm15290*

Gm15290 promotes adipogenesis in *ob/ob* mouse adipocytes by sponging miR-27b, which is associated with human obesity and T2D [242]. Overexpression of Gm15290 enhances C/EBPα, PPARγ, and AP2 expression in human multipotent adipose-derived stem cells 2 and 3, whereas decreased miR-27b levels and Gm15290 knockdown had the opposite effect, leading to a decrease in lipid accumulation and body weight *in vivo* [243].

3.2.17. *LncRNA RP11-20G13.3, LINC00968, AC011891.5, GYG2P1, RP11-529H2.1, and OLMALINC*

The lncRNA expression profiles of four obese children and four non-obese children was selected randomly and analyzed by microarray and showed that lncRNA RP11-20G13.3, LINC00968, and AC011891.5 were upregulated, whereas GYG2P1, RP11-529H2.1, and OLMALINC were downregulated in the obese group [244]. In addition, knockdown of RP11-20G13.3 in SW872 adipocytes reduced lipid accumulation and PPARγ, C/EBPα, and Adipoq expression during adipogenic differentiation. These results identified a group of lncRNAs that regulates adipogenesis *in vivo* and *in vitro*, although further studies are required to understand their mechanisms [244].

4. LncRNAs as biomarkers

The deregulation of the lncRNAs may occur during the development of AT-related diseases, altering the expression of their target genes and affecting underlying pathophysiological molecular and cellular pathways. LncRNAs act intracellularly and may also be secreted by adipocytes and transported via the bloodstream to other cells or tissues, where they are considered to be circulating lncRNAs [245]. Therefore, they may contribute to intercellular communication as autocrine, endocrine, or paracrine molecules [245,246], although the exact process of lncRNA release into the extracellular environment is unknown.

Circulating lncRNAs have been at the vanguard of biomarkers in recent years. The National Institutes of Health of the United States defines a biomarker as a specified property that is measured as an indicator of normal biological processes, pathogenic processes, or response to an exposure or intervention [247]. Despite the abundance of ribonucleases in various body fluids, studies have revealed the presence of lncRNAs in these samples that can successfully resist ribonuclease degradation activities. RNA-seq of human blood exosomes revealed the presence of many lncRNAs [248]. The remarkable stability of lncRNAs while circulating in human fluids, especially when incorporated in exosomes or apoptotic bodies, is one of the key benefits that makes them useful as diagnostic, prognostic, and monitoring biomarkers (Fig. 5A). Furthermore, lncRNAs may be released in an exosome-independent mechanism into bodily fluids, where they may form complexes with high-density lipoprotein or protein Argonaute 2, similar to miRNAs [249]. Therefore, circulating lncRNAs have been identified as highly sensitive, specific, and reproducible biomarkers for severe diseases, and they have been suggested as promising markers for some AT-related disorders, including diabetes and obesity (Fig. 5B), as will be reviewed in the next section. Despite the fact that many published studies fail to identify the lncRNAs' tissue of origin due to the lack of biopsies or their difficult access, bioinformatic tools can alternatively provide information about the cell types and tissues where they are usually expressed, demonstrating their relevance to disease mechanisms and developmental processes (Tables 1-3) [250–252].

4.1. *Circulating lncRNAs in obesity*

Observing changes in obesity-derived circulating lncRNA is crucial to understanding the underlying pathogenesis and pathophysiology of obesity. However, only a few studies have reported the presence of specific circulating lncRNAs in obese patients. The general quiescence of AT in the obese state may contribute to the vast majority of circulating lncRNAs being down-regulated in obesity. Despite being highly promising target molecules, further studies are needed to establish a list of lncRNAs that may be used as prognostic or monitoring biomarkers of obesity. In this section, we will summarize potential biomarker candidates.

4.1.1. *LncRNA-p5549, lncRNA-p21015, and lncRNA-p19461*

Sun *et al.* studied circulating lncRNAs profiles in obese participants and identified 40,914 lncRNAs. However, only three were selected for further analysis because of their differential, high signal, and stable detection. These circulating lncRNAs levels were quantified by qPCR in obese and normal-weight individuals. LncRNA-p5549, lncRNA-p21015, and lncRNA-p19461 were significantly downregulated in obese individuals. These analyses were repeated after the participants consumed a very low-calorie diet for 12 weeks and no significant changes were observed except for lncRNA-p19461, which showed significantly increased expression [253].

4.1.2. *AP001429.1*

A direct relationship has been established between obesity and various types of cancer, especially breast cancer. AP001429.1 has recently become a biomarker of breast cancer in obese patients. AP001429.1 is a lncRNA that may have a protective role against breast cancer. Its expression was measured in obese and non-obese individuals with breast cancer and it was found that AP001429.1 is downregulated in obese patients with breast cancer compared with non-obese individuals with breast cancer [254].

4.1.3. *lncRNA-small nucleolar RNA host gene 9 (LncRNA-SNHG9)*

LncRNA-SHNG9 was recently shown to be released by exosomes and its expression was diminished in blood samples of obese patients with endothelial dysfunction [255]. These results may indicate that lncRNA-SHNG9 promotes lipid metabolism; however, the mechanism is unclear and further studies are required to understand the mechanisms of lncRNA-SNHG9.

4.1.4. *LncRNA-SNHG12*

Childhood obesity is a significant emerging problem due to its association with related severe metabolic diseases. LncRNA-SNHG12 was isolated from plasma samples from adolescents and its expression was shown to be downregulated in obese compared with non-obese individuals, although there is still limited information about this molecule and its mechanism of action [256].
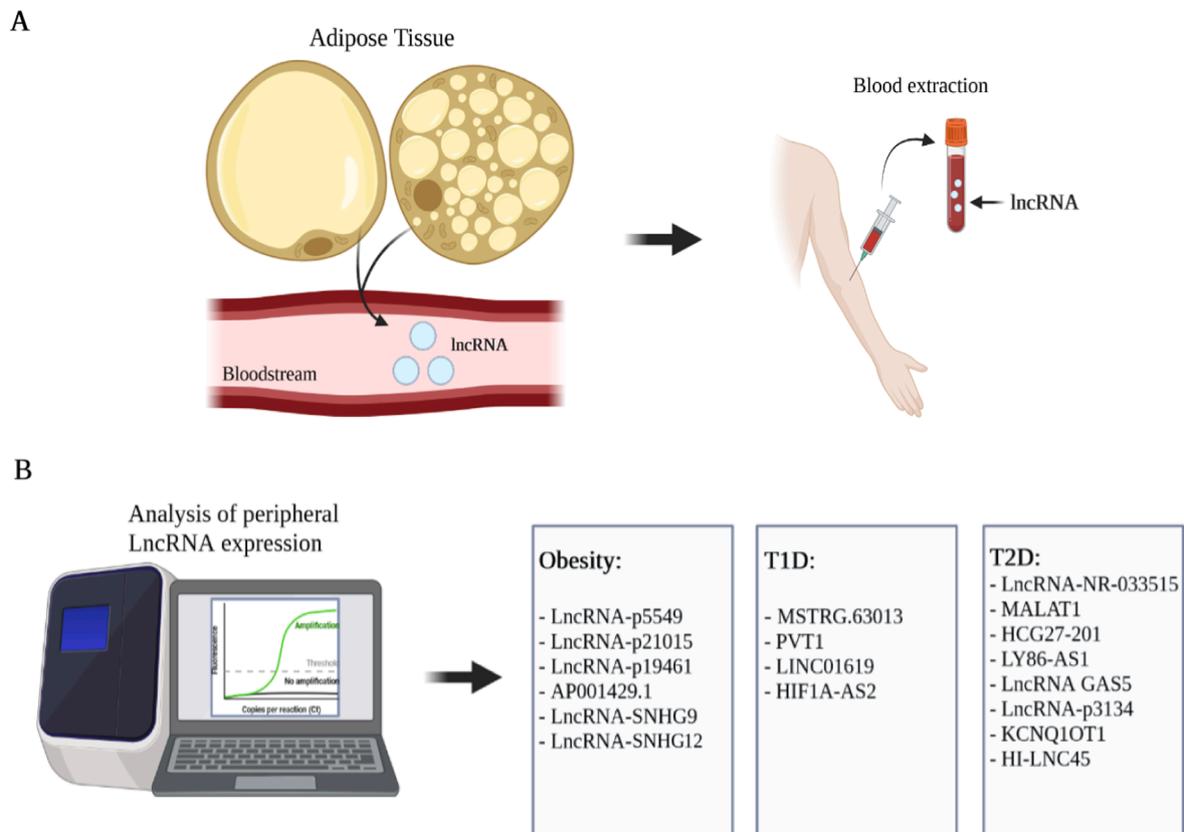
Fig. 5. LncRNAs as biomarkers in obesity and diabetes. (A) Adipocytes release lncRNAs into the bloodstream to reach their targets. These lncRNAs are collected from a blood sample for further isolation and purification. (B) The expression of circulating lncRNAs is measured to detect variations related to diseases, such as obesity and diabetes, to identify the lncRNAs involved in these diseases and develop new therapeutic targets.

Table 3
LncRNAs as potential candidates for biomarkers of obesity and diabetes.

LncRNA	Disease	Circulating levels vs control subjects	AT expression (LncBook or NONCODE ID)	References
LncRNA-p5549	Obesity	downregulated	Yes (HSALNG0105664)	[251,253]
LncRNA-p21015	Obesity	downregulated	Yes (HSALNG0012350)	[252,253]
LncRNA-p19461	Obesity	downregulated	Yes (HSALNG0101515)	[251,253]
AP001429.1	Obesity, breast cancer	downregulated	Yes (HSALNG0132979)	[250,252,254]
LncRNA-SNHG9	Obesity	downregulated	Yes (HSALNG0108960)	[250,252,255]
LncRNA-SNHG12	Obesity	downregulated	Yes (HSALNG0002075)	[250,252,256]
MSTRG.63013	T1D	upregulated	Unknown (novel transcript)	[282,283]
PVT1	T1D	unknown	Yes (HSALNG0068477)	[250,251,286]
LINC01619	T1D	upregulated	Yes (HSALNG0093041)	[250,251,275,287]
HIF1A-AS2	T1D	upregulated	Yes (HSALNG0101776)	[250–252,288]
lncRNA-NR_033515	T2D	upregulated	Unknown	[289]
MALAT1	T2D	upregulated	Yes (HSALNG0084905)	[250–252,290]
HCG27-201	T2D	downregulated	Yes (HSALNG0049246)	[251,252,292]
LY86-AS1	T2D	downregulated	Yes (HSALNG0047822)	[250,251,292]
LncRNA GAS5	T2D	downregulated	Yes (HSALNG0008545)	[250–252,293]
LncRNA-p3134	T2D	upregulated	Yes (HSALNG0090364)	[250–252,294]
KCNQ1OT1	T2D	upregulated	Yes (HSALNG0082235)	[250–252,295]
HI-LNC45	T2D	upregulated	Yes (NONHSAG020377.2)	[295,302]

4.2. Circulating lncRNA in diabetes

The rising prevalence of diabetes is a significant public health concern in the modern era, highlighting the need for the development of novel diagnostic methods to identify early metabolic abnormalities, such as insulin resistance. Accumulating evidence suggests that lncRNAs appear to be dysregulated in diabetes, and they may play a role in type 1 diabetes mellitus (T1D) and T2D, β-cell function, and glucose homeostasis [257–259]. Differential expression patterns of lncRNAs have been reported between healthy individuals and patients with both types of diabetes [260,261]. Given that a single lncRNA can modulate the expression of different transcription factors or mRNAs involved in diabetes related-pathways, lncRNAs are starting to be considered as potential biomarkers for early diagnosis and prognosis of T1D and T2D, as well as alternative therapeutic targets against this disease [262,263].

Extensive studies have been conducted to investigate the molecular and cellular basis of the relationship between excess adiposity and impaired glucose homeostasis that underpins T1D and T2D and numerous AT-centric mechanisms have been postulated. T1D and T2D are associated with a general state of inflammation in the body,

including WAT and BAT [66,264,265], which provokes macrophage recruitment, proinflammatory cytokine and chemokine upregulation, deregulation of adipokines, ER stress, oxidative stress, and apoptosis, resulting in a progressive loss of functionality [66,266–271]. As a result, information about AT-derived lncRNA is critical to gain a better understanding of the pathogenesis and pathophysiology of diabetes.

T1D is a prevalent chronic autoimmune disease in children and adolescents, and several studies show that lncRNAs can regulate the activation of the innate immune system and islet β-cell function, contributing to its pathogenesis. More importantly, dysregulated lncRNA expression is associated with the development of T1D [272,273], suggesting that these molecules could be used as biomarkers to assess the risk of this pathology [274,275]. The mechanisms involved in initializing the autoimmune response that leads to T1D are unknown. However, many of the genetic associations that have been identified so far are in non-coding regions of the genome. LncRNAs may coordinate the many immune functions by regulating the differentiation and function of innate and adaptive immune cells [276–280]. Inflammation of the pancreas triggers β-cell apoptosis and the absence of insulin production and secretion [281]. In this situation, the general metabolism is modulated to counteract the failure of the pancreas. Recent studies have shown that the lncRNA MSTRG.63013 is a critical node and two genes, namely *G3BP2* [282] and *CYCS* [283], are especially associated with this lncRNA, which are involved in many cell signaling pathways and RNA metabolism. In this regard, some critical lncRNAs could be potential biomarkers or regulators of T1D.

T1D progression is associated with a high risk of developing diabetic complications. The most critical secondary complications of T1D are diabetic nephropathy (DN) and retinopathy (DR). Genetic factors modulate the risk for complications in diabetes [284,285], but to date, no genes with significant effects on disease susceptibility have been identified. Studies in DN patients have reported that PVT1, or plasmacytoma variant translocation 1, is a lncRNA that encodes some alternative transcripts and increases cell proliferation. Furthermore, PVT1 amplification and overexpression inhibits apoptosis. Variants of PVT1 are associated with kidney failure-associated T1D. This transcript is abundantly expressed in kidney cells, which is strongly consistent with a potential role in metabolic dysregulation in this tissue preceding the development of renal failure in diabetes. Together, these findings suggest that PVT1 may be a critical factor in mediating susceptibility to this disease [286]. Other lncRNAs, such as LINC01619, have been reported to influence DN by inducing oxidative stress and podocyte damage via regulating miR-27a [275,287]. HIF1A-AS2 is another lncRNA that shows a potential role in DR throughout its stages and its interplay with hypoxia, oxidative stress, and angiogenesis via a MAPK/VEGF-dependent pathway [288].

On the other hand, the prevalence of T2D has increased in line with the worldwide rise in obesity in recent decades. LncRNAs specifically associated with T2D vascular complications have also been reported. The levels of lncRNA-NR_033515 were significantly upregulated in the serum of patients with DN, compared with normal patients, and its expression was associated with the clinical stages of this pathology [289]. A microarray-based study identified 303 differentially expressed lncRNAs in the retinas of mice with DR compared with non-diabetic mice, and the results were further corroborated by PCR analysis. These changes correlated with several processes that may be linked to the pathological neovascularization seen in DR. The highly conserved lncRNA, MALAT1, was found to be upregulated in the retinas of diabetic mice, suggesting that MALAT1 dysregulation may be associated with DR occurrence [290]. Furthermore, lncRNA MALAT1 was upregulated in the serum of T2D patients with diabetic kidney disease compared with those without diabetes and was correlated with specific markers of diabetic kidney disease (urine beta-2-microglobulin, urine alpha-1-microglobulin, and albumin-to-creatinine ratio) [291]. For example, the levels of lcnRNAs such as HCG27-201 and LY86-AS1 were down-regulated in peripheral blood mononuclear cells isolated from T2D

patients compared with controls [292]. Similarly, the levels of circulating lncRNA GAS5 were downregulated in the serum of patients with diabetes and correlated with the onset of the disease; however, circulating lncRNA GAS5 was also downregulated in patients with HbA1c levels between 5.9 % and 6.4 %, which is not considered clinically diabetic. These results suggested that other parameters besides conventional parameters, such as the measurement of circulating levels of specific lncRNAs, should be considered to predict the chances of developing diabetes [293].

Similarly, human lncRNA microarray analysis showed that lncRNA-p3134 was upregulated in the serum of patients with diabetes compared with those without diabetes [294]. The same study reported that lncRNA-p3134 was secreted by islet pancreatic beta-cells and further stored in exosomes in response to high glucose levels. Moreover, lncRNA-p3134 may mediate pancreatic beta-cell protection and promote insulin synthesis and secretion by enhancing specific regulators (Pdx-1, MafA, Tcf712, and GLUT2) in these cells [294].

More than 1,000 lncRNAs associated with beta-cell maturation and T2D have been identified to date in pancreatic beta-cells, such as lncRNAs KCNQ1OT1 and HI-LNC45, which were significantly upregulated in the islets isolated from patients with T2D compared with individuals without diabetes [295]. Furthermore, lncRNA HI-LNC25 is specifically found in human beta-cells and was also found to regulate the expression of the GLIS3, which is a key transcription factor containing several T2D risk variants [295,296].

Overall, different studies have reported altered levels of lncRNAs in patients with T2D [261], corroborating the potential relevance of ncRNAs in this disease. However, most studies focused on evaluating the differential expression patterns of these molecules; therefore, further validation to gain a better understanding of the exact mechanisms by which these molecules regulate diabetes pathophysiology is required.

5. Future perspectives and therapeutic applications

Since their discovery, many lncRNAs have been identified, and lncRNA research has become especially relevant due to the wide range of cellular functions in which they are involved. This functional variety makes lncRNAs potential therapeutic targets since numerous lncRNAs are frequently altered in AT-related pathologies, such as obesity and diabetes.

Although major advances in the study of lncRNAs have been achieved in recent years, their regulatory role is still a relatively young and unknown field, especially in AT. Moreover, the expression of lncRNAs affected by epigenetic alterations is potentially reversible, complicating the collection of conclusive data and, at the same time, providing an attractive and promising strategy for its clinical application. Most of the pharmacotherapy used in clinical practice have protein targets; therefore, these drugs frequently have unwanted side effects due to their interactions with other proteins [297]. Nucleic acid-targeting pharmaceuticals, such as lncRNAs, are a promising new field in the quest to identify new therapies because they have fewer systemic adverse effects than current treatments [298]. The obstacles currently present in the field of RNA therapies will, without a doubt, be conquered due to the promising innovations currently emerging from valuable preclinical work. The present review summarizes recent evidence for the possible roles of several lncRNAs in AT function, such as adipogenesis, lipid metabolism, and thermogenesis. The findings demonstrate significantly different lncRNA expression profiles between obese and normal-weight individuals *in vivo* and *in vitro*. Deregulation of lncRNA expression demonstrates that these molecules are involved in the metabolism of both white and brown/beige AT.

Future studies should focus on the potential application of lncRNA as biomarkers since lncRNAs can be detected in both intracellular and extracellular environments. An extensive list of lncRNAs that function as cancer biomarkers has been identified; however, the list is considerably shorter for diabetes and obesity; thus, further studies are required.

Validation, appropriate primer design, and normalization are essential steps in developing lncRNA measurement as a promising biomarker. Despite current limitations, the existence of these peripheral molecules in patients allows for early and non-invasive diagnosis, prognosis, and monitoring of AT-related disorders. LncRNAs have three main advantages for obesity treatment: (1) small-molecule drugs have been reported to regulate lncRNA expression and thus may be a novel treatment method for human obesity [299]; (2) lncRNAs are expressed at relatively low levels in tissues, indicating powerful regulation even at low doses; and (3) nucleic acid-based drugs are an emerging class of therapeutics with fewer potential side effects than protein-based drugs that could also interact with non-target proteins. Thus, future WAT and BAT lncRNA studies including *in vitro* and *in vivo* experiments may identify novel exciting targets to treat obesity.

In conclusion, lncRNAs are an emerging field with potentially relevant applications in AT metabolism. Integrating lncRNAs into therapeutic approaches for early treatment of AT-associated diseases, such as obesity, would be of high relevance.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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