

# Biochemical Pharmacology

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

--Manuscript Draft--

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<b>Abstract:</b>	<p>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.</p>
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Title: Role of long non-coding RNAs in adipose tissue metabolism and associated pathologies

Authors: Corral *et al.*

Ms. No. BP-D-22-01363

Dear Jacques:

Thank you for handling our manuscript and for your willingness to accept the revised version. We appreciate the Reviewers' comments. We have attached a point-by-point response to the Referees.

Sincerely yours,



Laura Herrero, PhD

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## Point-by-point response to the Referees' comments

**Note:** line numbers refer to the manuscript with tracked changes.

### REVIEWER #1

Long non-coding RNAs in adipose tissue metabolism and function is an interesting and emerging field and would benefit from a comprehensive review. This review brings together specific findings in both animal models and humans and has the potential to be a good resource for the current state of knowledge. Importantly, it lacks cohesion in its current form, it needs a better focus with more experimental detail linking the lncRNA to function and biological relevance to disease, with a more detailed message at the end.

#### Question 1

The introduction covers human adipose tissue biology and its relevance to health. This section is thorough but in places is repetitive and could be made more concise.

#### Answer 1

We agree with the Reviewer and we are thankful for this comment. The whole "Introduction" section has been thoroughly revised to avoid repetitions and made it more concise (lines 124, 191, and 198).

#### Question 2

Section 2 covers the very broad and complicated field of ncRNA. The final sentence "The wide functions of lncRNAs are reviewed elsewhere" should almost have been the opening sentence. This section certainly needs some figures to help the reader make sense of the complexity. In its current form it is very difficult to follow.

#### Answer 2

We do agree with the Reviewer about the complexity of the ncRNA field. Following the Reviewer's suggestion, we have moved the sentence "The wide functions of lncRNAs are reviewed elsewhere" from the end of Section 2 to line 358. In addition, we have included a new Figure 2 to help the reader to understanding the variety and classification of the ncRNAs.

#### Question 3

Section 3 reads a bit like a textbook and is just a list of lncRNA findings in the literature. The animal findings are nearly all related to brown adipocytes with no discussion as to why this is, and the application of this data to human therapeutics needs more detailed discussion. Some of the lncRNAs in the human section should really be in the animal model section as the results mainly refer to animal findings. Overall, this section could have been better organised and presented in a more interesting format with better links between the human and animal findings.

#### Answer 3

We thank the Reviewer for this very important comment to improve the manuscript. We have included a paragraph in Section 3 (lines 647-653) to explain and differentiate those lncRNA extensively studied in animal models from those studied and isolated from human samples:

“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.”

#### **Question 4**

Section 4: When discussing circulating lncRNA there was no discussion of origin tissue. Also, there was no discussion regarding the fact that the overwhelming number of circulating lncRNAs are down regulated in obesity which could just be a side effect of the general quiescence of adipose tissue in the obese state.

#### **Answer 4**

The Reviewer is right to point this out. Information about the tissue of expression and the subcellular localization of each lncRNA has been detailed in Tables 1 and 2 and Figure 4 (lines 442 and 385). Regarding the origin of circulating lncRNA, we have also included a sentence in section 4 (line 886):

“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) [251–253].”

A sentence to include the possibility that the quiescence of adipose tissue in obesity might contribute to the downregulation observed in the vast majority of circulating lncRNAs has been added in line 893.

#### **Question 5**

The final sections could have brought together the findings better and could have gone into a lot more detail about function, rather than just having a figure showing the overlap in lncRNAs between animals and humans and between brown and white fat. There was also no division between upper and lower human fat depots in figure 3 despite the fact that the introduction correctly states that these depots are functional and developmentally distinct. The use of lncRNAs as biomarkers was discussed but their benefit as such was not convincing, when compared to more traditional measures.

#### **Answer 5**

We thank the Reviewer for these important comments to improve the manuscript. To our knowledge, there are no publicly available databases describing the lncRNAs differentially expressed in the upper or lower human fat depots. Hotair is the only

lncRNA described to be exclusive to gluteal fat. This information has been specified in line 716.

Following the reviewer's suggestion, we have also included a sentence in section 4.2 (line 951) to better explain the benefit of using lncRNAs as biomarkers:

“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 [263,264].”

#### **Question 6**

Finally, the graphical abstract was very basic and uninformative.

#### **Answer 6**

Following the Reviewer suggestion, we have modified the Graphical abstract to include a summary of the relevant information presented in the manuscript such as the importance of lncRNAs in metabolism, those expressed in the adipose tissue and their potential role as biomarkers for obesity, T1D and T2D.

#### **REVIEWER #2**

The manuscript by Corral, *et al.* is a comprehensive review of the current knowledge of long noncoding RNA (lncRNA) as it pertains to adipose tissue in health and in metabolic disease. The introductory sections very nicely summarize the nature and role of the adipose tissue depots and noncoding RNAs. The manuscript is very well-written and easy to follow. Importantly, the authors have identified the critical lncRNAs implicated in adipose tissue regulation from both animal and human studies. The tables and figures are helpful to the reader. Overall, this is outstanding review paper. I only have minor comments:

#### **Question 1**

Line 152: For context and consistency with the rest of the section, it would be helpful to discuss whether anything is known about the role of pink adipose tissue in obesity and metabolic disorders.

#### **Answer 1**

The Reviewer is right to point this out. Following the Reviewer's suggestion, we have included a paragraph about the pink adipose tissue (lines 159-166):

“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].”

#### **Question 2**

Line 196: For the sentence beginning "In disorders such as T2D or obesity, and increment in fat deposition causes the release of FFAs..." do you mean "an increase in fat deposition"?

**Answer 2**

Following the Reviewer's suggestion, we have changed the sentence accordingly (line 208).

**Question 3**

Line 562: Should be "Surprisingly, overexpression of Paral1 did not reverse this effect..."

**Answer 3**

The Reviewer is right. We do apologize for the typo. The sentence has been modified accordingly.

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

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20 **ABSTRACT**

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2 21 The incidence of obesity and its related disorders has increased dramatically in recent years and has  
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4 22 become a pandemic. Adipose tissue is a crucial regulator of these diseases due to its endocrine capacity.  
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6 23 Thus, understanding adipose tissue metabolism is essential to finding new effective therapeutic  
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8 24 approaches. The “omic” revolution has identified new concepts about the complexity of the signaling  
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10 25 pathways involved in the pathophysiology of adipose tissue-associated disorders. Specifically, advances  
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12 26 in transcriptomics have allowed its application in clinical practice and primary or secondary prevention.  
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14 27 Long non-coding RNAs (lncRNAs) have emerged as critical regulators of adipose tissue since they can  
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16 28 modulate gene expression at the epigenetic, transcriptional, and post-transcriptional levels. They interact  
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18 29 with DNA, RNA, protein complexes, other non-coding RNAs, and microRNAs to regulate a wide range  
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20 30 of physiological and pathological processes. Here, we review the emerging field of lncRNAs, including  
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22 31 how they regulate adipose tissue biology, and discuss circulating lncRNAs, which may represent a  
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24 32 turning point in the diagnosis and treatment of adipose tissue-associated disorders. We also highlight  
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26 33 potential biomarkers of obesity and diabetes that could be considered as therapeutic targets.  
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33 35 **KEYWORDS:** lncRNA, adipose tissue, biomarkers, obesity, diabetes, therapeutics.  
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38 37 **RUNNING TITLE:** long non-coding RNAs in adipose tissue  
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42 **ABBREVIATIONS**

43 AdipoQ, adiponectin

44 ADSC, adipocyte-derived stem cell

45 ASAT, abdominal subcutaneous adipose tissue

46 ASMER, adipocyte-specific metabolic-related lncRNA

47 AT, adipose tissue

48 BAT, brown adipose tissue

49 Blnc1, brown fat lncRNA 1

50 BMSC, bone marrow stem cells

51 C/EBP, CCAAT enhancer binding protein

52 DIO3OS, DIO3 opposite strand

53 DN, diabetic nephropathy

54 DR, diabetic retinopathy

55 D3, iodothyronine deiodinase 3

56 ecCEBPA, extra-coding CEBP $\alpha$

57 FABP4, fatty acid binding protein 4

58 FFA, free fatty acids

59 FOXC2, forkhead box protein C2

60 GSAT, gluteofemoral subcutaneous white adipose tissue

61 HFD, high-fat diet

62 hnRNPU, heterogeneous nuclear ribonucleoprotein U

63 HOTAIR, HOX antisense intergenic RNA

64 lncRNA, long non-coding RNA

65 lnc-RAP, polyadenylated long non-coding RNA

66 miRNA, microRNA

67 mRNA, messenger RNA

68 ncRNA, non-coding RNA

69 NEAT, nuclear enriched abundant transcript 1

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- 70 Para1, PPARG activating RBM14 associated lncRNA 1
  - 71 PGC1, peroxisome proliferator-activated receptor gamma coactivator 1
  - 72 PPAR, peroxisome proliferator-activated receptor
  - 73 PRDM16, PR domain containing 16
  - 74 SAT, subcutaneous white adipose tissue
  - 75 slincRAD, super-long intergenic ncRNA functioning in adipocyte differentiation
  - 76 SRA, steroid receptor RNA activator
  - 77 T1D, type 1 diabetes mellitus
  - 78 T2D, type 2 diabetes mellitus
  - 79 UCP1, uncoupling protein 1
  - 80 VAT, visceral white adipose tissue
  - 81 WAT, white adipose tissue
  - 82 Xist, X-inactive specific transcript

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98 **1. Introduction**

99 **1.1. Overweight and obesity**

100 Overweight and obesity have become significant public health issues worldwide and are defined by the  
101 World Health Organization (WHO) as excessive and abnormal accumulation of body fat that is related  
102 to adverse health effects [1]. Epidemiological studies have identified obesity and overweight as risk  
103 factors for the development of several diseases that affect multiple body systems, such as  
104 musculoskeletal complications, metabolic inflexibility, diabetes mellitus, cardiovascular risk, several  
105 types of cancer, chronic respiratory diseases, and mental health problems [2–4]. Chronic excessive body  
106 fat has been associated with increased mortality, with over 4 million related deaths worldwide [5,6].  
107 The life expectancy of those living with obesity is five years less than those with a normal weight [7,8].  
108 Recent data from the WHO European Region showed that overweight and obesity affect almost 60% of  
109 adults (>1.9 billion) and is the fourth most common risk factor for noncommunicable diseases.  
110 However, both overweight and obesity continue to grow in adults as well as children, affecting one in  
111 three children (~30%) [9,10]. This percentage has been increasing since the COVID19 pandemic  
112 [11,12]. The prevalence of obesity increases with age and is highest in people aged over 40 years. The  
113 prevalence is lower among females (54%) than males (63%) across the WHO European Region, but is  
114 close to or exceeding 70% for males in most countries [9]. Mediterranean and eastern European  
115 countries present the highest levels of both overweight and obesity, where it predominantly affects  
116 people with lower educational attainment [13]. Despite the relative stabilization of the trend in  
117 overweight and obesity in developing countries, current interventions to combat the overweight  
118 epidemic need to be maintained and strengthened since the prevalence of overweight and obesity in  
119 these regions remains very high.

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

126 **1.2. White and brown AT**

127 **AT and its multiple functions**

128 AT is the largest organ in the body, representing 10%–15% of the total body weight in healthy men and  
129 20%–25% in healthy women. In addition to buffering the daily influx of dietary nutrients and  
130 maintaining energy homeostasis, AT is also the safest place for the long-term storage of lipids [14]. AT  
131 was long considered to be a simple, static, lipid-storage tissue. Today, AT is known to be an active  
132 endocrine and secretory organ with multiple functions crucial for survival, including thermoregulation,  
133 lactation, immune responses, reproduction, and satiety [15,16]. There are two main types of AT in  
134 mammals, white adipose tissue (WAT) and brown adipose tissue (BAT), which have completely  
135 opposite functions, morphology, and developmental lineages [17].

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

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

151 Women have another type of AT known as pink AT. Pink adipocytes are milk-secreting alveolar cells  
152 that develop from subcutaneous white adipocytes during pregnancy and lactation. After the lactation  
153 period concludes, they transdifferentiate to white or brown adipocytes again. In addition to being

154 involved in milk production, pink adipocytes are able to secrete molecules that regulate metabolism  
1 similar to WAT or BAT. These include leptin, a key hormone in obesity. For this reason it is also  
2 similar to WAT or BAT. These include leptin, a key hormone in obesity. For this reason it is also  
3 considered as an endocrine regulator and may be involved in metabolic syndrome [22,23].  
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### 8 9 **Adipose tissue distribution: does location matter?**

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11 159 Human BAT is predominantly located in the supraclavicular depots in the neck region. A small  
12 percentage of brown adipocytes can also be found in the axillary, paravertebral, and kidney areas [24].  
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15 161 On the other hand, in mice, BAT is mostly distributed on the back, between the shoulder blades, and a  
16 small amount is present in the perirenal and perivascular regions (Figure 1).  
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20 163 In mammals, WAT is distributed throughout the body and is classified according to its location into two  
21 depots: visceral adipose tissue (VAT; including omental, mesenteric, retroperitoneal, gonadal, and  
22 pericardial WAT) and subcutaneous adipose tissue (SAT) (Figure 1). SAT is further subdivided into  
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24 165 gluteofemoral subcutaneous adipose tissue (GSAT; lower body regions in the thighs, hips, and  
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26 166 buttocks), upper body SAT (arms, trunk, and abdomen), and abdominal subcutaneous adipose tissue  
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28 167 (ASAT) [25]. Each depot has different metabolic functions as well as different, molecular, and  
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31 168 physiological features, although the mechanisms that drive these differences are not fully understood.  
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35 170 Compared with SAT, an excess of lipid accumulation in VAT is associated with a greater risk of  
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37 171 metabolic comorbidities, including glucose intolerance, hyperinsulinemia, and hypertriglyceridemia,  
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39 172 which can lead to cardiovascular disease and type 2 diabetes mellitus (T2D) [26,27]. Several possible  
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41 173 explanations for these differences have been extensively discussed in the literature. One explanation is  
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43 174 that VAT is more metabolically active and has a greater capacity for lipolysis, which generates free fatty  
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45 175 acids (FFAs) [28]. This, together with the anatomical location of VAT and its close proximity to the  
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47 176 liver, leads to a greater exposure of insulin-sensitive hepatocytes to both FFA and adipokines [28,29].  
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51 177 Another major difference between VAT and SAT is their cellularity and adipogenic capacity. The  
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53 178 development of preadipocytes from mesenchymal stem cells (MSCs) to adipocytes varies according to  
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55 179 their location [30,31]. The percentage of other cells in AT, including stem cells, macrophages,  
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57 180 neutrophils, lymphocytes, and endothelial cells, varies greatly based on their location and could also be  
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59 181 responsible for the differences seen between AT types [32]. Karpe and Pinnick (2015) reported that the  
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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.

#### **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].



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210 ASAT shows a hypertrophic response with limited capacity to recruit new adipocytes, whereas GSAT  
211 demonstrates a proliferative response to weight gain [30,31,47,48]. Thus, GSAT is considered  
212 protective against metabolic-related diseases, while the opposite has been described for ASAT [33]. A  
213 greater accumulation of ASAT increases the risk of cardiovascular disease and T2D, similar to that of  
214 VAT [49,50]. The mechanisms underlying these depot-specific differences are complex and not fully  
215 understood. Several factors, including hormones, transcription factors, and cell signaling molecules,  
216 that could influence these differences have been proposed [47].  
217 Furthermore, hypertrophic adipocytes showed reduced expression of adipogenic markers and alterations  
218 in the profile of secreted adipokines. Increased infiltration of proinflammatory macrophages has been  
219 observed in expanded VAT [51,52]. Consequently, adipocytes release inflammatory cytokines, which  
220 diminish the production of protective molecules such as adiponectin (Adipoq). Thus, normal  
221 adipogenesis and differentiation are compromised, leading to dysfunctional AT [39,42,46].

### 222 **Hypoxia and impaired angiogenesis**

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

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

### 233 **Inflammation and fibrosis**

234 Various cytokines are released in response to normal AT expansion. However, in obesity, hypertrophic  
235 adipocytes trigger signals that activate inflammation-related metabolic pathways. Inflammation causes  
236 adaptive responses in adipocytes in order to attenuate its adverse effects. Nevertheless, when  
237 inflammation becomes chronic, maladaptive responses emerge, leading to a pathological state. Some

238 mechanisms that lead to downstream inflammatory signaling include hypoxia, FFA accumulation, and  
1  
2 239 mechanical stress caused by expansion through the extracellular matrix [58].  
3  
4 240 The secretome of hypertrophic adipocytes is altered and adipocytes begin to release proinflammatory  
5  
6 241 cytokines that promote immune cell infiltration, including macrophages, T cells, and mast cells [59].  
7  
8 242 The cytokines secreted by adipocytes include tumor necrosis factor alpha (TNF $\alpha$ ), interleukin (IL) 6,  
9  
10 243 IL8, monocyte chemotactic protein 1, inducible nitric oxide synthase, transforming growth factor beta  
11  
12 244 1, C-reactive protein, and soluble intercellular adhesion molecule 1 [60,61]. An increase in adipocyte  
13  
14 245 size is closely related to macrophage infiltration into AT and adipocyte death. During obesity,  
15  
16 246 macrophages constitute up to 40% of all AT cells [61]. The proinflammatory molecules released by  
17  
18 247 macrophages and other molecules produced by different immune cells have direct effects on cellular  
19  
20 248 metabolism and block insulin action to limit energy accumulation and promote angiogenesis to prevent  
21  
22 249 hypoxia [58,62–64].  
23  
24  
25  
26 250 Chronic inflammation is usually related to tissue remodeling and fibrosis, especially in pathological  
27  
28 251 states. During fibrosis there is an excessive deposition of extracellular matrix components which  
29  
30 252 negatively affects tissue function [65]. The relationship between fibrosis and obesity is unclear. Some  
31  
32 253 studies have shown a positive correlation between fibrosis and metabolic disease in murine models and  
33  
34 254 humans [66–68]. However, other studies have not supported this correlation and have reported the  
35  
36 255 involvement of other factors, such as BMI and hyperplastic expansion, and proposed that fibrosis limits  
37  
38 256 hypertrophy expansion and acts as an adaptative feature to preserve adipocyte function [69–72]. In  
39  
40 257 parallel, unresolved inflammation triggers adipocyte fibrosis, metabolic inflexibility, dysregulation of  
41  
42 258 adipocyte function, and cell death [58].  
43  
44  
45

#### 46 259 **Mitochondrial dysfunction**

47  
48  
49 260 Mitochondria play a crucial role in fatty acid metabolism and, therefore, in adipogenesis [73,74]. A  
50  
51 261 sequence of disorders leads to mitochondrial dysfunction, which has severe consequences, including  
52  
53 262 insulin resistance and inflammation [75]. Obesity is strongly related to ER stress and reactive oxygen  
54  
55 263 species production, which are two closely mitochondrial dysfunction-related processes. When fatty acid  
56  
57 264 oxidation and mitochondrial biogenesis rates are diminished, mitochondrial DNA is reduced, triggering  
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265 fibrosis, inflammation, and apoptosis [66,76]. Similar results have been found in humans [77–81] and  
266 obese patients with T2D [82].  
267 These mechanisms, including hypertrophy, hypoxia, inflammation, fibrosis, and mitochondrial  
268 dysfunction, are some of the main drivers of the development of AT-related disorders.

## 269 270 **2. Non-coding RNA (ncRNA)**

### 271 **2.1. Types and functions**

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

284 Our understating of the different types of ncRNAs is increasing exponentially with the development of  
285 next-generation sequencing techniques and bioinformatics analysis. ncRNAs are classified as small  
286 ncRNAs (length <200 nucleotides), including ribosomal RNA, transfer RNA, microRNA (miRNA),  
287 small nuclear RNA, small interfering RNA, PIWI-interacting RNA, and long ncRNAs (length >200  
288 nucleotides) [95], which are further subdivided into circular (circRNA) and linear RNAs. Among these,  
289 the main groups of ncRNAs involved in AT metabolism and associated pathologies are miRNA and  
290 lncRNAs. The miRNAs are by far the most studied family of ncRNAs in this context. These molecules  
291 are small RNAs (18–22 nucleotides) that act as negative regulators of gene expression by binding to  
292 short complementary regions of target mRNAs [96–98]. All mRNAs are predicted to have more than

293 60% of their 3' untranslated region (UTR) target sites for miRNAs, indicating tight control and  
294 participation in both normal cell homeostasis and illness [99]. The circRNAs are another example of  
295 lncRNAs recently studied in AT. They are produced by alternative splicing of RNAs, act as miRNA  
296 sponges and contain RNA-binding protein (RBP) binding sites, regulating alternative splicing and gene  
297 expression. The roles of linear RNAs (from now on referred as lncRNAs) will be explained in depth in  
298 the next section in which we describe the recent findings in the field of lncRNAs, and their association  
299 with AT.

300

## 301 **2.2. LncRNAs**

302 In the 1990s, the pioneering discovery of the uncharacterized ncRNAs, H19 and X-inactive specific  
303 transcript (Xist) 1, led to the early belief that lncRNAs were transcriptional noise with little or no  
304 functional significance [100,101]. Although lncRNAs were discovered in the early 2000s, later studies  
305 showed that they were critical for a wide range of biological functions [86,102]. As mentioned  
306 previously, lncRNAs are a heterogeneous group of ncRNA that range in size from 200 nucleotides to  
307 20 kb. The nucleotide chains have the remarkable capacity to acquire various complex secondary and  
308 tertiary structures, enabling them to fulfill specialized roles required for survival [103]. Due to their  
309 structural diversity, lncRNAs can interact with DNA, RNA, and proteins and perform several regulatory  
310 activities, as we will describe. A systematic integration of annotations of existing databases revealed  
311 that there are almost 270,000 lncRNA transcripts annotated in humans [104–110]. Their nomenclature  
312 and symbols have been certified by the HUGO Gene Nomenclature Committee [111].

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

321 In general, lncRNAs are intracellular (and could be released into the circulation) and stable with  
1  
2 322 expression patterns that are unique to each cell type, tissue, and stage in the development and function  
3  
4 323 of each cell. They are expressed at a lower rate than mRNAs in a given cell type [116,117]. Therefore,  
5  
6 324 identifying the evolutionary conservation of functional sequences in the genome is one of the most solid  
7  
8 325 and accurate characteristics, highlighting their involvement as potential regulatory elements in essential  
9  
10 326 biological processes [118]. The skepticism concerning the evolutionary conservation of lncRNAs  
11  
12 327 extends to controversy about their functionality and biological relevance [119–123]. In 2015, a study  
13  
14 328 on the non-coding transcriptomes of 17 diverse species revealed that the bodies of the non-coding genes  
15  
16 329 are not conserved [124]. However, their 5' ends contained short conserved sequences [123], which  
17  
18 330 revealed a higher level of expression patterns in diverse tissues, particularly those involved in  
19  
20 331 development [125].

24 332 The structure, function, localization, and interaction with other biomolecules are applied to classify the  
25  
26 333 wide diversity of lncRNAs [126]. The wide functions of lncRNAs are reviewed elsewhere [127–131].  
27  
28 334 Regarding their location within the genome, lncRNAs are categorized into various types, including  
29  
30 335 sense lncRNAs, antisense lncRNAs, bidirectional lncRNAs, intronic lncRNAs, intergenic lncRNAs,  
31  
32 336 promoter-associated lncRNAs, and UTR-associated lncRNAs [116,132]. In addition, lncRNA  
33  
34 337 classification according to the intracellular location could be used to predict their mechanism of action.  
35  
36 338 Whereas mature mRNAs are only found in the cytoplasm, most lncRNAs are mainly located in the  
37  
38 339 nucleus [116,133] and are likely exported to the cytoplasm. Numerous RNA polymerase II-transcribed  
39  
40 340 lncRNAs are processed inefficiently and remain in the nucleus. Furthermore, analysis of subcellular  
41  
42 341 lncRNAs revealed nuclear retention elements or sequence motifs in *cis*-elements and *trans*-factors,  
43  
44 342 indicating that their export involves a default mechanism [134,135]. In the absence of an active *cis*-  
45  
46 343 element, it is probable that capped and polyadenylated stable RNA serves as a nuclear export substrate  
47  
48 344 [136]. Thus, the location of lncRNAs in the nucleus is coordinated at multiple levels (reviewed in [131]),  
49  
50 345 from transcription and processing to nuclear export, using multiple sequence motifs. The functions of  
51  
52 346 these lncRNAs have been linked to a variety of nuclear activities, including the assembly of nuclear  
53  
54 347 domains, directing chromatin architecture and remodeling, resetting epigenetic marks, and regulating  
55  
56 348 mRNA transcription (reviewed in [130,131,137]). In addition, nuclear functional lncRNAs can perform  
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1 349 in both *cis* (when their actions are limited to the chromosome from which they are transcribed) and *trans*  
2 350 (when they influence genes on other chromosomes) directions [138].  
3

4 351 A considerable proportion of lncRNAs are exported to the cytosol and are thought to use analogous  
5  
6 352 processing and export pathways, similar to mRNAs [139]. When lncRNAs reach the cytoplasm, they  
7  
8 353 undergo a sorting procedure that either sends them to different organelles (e.g., mitochondria, ER,  
9  
10 354 ribosomes, exosomes) or spreads them out in the cytoplasm where they bind to different RBPs.  
11  
12 355 LncRNAs regulate signal transduction pathways, translational programs, and posttranscriptional gene  
13  
14 356 expression in the cytoplasm. For example, some lncRNAs can regulate mRNA translation and stability  
15  
16 357 [140], protein activity [141], and levels through protein post-translational modifications [141,142].  
17  
18 358 Additionally, lncRNAs act as miRNA sponges by binding to complementary sites and influence gene  
19  
20 359 expression by competing with endogenous RNAs [143,144].  
21  
22  
23

24 360 Analysis of the human mitochondria transcriptome revealed that various lncRNAs are recruited into the  
25  
26 361 mitochondria, indicating other subcellular localizations [145]. The molecular mechanisms underlying  
27  
28 362 mitochondrial lncRNAs remain unclear, although they may play an essential role in regulating  
29  
30 363 mitochondrial function and dynamics in the coordinated signaling system to maintain homeostasis of  
31  
32 364 entire cells (extensively reviewed in [146,147]). Some other lncRNAs are sublocalized in exosomes by  
33  
34 365 binding specific motifs via RBPs [148]. This sublocation may be related to their function as possible  
35  
36 366 biomarkers, as described in section 4 “LncRNAs as biomarkers” of this review. In addition, high-  
37  
38 367 throughput sequencing of ribosome-protected fragments (Ribo-seq) analysis demonstrated that  
39  
40 368 lncRNAs interact with ribosomes [149–151]. Although this is controversial (reviewed in [131,152]),  
41  
42 369 some studies have demonstrated that lncRNAs may encode small polypeptides (also known as  
43  
44 370 micropeptides) in certain circumstances [153], which raises the question whether lncRNAs are non-  
45  
46 371 coding molecules. However, other studies have revealed that lncRNA association with ribosomes does  
47  
48 372 not always indicate that they are actively translated [154].  
49  
50  
51  
52

53 373 In summary, lncRNAs can regulate gene expression at the epigenetic (e.g., DNA methylation, histone  
54  
55 374 modification), transcriptional (e.g., recruitment of transcription factors), and post-transcriptional (e.g.,  
56  
57 375 modulation of miRNA and mRNA integrity) level (Figure 3). Furthermore, lncRNAs may interact with  
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376 DNA, RNA, miRNA, and protein complexes in order to perform their role and control a variety of  
377 physiological and pathological processes.

378

### 379 **3. LncRNAs in AT**

380 In the last few years, it has been postulated that lncRNAs act as coregulators in a wide range of  
381 processes, including AT development and function. As mentioned, numerous mechanisms are  
382 responsible for proper adipogenesis and functioning of WAT. BAT has is a myriad of activators, co-  
383 activators, transcription factors, and even miRNAs that have been described to play pivotal roles in the  
384 generation of adipocyte precursors (engrailed-1, myogenic factor 5), adipogenesis leading to mature  
385 brown adipocytes [PR domain containing 16 (PRDM16), peroxisome proliferator-activated receptor  
386 gamma (PPAR $\gamma$ ), and peroxisome proliferator-activated receptor gamma coactivator 1 (PGC1 $\gamma$ )], and  
387 transdifferentiation from white to beige adipocytes (irisin, meteorin-like protein) [155]. Thus, promoting  
388 the thermogenic potential is a tightly regulated process in which new regulators are constantly being  
389 discovered. Although these pathways have been studied extensively, it remains unclear how they are  
390 regulated by lncRNAs. Since most of these pathways have been described in animal models, it is crucial  
391 to unequivocally identify those related to human lncRNAs in terms of genomic or splicing signal  
392 sequence conservation, similar secondary structures, or syntenic transcription [156]. This would provide  
393 a strong background for the potential use of ncRNAs as therapeutic tools to treat metabolic diseases.  
394 The following section describes some of the lncRNAs responsible for regulating AT expansion and  
395 function that have been shown to be important in recent studies. The lncRNAs described in this section  
396 are summarized in Tables 1 and 2. The subcellular localization of each lncRNA has been collected from  
397 the databases LncATLAS [157] and BioGPS [158] and the tissue expression of these lncRNAs is shown  
398 in Figure 4.

399

#### 400 **3.1. LncRNAs involved in AT in animal models**

##### 401 **Steroid receptor RNA activator (SRA)**

402 The steroid receptor RNA activator 1 (*Sra1*) gene encodes lncRNAs of different lengths and mRNA by  
403 alternative splicing [159]. SRA lncRNA is involved in numerous metabolic processes, including

1  
2 405 mammary gland development and muscle differentiation, and is related to the development of cancers,  
3  
4 406 such as ovarian cancer [160]. Furthermore, SRA was the first lncRNA reported to be present in  
5  
6 407 adipocytes [161].

7  
8 408 SRA is highly expressed in WAT and BAT [159] and increases twofold during adipocyte differentiation.  
9  
10 409 Its overexpression in the stromal cell line, ST2, induces differentiation of adipocytes *in vitro*, whereas  
11  
12 410 knockdown showed the opposite effects in 3T3-L1 white adipocytes [162]. In addition, SRA promotes  
13  
14 411 glucose uptake and reduces insulin resistance and *Sra* knockdown in mature 3T3-L1 adipocytes led to  
15  
16 412 a reduced number of insulin receptors [163]. Furthermore, *Sra* knockout in the WAT of mice led to  
17  
18 413 resistance to high-fat diet (HFD)-induced obesity and a healthier phenotype with increased glucose  
19  
20 414 tolerance, decreased fatty liver, decreased adipogenesis, reduced expression of inflammation-related  
21  
22 415 genes, reduced plasma TNF- $\alpha$  levels, and improved insulin sensitivity [159]. Regarding its molecular  
23  
24 416 mechanism, SRA binds to and coactivates *Ppar $\gamma$* , which is the master transcriptional regulator of  
25  
26 417 adipogenesis [162]. These results indicate that SRA is an essential regulator of obesity, fatty liver, and  
27  
28 418 glucose homeostasis *in vivo* and may be a potential therapeutic target.  
29  
30

### 31 **Adiponectin antisense (Adipoq-AS)**

32  
33 419 Within the *Adipoq* locus, Adipoq-AS is transcribed from the opposite strand to the *Adipoq* mRNA in  
34  
35 420 mice and humans, presenting an overlapping sequence [164]. Like *Adipoq* mRNA, Adipoq-AS is  
36  
37 421 expressed in AT and increases during differentiation of 3T3-L1 white adipocytes. Although the  
38  
39 422 expression levels of Adipoq-AS are lower than those of *Adipoq* mRNA, the half-life of Adipoq-AS is  
40  
41 423 more than double that of *Adipoq* mRNA [164].

42  
43 424 Adipoq is a hormone secreted by adipocytes that plays a complex but significant role in adipogenesis.  
44  
45 425 It regulates glucose and lipid metabolism, and its overexpression was shown to increase insulin  
46  
47 426 sensitivity in 3T3-L1 cells and enhance cell proliferation. [165]. *Ob/ob* mice (genetically obese mouse  
48  
49 427 model) overexpressing the *Adipoq* gene were shown to have a metabolically healthy phenotype but were  
50  
51 428 predisposed to fat deposition [166]. In 2018, Cai *et al.* found that Adipoq-AS lncRNA delivered via  
52  
53 429 adenovirus injection in HFD-fed animals prevented weight gain, reduced fat mass, and reduced the  
54  
55 430 adipocytes size in both the WAT and BAT depots. Conversely, expression of *Ucp1*, *Pgcl $\alpha$* , and *Prdm16*  
56  
57 431 was increased in the epididymal and inguinal WAT and in BAT. Circulating levels of Adipoq were also  
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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 [164]. 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 [167].

#### **AK079912**

Uc009csb.1, also known as AK079912, is a lncRNA that was initially related to white adipogenesis [168]. 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 [169].

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 [169]. 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 PGC1 $\alpha$  and as a mediator of PPAR $\gamma$ -induced transcriptional activation of thermogenic genes [169].

#### **Xist**

Wu *et al.* recently proposed Xist as a potential regulator of BAT differentiation [170]. This lncRNA has been widely related to pathological conditions, such as cancer, fibrosis, and inflammation [171]. 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*)  $\alpha$ , and *Ppar $\gamma$*  [170]. 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/ebp $\alpha$*  to regulate brown differentiation [170]. Although there is no evidence of

1 459 a potential adipogenic role in human BAT, if confirmed, this could provide new insight into the  
2 460 biological differences of BAT between men and women beyond hormonal control.

#### 3 4 461 **LncRNA-BATE1 and LncRNA-BATE10**

5  
6 462 In 2015, murine transcriptome profiling analysis revealed that 40 lncRNAs were upregulated during  
7  
8 463 BAT adipogenesis [172]. Both lnc-BATE1 and lnc-BATE10 were found to be specifically highly  
9  
10 464 expressed in murine brown adipocytes both *in vivo* and *in vitro*. Knockdown of these lncRNAs did not  
11  
12 465 cause a significant impact on lipid accumulation during brown adipogenesis but reduced the expression  
13  
14 466 of common BAT marker genes, such as *Ucp1* and *Pgc1a*. Furthermore, ablation of these regulatory  
15  
16 467 RNAs reduced the expression of *Ucp1* and *Pgc1a* during the transdifferentiation of white adipocytes  
17  
18 468 into beige adipocytes, suggesting a pivotal role of lnc-BATE1 and lnc-BATE10 in browning [172,173].  
19  
20 469 Knockdown of *lnc-BATE1* resulted in lower mitochondrial oxygen consumption [172], whereas  
21  
22 470 suppression of *lnc-BATE10* hindered norepinephrine-mediated thermogenesis in brown adipocytes  
23  
24 471 [173].

25  
26 472 It was shown that lnc-BATE1 can act in *trans* to regulate brown adipogenesis by controlling the  
27  
28 473 expression of BAT-specific genes (including *Dio2*, *Ucp1*, and *Ppara*) and adipogenic genes (such as  
29  
30 474 *C/ebpa* and *Pparγ*). RNA immunoprecipitation analysis revealed that lnc-BATE1 interacts with  
31  
32 475 heterogeneous nuclear ribonucleoprotein U (hnRNPU) to form a functional ribonucleoprotein [172].  
33  
34 476 Meanwhile, lnc-BATE10 competitively binds Celf1, which is an RNA-binding protein that targets  
35  
36 477 *Pgc1a* mRNA, causing its degradation [173].

#### 37 38 478 **CCCTC-binding factor (zinc finger protein)-like, opposite strand (Ctcflos)**

39  
40 479 Bast-Habersbrunner *et al.* used whole-transcriptome analysis of primary beige preadipocytes from  
41  
42 480 different mouse strains to identify 198 lncRNAs [174] that were correlated with UCP1 expression,  
43  
44 481 significantly regulated during white-to-brown differentiation, and responded to rosiglitazone *in vitro*. In  
45  
46 482 parallel, they analyzed lncRNA expression in cold-induced BAT from BL/6J mice. These *in vitro* and  
47  
48 483 *in vivo* approaches to examining browning and thermogenesis control identified seven common  
49  
50 484 regulatory lncRNAs, among which the top three were isoforms of Ctcflos lncRNA [174].  
51  
52 485 Knockdown of Ctcflos variants during browning *in vitro* reduced *Ucp1* mRNA levels without affecting  
53  
54 486 lipid accumulation. Similarly, lack of Ctcflos impaired brown adipocyte differentiation and function;

1 487 however, this was not seen in white adipocytes, suggesting a selective role in thermogenic adipocytes  
2 488 [175]. Besides the regulation of the thermogenic gene expression, the authors demonstrated that Ctcfl  
3  
4 489 regulates alternative splicing of target genes, such as *Prdm16*, suggesting that this lncRNA is capable  
5  
6 490 of regulating gene expression to select more active isoforms [175].  
7

#### 8 9 491 **ADNCR**

10 492 ADNCR is a competing endogenous RNA for miR-204, which is involved in adipocyte differentiation  
11  
12 493 and inhibits the expression of Sirtuin 1 (SIRT1; a repressor of the *Pparγ* gene) to promote adipogenesis  
13  
14 494 [176,177]. ADNCR sponges miR-204, leaving free SIRT1 to bind to its cofactors, nuclear receptor co-  
15  
16 495 repressor and silencing mediator of retinoid and thyroid hormone receptors. This leads to inhibition of  
17  
18 496 *Pparγ* expression and adipocyte differentiation in 3T3-L1 cells [178–180]. SIRT1 overexpression  
19  
20 497 decreased adipogenesis in 3T3-L1 cells, whereas silencing of SIRT1 via RNA interference enhanced  
21  
22 498 adipogenesis [179]. ADNCR was the most downregulated lncRNA during differentiation of bovine  
23  
24 499 adipocyte-derived stem cells (ADSCs). Li *et al.* reported that ADNCR overexpression impaired  
25  
26 500 adipogenesis, decreased the number of mature adipocytes, increased SIRT1 levels, and significantly  
27  
28 501 decreased the expression of PPAR $\gamma$ , C/EBP $\alpha$ , and fatty acid binding protein 4 (FABP4), whereas  
29  
30 502 ADNCR knockdown increased PPAR $\gamma$  and FABP4 expression [178].  
31  
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34

#### 35 503 **PU.1 antisense (PU.1-AS) lncRNA**

36 504 PU.1 regulates a wide range of pathways, including adipogenesis. *PU.1* is strongly related to insulin  
37  
38 505 resistance and inhibition of adipocyte differentiation in 3T3-L1 cells. PU.1-AS lncRNA is transcribed  
39  
40 506 from the opposite DNA strand and overlaps with sense *PU.1* mRNA [181]. Several studies have  
41  
42 507 confirmed the inhibitory role of PU.1-AS in different animal models, including murine [182] and  
43  
44 508 porcine [183] adipocytes. PU.1-AS knockdown inhibits adipogenesis and promotes the expression of  
45  
46 509 PU.1 protein in both preadipocytes and adipocytes. Furthermore, repression of PU.1-AS led to  
47  
48 510 decreased *Adipoq* expression and secretion in mature adipocytes of C57BL/6 male mice [182]. These  
49  
50 511 results indicate that PU.1 is an inhibitor of preadipocyte differentiation and is blocked by PU.1-AS to  
51  
52 512 promote adipogenesis.  
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515 **Super-long intergenic ncRNA functioning in adipocyte differentiation (slincRAD)**

516 SlincRAD is an essential lncRNA for AT expansion. Its expression is upregulated in the early stages of  
517 3T3-L1 differentiation and decreases to remain stable during the later stages [184]. Zhang *et al.*  
518 demonstrated that slincRAD knockdown in 3T3-L1 cells led to impaired expression of adipogenic  
519 markers and an imbalanced AT development, with smaller adipocytes, decreased lipid accumulation,  
520 and decreased *Ppar $\gamma$*  and *Fabp4* expression. Furthermore, these adipocytes showed unregulated glucose  
521 and lipid metabolism, defective epigenetic regulation, and impaired adipogenesis [185]. Although the  
522 mechanisms of slincRAD remain unclear, it appears to be involved in clonal expansion together with  
523 DNA methyltransferase 1 (DNMT1), regulating adipogenesis via epigenetic processes [184].

524 **Lnc-U90926**

525 Lnc-U90926 is an adipogenesis regulator whose expression is negatively correlated with adipocyte  
526 differentiation in 3T3-L1 cells [186]. It is mainly expressed in WAT and its levels are lower in obese  
527 mice. Overexpression of Lnc-U90926 impaired adipogenesis, decreased lipid accumulation, decreased  
528 mRNA levels of *Ppar $\gamma$ 2*, *Fabp4*, and *Adipoq* (but not *C/ebp $\alpha$* ), and reduced protein levels of PPAR $\gamma$ 2  
529 and FABP4. In contrast, knockdown of Lnc-U90926 showed the opposite effects and enhanced  
530 adipogenesis, with significant increases in *Ppar $\gamma$ 2*, *C/ebp $\alpha$* , *Fabp4*, and *Adipoq* mRNA levels, PPAR $\gamma$   
531 and FABP4 protein levels, and lipid accumulation [186]. These results suggest that Lnc-U90926 inhibits  
532 *Ppar $\gamma$ 2* promoter transactivation. However, further studies are needed to determine its mechanism of  
533 action since Lnc-U90926 is located in the cytoplasm and it does not seem to interact directly with the  
534 *Ppar $\gamma$ 2* promoter [186].

535 **GM13133**

536 You *et al.* published novel data about GM13133, a 736-bp lncRNA transcribed in the opposite direction  
537 from the first intron of PRDM16 in mice; however, no homology or synteny has been observed in  
538 humans. It was found to be predominantly expressed in BAT, although its expression is not modified  
539 by cold or  $\beta$ 3-adrenergic agonist treatment [187]. Overexpression of GM13133 *in vitro* increased the  
540 expression of BAT markers and mitochondrial DNA, although there is not enough evidence to show  
541 whether it impacts thermogenic activity. Although oxygen consumption rates were measured, the results  
542 showed no differences in basal respiration or proton leak compared with control cells and the lack of a

543 normalization method may invalidate these results. In addition, no evidence of *Gm13133* ablation *in*  
1 *vitro* was presented [187]; therefore, further *in vivo* studies should be carried out to evaluate the potential  
2 544  
3 of this lncRNA.  
4 545  
5

#### 6 546 **Nuclear enriched abundant transcript 1 (NEAT1)**

8 547 NEAT1 is a lncRNA that is highly abundant in nuclei, essential for paraspeckles, and involved in  
9  
10 adipogenesis [188]. NEAT1 expression presents a variable profile during adipocyte differentiation and  
11 548  
12 regulates *Ppar $\gamma$ 2* splicing during adipogenic differentiation of 3T3-L1 cells. Furthermore,  
13 549  
14 downregulation of NEAT1 decreases lipid accumulation and reduces the expression of *C/ebpa* and  
15 550  
16 *Ppar $\gamma$*  but re-expression of NEAT1 rescues the adipogenic phenotype [77,188]. The published  
17 551  
18 information on its mechanism of action is minimal. It appears that NEAT1 regulates *Ppar $\gamma$*  splicing  
19 552  
20 during adipogenesis via SRp40, which is a protein responsible for regulating the alternative splicing of  
21 553  
22 pre-mRNA [188].  
23 554  
24

#### 26 555 **PPARG activating RBM14 associated lncRNA 1 (Paral1)**

28 556 Paral1 is exclusive to mature adipocytes. Its expression is positively correlated with PPAR $\gamma$  expression  
29  
30 and a decrease in diet-induced obesity or genetic mouse models of obesity [189]. Little is known about  
31 557  
32 its mechanism, except that Paral1 acts by co-activating and upregulating *Ppar $\gamma$*  transcriptional activity.  
33 558  
34 In 3T3-L1 cells, Paral1 downregulation significantly decreased lipid accumulation and adipogenic gene  
35 559  
36 expression *in vitro*. Surprisingly, overexpression of Paral1 did not reverse this effect, demonstrating that  
37 560  
38 Paral1 is necessary but not sufficient for adipogenesis [189].  
39 561  
40

#### 42 562 **Lnc-leptin**

44 563 Lnc-leptin plays a regulatory role in *leptin* expression and is necessary to maintain *leptin* levels. Its  
45  
46 expression is closely correlated with *leptin* expression in adipocytes from mouse inguinal and  
47 564  
48 epididymal WAT [190]. Moreover, knockdown of lnc-leptin showed impaired adipogenesis, whereas  
49 565  
50 overexpression of lnc-leptin did not affect *leptin* or other adipocyte markers. These results provide  
51 566  
52 evidence that lnc-leptin is necessary but not sufficient to regulate *leptin* expression and its effects on  
53 567  
54 adipogenesis [190]. Although its mechanisms remain unclear, the authors proposed that lnc-leptin forms  
55 568  
56 a loop with the *lep* loci to enhance its expression.  
57 569  
58

#### 60 570 **Polyadenylated lncRNA**

571 Polyadenylated lncRNA (lnc-RAP-n) is a group of 10 lnc-RNAs that are required for the differentiation  
572 and maturation of adipocytes and were identified in a study on primary adipocytes from mouse WAT  
573 and BAT. Twenty lnc-RAPs were upregulated during adipocyte differentiation and knockdown using  
574 RNA interference impaired white preadipocyte differentiation and reduced the expression of *Adipoq*,  
575 *C/ebpa*, *Fabp4*, and *Pparγ* [191]. Among the 20 lnc-RAPs, lnc-RAP-1, also known as Functional  
576 Intergenic Repeating RNA Element (Firre), was localized on the X-chromosome. Firre mediates the  
577 expression of indispensable adipogenic factors binding to hnRNPU in *trans* [192,193].

#### 578 **Plnc1**

579 Zhu *et al.* identified Plnc1 as a regulator of adipogenesis as it is transcribed ~25,000 bp upstream of the  
580 *Pparγ2* gene. They reported that Plnc1 was upregulated in obese mice and its knockdown inhibited  
581 adipocyte differentiation in ST2 cells and bone marrow stem cells (BMSCs) and diminished the  
582 expression of adipocytes markers, such as *Pparγ2*, *C/Ebpa*, and adipocyte protein 2 (*Ap2*), whereas  
583 Plnc1 overexpression showed the opposite results [194].

584 Plnc1 decreases *Pparγ* promoter methylation of the CpG region and promotes its expression, enhancing  
585 adipocyte differentiation and, consequently, adipogenesis [194].

#### 586 **AK142386 and AK133540**

587 AK142386 and AK133540 were both described by Chet *et al.* after performing lncRNA microarray  
588 analysis to evaluate the expression profiles of WAT and BAT from C57BL/6 J mice. AK142386 and  
589 AK133540 target *Hoxa3* and *Acad10* to regulate WAT and BAT adipogenesis and metabolism.  
590 Unfortunately, information about their role is limited and further studies are required to understand their  
591 mechanisms [195].

#### 592 **TCONS\_00041960**

593 TCONS\_00041960 was shown to be involved in adipogenic and osteogenic differentiation in  
594 glucocorticoid-treated BMSCs from Sprague–Dawley rats. TCONS\_00041960 enhances osteogenic  
595 differentiation and inhibits adipogenesis by targeting miR-125a-3p, which is a regulator of  
596 glucocorticoid induced leucine zipper, that inhibits PPARγ [196]. However, there is insufficient  
597 information on this lncRNA and further studies are required.

#### 598 **Gm15051, Tmem189, and Cebpd**

599 Microarray technology identified Gm15051, Tmem189, and Cebpd as potential regulators of brown  
1 adipogenesis in C57BL/6 J mice. These lncRNAs were selected among 1,064 lncRNAs due to their  
2  
3  
4 601 proximity to *Hoxa1*, *C/ebpβ*, and *C/ebpδ* genes, which play a crucial role in adipogenesis [197].  
5

### 6 602 **LncRNA 2310069B03Rik**

7  
8  
9 603 RNA sequencing (RNA-seq) analysis of BAT and inguinal WAT of cold-stimulated mice revealed  
10  
11 604 2310069B03Rik as the only lncRNA that was upregulated in both tissues [198]. This lncRNA was also  
12  
13 605 upregulated in both tissues after  $\beta$ 3-adrenergic stimulation and PPAR $\gamma$  agonist treatment. However,  
14  
15 606 subsequent experiments were not able to clearly demonstrate a cause and effect relationship to consider  
16  
17 607 this lncRNA as a potential candidate at this stage [198].  
18  
19  
20 608

### 22 609 **3.2. LncRNAs involved in adipose tissue in humans**

23  
24 610 In this section we have listed some lncRNAs that have been identified in human AT. Although the vast  
25  
26 611 majority of lncRNAs have been studied in animal models, in recent years homologous lncRNAs have  
27  
28 612 been found in humans. However, their implementation in human therapy still has many limitations due  
29  
30 613 to the little available information of lncRNAs in humans, and due to the fact that obtaining human  
31  
32 614 samples is sometimes complicated, especially for BAT. Because of this, many of these lncRNAs have  
33  
34 615 been more extensively studied in animals than in humans. In this section we focus specifically on those  
35  
36 616 that have been isolated from human samples.  
37  
38  
39

### 40 617 **H19**

41  
42 618 LncRNA H19 is a maternal imprinted gene located on human chromosome 11 whose regulatory roles  
43  
44 619 in diseases, such as cancer [199] and diabetes [200], have been widely described. In addition to this  
45  
46 620 myriad of roles, Schmidt *et al.* reported that its expression changed in BAT from mice exposed to cold  
47  
48 621 or fed an HFD. The authors used gain and loss-of-function approaches in primary brown preadipocytes  
49  
50 622 to describe a regulatory role of H19 in brown adipogenesis and oxidative metabolism [201]. *In vivo*, the  
51  
52 623 ubiquitous overexpression of H19 in HFD-fed mice prevented weight gain by increasing energy  
53  
54 624 expenditure, whereas selective knockdown of H19 in fat made HFD-fed mice more prone to obesity. In  
55  
56 625 lean and obese humans, H19 expression was shown to be inversely correlated with BMI in subcutaneous  
57  
58 626 and visceral WAT and positively related to *UCPI* mRNA levels [201].  
59  
60  
61  
62  
63  
64  
65

1 627 Concerning gene expression, H19 acts as a *trans* regulator to bind the methylated binding factor,  
2 628 downregulate the expression of paternally inherited genes that predispose to obesity, and reduce  
3  
4 629 mitochondrial biogenesis exclusively in BAT [201]. Although Schmidt *et al.* showed no impact of H19  
5  
6 630 on WAT, Huang *et al.* proposed a different mechanism. H19 has been shown to drive the fate of BMSCs  
7  
8 631 toward an osteogenic program [202]. It appears to play an inhibitory role in adipogenic differentiation  
9  
10 632 of BMSCs via epigenetic modification along with miR-675, which targets histone deacetylases  
11  
12 633 (essential molecules in adipogenesis). H19 and miR-675 are downregulated during adipogenic  
13  
14 634 differentiation and knockdown of H19 increases the expression of PPAR $\gamma$ , C/EBP $\alpha$ , and FABP4,  
15  
16 635 whereas overexpression of H19 and miR-675 compromises adipogenesis [203,204]. Furthermore, the  
17  
18 636 expression levels of H19 are negatively correlated with miR-188. Downregulation of H19 leads to  
19  
20 637 overexpression of miR-188, inhibits the effect of ligand-dependent corepressor, and promotes  
21  
22 638 adipogenesis in WAT [205,206]. Thus, the observations by Schmidt *et al.* who found that H19 had no  
23  
24 639 impact on white adipogenesis may be explained by the early role of H19 selecting an osteogenic fate of  
25  
26 640 precursor cells to the detriment of preadipocytes.  
27  
28  
29  
30

### 31 **Brown fat lncRNA 1 (Blnc1)**

32  
33 642 Zhao *et al.* used transcriptional profiling arrays to identify 21 lncRNAs that were overexpressed in BAT  
34  
35 643 and  $\beta$ 3 adrenergic-stimulated WAT, and during brown adipocyte differentiation. Among these, three  
36  
37 644 were highly conserved intergenic lncRNAs, but only one affected adipogenesis when silenced. This  
38  
39 645 lncRNA, identified as AK038898, was then renamed Blnc1 [207].  
40  
41

42 646 *In vitro* gain and loss-of-function studies revealed Blnc1 as a key factor during thermogenic adipocyte  
43  
44 647 development in brown and beige adipocytes. A full-length human transcript of Blnc1 was created and  
45  
46 648 different truncated mutants were transfected into mouse brown preadipocytes [208]. This allowed  
47  
48 649 identification of the conserved region that is required to promote the thermogenic program by stabilizing  
49  
50 650 the Blnc1/Zbtb7b/hnRNPU/EBF2 ribonucleoprotein complex [208,209]. Early B-cell factor 2 (EBF2)  
51  
52 651 collaborates with PPAR $\gamma$  to enhance the expression of crucial BAT markers, such as PRDM16, which  
53  
54 652 are critical for the development of the thermogenic phenotype [210].  
55  
56  
57

58 653 Finally, an *in vivo* approach in which fat-specific Blnc1 transgenic mouse and conditional knockouts  
59  
60 654 were fed an HFD demonstrated that Blnc1 is also critical for maintaining adaptive thermogenesis [211].  
61  
62  
63  
64  
65



655 **Lnc-dPrdm16**

1  
2 656 In 2018, a *de novo* reconstruction of the transcriptome of human fetal BAT, subcutaneous WAT, and  
3  
4 657 omental WAT using deep RNA-seq yielded two main improvements to the preexisting lncRNA  
5  
6 658 database, GENCODE. First, it revealed more than 2,000 new unannotated lncRNAs and second, it  
7  
8 659 showed that lncRNAs are almost 25 times more tissue-specific than mRNAs [212]. This *in silico*  
9  
10  
11 660 analysis also revealed 54 pairs of conserved lncRNA–mRNA between mice and humans related to  
12  
13 661 canonical pathways in AT. Among these, the authors focused on lnc-dPrdm16, which is located  
14  
15 662 divergently from Prdm16. *In vitro*, knockdown of lnc-dPrdm16 reduced lipid accumulation and  
16  
17 663 expression of BAT markers during differentiation of white and brown adipocytes [212].

18  
19  
20 664 In addition, lnc-dPrdm16 silencing via shRNA-associated adenovirus reduced the expression of BAT  
21  
22 665 markers when injected into WAT and BAT after browning and cold-induced thermogenesis,  
23  
24 666 respectively [212]. Although the regulatory mechanisms have not yet been elucidated, it is interesting  
25  
26 667 to highlight that lnc-dPrdm16 silencing reduced *PRDM16* mRNA levels in WAT but not BAT, which  
27  
28 668 raises the question whether the regulatory mechanism of this lncRNA could be depot-specific or related  
29  
30 669 to PRDM16.

31  
32  
33 670 **HOX antisense intergenic RNA (HOTAIR)**

34  
35 671 Further studies are required to understand the role of HOTAIR, which remains controversial. HOTAIR  
36  
37 672 was initially shown to be exclusively related to subcutaneous preadipocyte differentiation in human  
38  
39 673 gluteal fat. Its ectopic expression upregulated the adipogenic markers *PPAR* $\gamma$ , lipoprotein lipase, and  
40  
41 674 *FABP4* but did not increase the proliferation rate [213,214]. Later studies corroborated the importance  
42  
43 675 of HOTAIR in adipogenesis. Silencing HOTAIR diminished the expression of adipogenic markers and  
44  
45 676 led to defects in adipogenesis in mice [215,216]. Furthermore, the results in human cells were similar.  
46  
47 677 HOTAIR knockout in AT resulted in gluteal–femoral fat defects [217] evidencing its indispensable role  
48  
49 678 in the development of adipocytes. However, Kuo *et al.* recent demonstrated that HOTAIR  
50  
51 679 overexpression in human abdominal preadipocytes showed anti-adipogenic effects along with  
52  
53 680 significant changes in both DNA methylation and gene expression during abdominal adipogenesis  
54  
55 681 [218]. These findings indicate that HOTAIR may play an important role in the epigenetic regulation of  
56  
57 682 adipogenesis, although further studies are required.  
58  
59  
60  
61  
62  
63  
64  
65

683 **UC.417**

1  
2 684 You *et al.* identified 1,064 lncRNAs that were differentially expressed during brown adipocyte  
3  
4 685 differentiation in mice. Among these, the ultra-conserved lncRNA UC.417 was highly upregulated in  
5  
6 686 mature brown adipocytes compared with brown preadipocytes [197]. UC.417 exhibits high homology  
7  
8 687 within species, including 100% sequence homology between mice and humans. However, unlike Inc-  
9  
10  
11 688 BATE, UC.417 is postulated to be a negative regulator of brown adipogenesis and thermogenesis since  
12  
13 689 its overexpression caused a reduction in fat accumulation in BAT, limited expression of thermogenic  
14  
15 690 markers, and reduced mitochondrial size, number, and respiration [219]. In parallel, cold and chemical-  
16  
17 691 induced thermogenesis caused a reduction of UC.417 levels; however, knockdown of *UC.417* in brown  
18  
19 692 preadipocytes did not exert any effects during differentiation. Gene chip analysis of preadipocytes  
20  
21 693 overexpressing UC.417 suggested its role in the p38 MAPK pathway [219]; however, further studies  
22  
23 694 are required since different isoforms of p38 may exhibit opposite roles in brown fat differentiation [220].

26 695 **DIO3 opposite strand upstream RNA (DIO3OS)**

28  
29 696 DIO3 encodes type 3 iodothyronine deiodinase (D3), which inactivates the thyroid hormones, T4 and  
30  
31 697 T3, converting them into inactive metabolites. T3 has been shown to play a crucial role in brown  
32  
33 698 adipocyte differentiation during embryogenesis [221]. Knockout of BAT-specific *Dio3* triggered early  
34  
35 699 exposure of embryonic BAT to T3, resulting in a long-term upregulation of thermogenic genes [221].

37  
38 700 Mouse and human DIO3OS, which show around 25% homology, overlap with the DIO3 gene, although  
39  
40 701 they are transcribed in opposite directions. *In vitro*, CRISPR–Cas9 knockdown of *Dio3os* in mouse  
41  
42 702 embryonic fibroblasts activated DIO3 expression, which reduced T3 levels and PRDM16 expression  
43  
44 703 and thus, inhibited brown adipogenesis. Conversely, *Dio3os* overexpression promoted brown  
45  
46 704 adipogenesis and thermogenesis, although this was ablated when *Dio3* was also overexpressed,  
47  
48 705 suggesting *Dio3* inhibition as the primary mechanism involved in DIO3OS-induced adipogenesis. These  
49  
50 706 results were also reproduced *in vivo* by injecting a *Dio3os* adeno-associated virus into the interscapular  
51  
52 707 BAT of mice neonates. Five weeks later, lower body weight gain, increased BAT mass, and reduced D3  
53  
54 708 content were observed [222].

57  
58 709 In addition to direct inhibition of *Dio3* expression, other mechanisms may explain the regulatory roles  
59  
60 710 of *Dio3os* lncRNA. Specifically, *Dio3os* binds and inhibits miRNA-328 in hepatocellular carcinoma

1 [223] and miRNA-122, which suppresses cell proliferation in pancreatic cancer cells [224]. It is  
2 attractive to speculate that the latter mechanism may also be involved in Dio3os-mediated adipogenesis  
3  
4 since miRNA-122 has been negatively associated with BAT activity in humans [225].  
5

### 6 **LINC00473**

7  
8  
9 In 2020, Tran *et al.* investigated the potential role of LINC00473 as a regulator of thermogenesis in  
10  
11 human adipocytes [226]. LINC00473 is located on chromosome 6 and has been classified as an  
12  
13 oncogenic lncRNA as it has been shown to promote cell proliferation, migration, and invasion in several  
14  
15 types of cancer cells [227,228].  
16

17  
18 RNA-seq analysis of norepinephrine-stimulated adipocytes from abdominal subcutaneous fat and  
19  
20 supraclavicular AT revealed that LINC00473 was among the most upregulated genes following  
21  
22 thermogenic induction and adipogenesis [226]. Although initially there is a low abundance of this  
23  
24 lncRNA in the nuclei of the cells, it may regulate thermogenesis via activation of the Ucp1 promoter in  
25  
26 a cAMP/CREB-dependent mechanism. After norepinephrine or forskolin-mediated induction,  
27  
28 LINC00473 translocates to the cytoplasm where it participates in the stabilization between lipid droplets  
29  
30 and mitochondria, coordinating lipolysis [226]. Finally, a regulatory mechanism as a competitive  
31  
32 endogenous lncRNA cannot be ruled out, although this has not been empirically demonstrated. In cancer  
33  
34 cells, LINC00473 sequesters miR-15a, which acts as a tumor suppressor and has been demonstrated to  
35  
36 participate in human adipocyte differentiation [229].  
37  
38

### 39 **HoxA-AS3**

40  
41  
42 HoxA-AS3 lncRNA is encoded by the *HoxA* loci and plays a regulatory role in MSC differentiation. Its  
43  
44 expression is upregulated during adipogenesis of human and mouse BMSCs, whereas it is  
45  
46 downregulated in osteogenic differentiation [230]. Furthermore, *in vitro*, knockdown of *HoxA-AS3*  
47  
48 showed impaired adipogenesis and decreased the expression of adipogenic markers *PPAR $\gamma$* , *C/EBP $\alpha$* ,  
49  
50 *ADIPOQ*, and *FABP4* in hBMCs while promoting the expression of osteogenic markers, calcium  
51  
52 deposition and bone formation. *In vivo*, *HoxA-AS3* knockdown enhanced bone formation 2.6-fold and  
53  
54 2.2-fold in the HoxA-AS3-sh1 and HoxA-AS3-sh2 human MSC groups, respectively [230].  
55  
56  
57 Hox is believed to act via EZH2, which is a component of the polycomb repressive complex that works  
58  
59 as a switch for adipogenesis and osteogenesis, repressing transcription of osteogenic genes by catalyzing  
60  
61

1 739 the methylation of histone 3 lysine 27 [230]. These results demonstrate that HoxA-AS3 is required to  
2 740 inhibit osteogenic differentiation and promote adipogenesis.  
3

#### 4 741 **MIR31HG**

5  
6 742 The *MIR31* gene is located on chromosome 9 and encodes MIR31HG (also known as LOC554202).

7  
8  
9 743 Initially, MIR31HG was exclusively related to cancer and cell proliferation [175,231,232] but it was

10  
11 744 later identified as a regulator of osteogenic and adipogenic differentiation. MIR31HG is involved in

12  
13 745 adipocyte differentiation *in vitro* and *in vivo* in primary ADSCs from healthy humans and shows a

14  
15 746 variable expression profile during adipocyte differentiation. Moreover, knockdown of *MIR31HG*

16  
17 747 inhibited adipocyte differentiation and enhanced osteogenic differentiation, whereas *MIR31HG*

18  
19 748 overexpression promoted adipogenesis [233].

20  
21  
22 749 MIR31HG acts directly on the *FABP4* gene, triggering histone methylation and acetylation, enhancing

23  
24 750 its expression. Depletion of MIR31HG by gene silencing compromises adipogenesis [233]. In addition,

25  
26 751 MIR31HG promotes inflammation via nuclear factor- $\kappa$ B (NF- $\kappa$ B), which promotes osteogenic

27  
28 752 differentiation of human ADSCs [234].  
29  
30

#### 31 753 **Forkhead box protein C2 antisense (FoxC2-AS1)**

32  
33 754 Wang *et al.* investigated the potential mechanism of lncRNA FoxC2-AS1 as a regulator of white

34  
35 755 adipocyte differentiation and browning in human subcutaneous adipocytes [235]. FoxC2-AS1 is located

36  
37 756 on chromosome 16 and transcribed from the negative strand of *FOXC2* [235]. *FOXC2-AS1* is

38  
39 757 downregulated during white adipogenesis but its transcription is increased after browning stimulation.

40  
41  
42 758 Gain and loss-of-function studies showed no effect on white adipogenesis but it may promote the

43  
44 759 browning process of white adipocytes. To support this theory, the authors presented protein levels of

45  
46 760 key markers measured by Western Blot and oxygen consumption rates measured by Seahorse [235].

47  
48  
49 761 Unfortunately, the quantification of the Western Blot did not match the blots shown in the figures and

50  
51 762 the Seahorse analysis lacked biological replicates; therefore, in our opinion, more robust evidence

52  
53 763 should be presented to consider this antisense lncRNA as a potential regulator of thermogenesis.  
54

#### 55 764 **HOXA11-AS1**

56  
57  
58 765 Nuermaiti *et al.* demonstrated that HoxA11-AS1 is involved in adipocyte differentiation. The

59  
60 766 expression levels of HOXA11-AS1 were higher in differentiated human ADSCs compared with control  
61  
62  
63  
64  
65

767 undifferentiated ADSCs and was positively correlated with the expression levels of adipogenic genes,  
768 such as *C/EBP $\alpha$* , *CIDEA*, *Perilipin*, and *Diacylglycerol acyltransferase 2* [236]. Furthermore, *HOXA11-*  
769 *AS1* knockdown impaired adipocyte differentiation, decreased lipid accumulation, and reduced the  
770 expression of adipogenic genes. Finally, expression levels of *HOXA11-AS1* and adipogenic markers  
771 were higher in obese individuals compared with non-obese individuals. These results demonstrate the  
772 role of *HOXA11-AS1* in adipogenesis [236].

### 773 **Adipogenic differentiation-induced noncoding RNA (ADINR)**

774 *ADINR* is located ~450 bp upstream of the *C/EBP $\alpha$*  gene and is co-expressed with *C/EBP $\alpha$*  during  
775 adipogenic differentiation. In human MSCs, *ADINR* is drastically upregulated 20 to 30-fold during  
776 differentiation. Moreover, *ADINR* knockdown is related to a decrease in *C/EBP $\alpha$*  and *PPAR $\gamma$*  expression  
777 and leads to defects in adipogenesis that is not reversible through the expression of *ADINR* in *trans*  
778 [237]. Although its mechanism of action remains unclear, the authors propose a model in which *ADINR*  
779 promotes *C/EBP $\alpha$*  transcription activity in *cis* through *PA1*, which is a subunit of the histone methylation  
780 complex *MLL3/4*, although further studies are needed to corroborate this hypothesis [237].

### 781 **Maternally expressed gene 3 (MEG3)**

782 *MEG3* is an imprinted gene located on chromosome 14 in humans and chromosome 12 in mice [238].  
783 This lncRNA is involved in the adipogenic and osteogenic differentiation of human ADSCs [196].  
784 Numerous studies have identified the effect of *MEG3* on adipogenesis but there is controversy  
785 concerning its mechanism. *MEG3* inhibits adipogenic differentiation sponging miR-140-5p, which  
786 promotes adipogenesis, and its expression is downregulated during adipogenic differentiation in rat  
787 BMSCs [239] and human ADSCs [240].

### 788 **Extra-coding C/EBP $\alpha$ (ecCEBPA)**

789 *EcCEBPA* was discovered by Di Ruscio *et al.* in the HL-60 and U937 leukemic cell lines. It is encoded  
790 from the upstream *C/EBP $\alpha$*  gene on chromosome 19 and interacts with *DNMT1*. Consequently, the  
791 *C/EBP $\alpha$*  promoter is prevented from being methylated, leading to its overexpression. This mechanism  
792 could promote adipogenesis epigenetically but there is still very little information about its role in AT  
793 [241].

795 **Adipocyte-specific metabolic related lncRNA (ASMER)**

1  
2 796 Gao *et al.* found that adipocyte-specific metabolic-related lncRNAs (ASMER) 1 and 2 were upregulated  
3  
4 797 in the AT of obese humans and mice, suggesting that they play a significant role in adipogenesis,  
5  
6 798 lipolysis, and obesity. Knockdown of both ASMERs led to a significant decrease in Adipoq release,  
7  
8 799 PPAR $\gamma$  expression, and lipid accumulation [242].

10  
11 800 **Gm15290**

12  
13 801 Gm15290 promotes adipogenesis in *ob/ob* mouse adipocytes by sponging miR-27b, which is associated  
14  
15 802 with human obesity and T2D [243]. Overexpression of Gm15290 enhances C/EBP $\alpha$ , PPAR $\gamma$ , and AP2  
16  
17 803 expression in human multipotent adipose-derived stem cells 2 and 3, whereas decreased miR-27b levels  
18  
19 804 and Gm15290 knockdown had the opposite effect, leading to a decrease in lipid accumulation and body  
20  
21 805 weight *in vivo* [244].

22  
23  
24 806 **LncRNA RP11-20G13.3, LINC00968, AC011891.5, GYG2P1, RP11-529H2.1, and OLMALINC**

25  
26 807 The lncRNA expression profiles of four obese children and four non-obese children was selected  
27  
28 808 randomly and analyzed by microarray and showed that lncRNA RP11-20G13.3, LINC00968, and  
29  
30 809 AC011891.5 were upregulated, whereas GYG2P1, RP11-529H2.1, and OLMALINC were  
31  
32 810 downregulated in the obese group [245]. In addition, knockdown of RP11-20G13.3 in SW872  
33  
34 811 adipocytes reduced lipid accumulation and PPAR $\gamma$ , C/EBP $\alpha$ , and Adipoq expression during adipogenic  
35  
36 812 differentiation. These results identified a group of lncRNAs that regulates adipogenesis *in vivo* and *in*  
37  
38 813 *vitro*, although further studies are required to understand their mechanisms [245].

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43  
44 815 **4. LncRNAs as biomarkers**

45  
46 816 The deregulation of the lncRNAs may occur during the development of AT-related diseases, altering  
47  
48 817 the expression of their target genes and affecting underlying pathophysiological molecular and cellular  
49  
50 818 pathways. LncRNAs act intracellularly and may also be secreted by adipocytes and transported via the  
51  
52 819 bloodstream to other cells or tissues, where they are considered to be circulating lncRNAs [246].  
53  
54 820 Therefore, they may contribute to intercellular communication as autocrine, endocrine, or paracrine  
55  
56 821 molecules [246,247], although the exact process of lncRNA release into the extracellular environment  
57  
58 822 is unknown.

1 823 Circulating lncRNAs have been at the vanguard of biomarkers in recent years. The National Institutes  
2 824 of Health of the United States defines a biomarker as a specified property that is measured as an indicator  
3  
4 825 of normal biological processes, pathogenic processes, or response to an exposure or intervention [248].  
5  
6 826 Despite the abundance of ribonucleases in various body fluids, studies have revealed the presence of  
7  
8 827 lncRNAs in these samples that can successfully resist ribonuclease degradation activities. RNA-seq of  
9  
10 828 human blood exosomes revealed the presence of many lncRNAs [249]. The remarkable stability of  
11  
12 829 lncRNAs while circulating in human fluids, especially when incorporated in exosomes or apoptotic  
13  
14 830 bodies, is one of the key benefits that makes them useful as diagnostic, prognostic, and monitoring  
15  
16 831 biomarkers (Figure 5A). Furthermore, lncRNAs may be released in an exosome-independent  
17  
18 832 mechanism into bodily fluids, where they may form complexes with high-density lipoprotein or protein  
19  
20 833 Argonaute 2, similar to miRNAs [250]. Therefore, circulating lncRNAs have been identified as highly  
21  
22 834 sensitive, specific, and reproducible biomarkers for severe diseases, and they have been suggested as  
23  
24 835 promising markers for some AT-related disorders, including diabetes and obesity (Figure 5B), as will  
25  
26 836 be reviewed in the next section. Despite the fact that many published studies fail to identify the lncRNAs'  
27  
28 837 tissue of origin due to the lack of biopsies or their difficult access, bioinformatic tools can alternatively  
29  
30 838 provide information about the cell types and tissues where they are usually expressed, demonstrating  
31  
32 839 their relevance to disease mechanisms and developmental processes (Tables 1-3) [251–253].  
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#### 39 840 **4.1. Circulating lncRNAs in obesity**

40  
41 841 Observing changes in obesity-derived circulating lncRNA is crucial to understanding the underlying  
42  
43 842 pathogenesis and pathophysiology of obesity. However, only a few studies have reported the presence  
44  
45 843 of specific circulating lncRNAs in obese patients. The general quiescence of AT in the obese state may  
46  
47 844 contribute to the vast majority of circulating lncRNAs being down-regulated in obesity. Despite being  
48  
49 845 highly promising target molecules, further studies are needed to establish a list of lncRNAs that may be  
50  
51 846 used as prognostic or monitoring biomarkers of obesity. In this section, we will summarize potential  
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53 847 biomarker candidates.  
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#### 57 848 58 59 849 **lncRNA-p5549, lncRNA-p21015, and lncRNA-p19461**

1 850 Sun *et al.* studied circulating lncRNAs profiles in obese participants and identified 40,914 lncRNAs.  
2 851 However, only three were selected for further analysis because of their differential, high signal, and  
3  
4 852 stable detection. These circulating lncRNAs levels were quantified by qPCR in obese and normal-  
5  
6 853 weight individuals. lncRNA-p5549, lncRNA-p21015, and lncRNA-p19461 were significantly  
7  
8 854 downregulated in obese individuals. These analyses were repeated after the participants consumed a  
9  
10  
11 855 very low-calorie diet for 12 weeks and no significant changes were observed except for lncRNA-  
12  
13 856 p19461, which showed significantly increased expression [254].  
14

#### 15 857 **AP001429.1**

17 858 A direct relationship has been established between obesity and various types of cancer, especially breast  
18  
19  
20 859 cancer. AP001429.1 has recently become a biomarker of breast cancer in obese patients. AP001429.1  
21  
22 860 is a lncRNA that may have a protective role against breast cancer. Its expression was measured in obese  
23  
24 861 and non-obese individuals with breast cancer and it was found that AP001429.1 is downregulated in  
25  
26 862 obese patients with breast cancer compared with non-obese individuals with breast cancer [255].  
27  
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#### 29 863 **lncRNA-small nucleolar RNA host gene 9 (lncRNA-SNHG9)**

30  
31 864 lncRNA-SHNG9 was recently shown to be released by exosomes and its expression was diminished in  
32  
33 865 blood samples of obese patients with endothelial dysfunction [256]. These results may indicate that  
34  
35 866 lncRNA-SHNG9 promotes lipid metabolism; however, the mechanism is unclear and further studies are  
36  
37 867 required to understand the mechanisms of lncRNA-SNHG9.  
38  
39

#### 40 868 **lncRNA-SNHG12**

41  
42 869 Childhood obesity is a significant emerging problem due to its association with related severe metabolic  
43  
44 870 diseases. lncRNA-SNHG12 was isolated from plasma samples from adolescents and its expression was  
45  
46 871 shown to be downregulated in obese compared with non-obese individuals, although there is still limited  
47  
48 872 information about this molecule and its mechanism of action [257].  
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51 873

#### 52 53 874 **4.2. Circulating lncRNA in diabetes**

54  
55 875 The rising prevalence of diabetes is a significant public health concern in the modern era, highlighting  
56  
57 876 the need for the development of novel diagnostic methods to identify early metabolic abnormalities,  
58  
59 877 such as insulin resistance. Accumulating evidence suggests that lncRNAs appear to be dysregulated in  
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1 878 diabetes, and they may play a role in type 1 diabetes mellitus (T1D) and T2D,  $\beta$ -cell function, and  
2 879 glucose homeostasis [258–260]. Differential expression patterns of lncRNAs have been reported  
3  
4 880 between healthy individuals and patients with both types of diabetes [261,262]. Given that a single  
5  
6 881 lncRNA can modulate the expression of different transcription factors or mRNAs involved in diabetes  
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8 882 related-pathways, lncRNAs are starting to be considered as potential biomarkers for early diagnosis and  
9  
10 883 prognosis of T1D and T2D, as well as alternative therapeutic targets against this disease [263,264].  
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12 884 Extensive studies have been conducted to investigate the molecular and cellular basis of the relationship  
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14 885 between excess adiposity and impaired glucose homeostasis that underpins T1D and T2D and numerous  
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16 886 AT-centric mechanisms have been postulated. T1D and T2D are associated with a general state of  
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18 887 inflammation in the body, including WAT and BAT [66,265,266], which provokes macrophage  
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20 888 recruitment, proinflammatory cytokine and chemokine upregulation, deregulation of adipokines, ER  
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22 889 stress, oxidative stress, and apoptosis, resulting in a progressive loss of functionality [66,267–272]. As  
23  
24 890 a result, information about AT-derived lncRNA is critical to gain a better understanding of the  
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26 891 pathogenesis and pathophysiology of diabetes.  
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28  
29 892 T1D is a prevalent chronic autoimmune disease in children and adolescents, and several studies show  
30  
31 893 that lncRNAs can regulate the activation of the innate immune system and islet  $\beta$ -cell function,  
32  
33 894 contributing to its pathogenesis. More importantly, dysregulated lncRNA expression is associated with  
34  
35 895 the development of T1D [273,274], suggesting that these molecules could be used as biomarkers to  
36  
37 896 assess the risk of this pathology [275,276]. The mechanisms involved in initializing the autoimmune  
38  
39 897 response that leads to T1D are unknown. However, many of the genetic associations that have been  
40  
41 898 identified so far are in non-coding regions of the genome. LncRNAs may coordinate the many immune  
42  
43 899 functions by regulating the differentiation and function of innate and adaptive immune cells [277–281].  
44  
45 900 Inflammation of the pancreas triggers  $\beta$ -cell apoptosis and the absence of insulin production and  
46  
47 901 secretion [282]. In this situation, the general metabolism is modulated to counteract the failure of the  
48  
49 902 pancreas. Recent studies have shown that the lncRNA MSTRG.63013 is a critical node and two genes,  
50  
51 903 namely *G3BP2* [283] and *CYCS* [284], are especially associated with this lncRNA, which are involved  
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53 904 in many cell signaling pathways and RNA metabolism. In this regard, some critical lncRNAs could be  
54  
55 905 potential biomarkers or regulators of T1D.  
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906 T1D progression is associated with a high risk of developing diabetic complications. The most critical  
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2 907 secondary complications of T1D are diabetic nephropathy (DN) and retinopathy (DR). Genetic factors  
3  
4 908 modulate the risk for complications in diabetes [285,286], but to date, no genes with significant effects  
5  
6 909 on disease susceptibility have been identified. Studies in DN patients have reported that PVT1, or  
7  
8 910 plasmacytoma variant translocation 1, is a lncRNA that encodes some alternative transcripts and  
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10  
11 911 increases cell proliferation. Furthermore, PVT1 amplification and overexpression inhibits apoptosis.  
12  
13 912 Variants of PVT1 are associated with kidney failure-associated T1D. This transcript is abundantly  
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15 913 expressed in kidney cells, which is strongly consistent with a potential role in metabolic dysregulation  
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17 914 in this tissue preceding the development of renal failure in diabetes. Together, these findings suggest  
18  
19 915 that PVT1 may be a critical factor in mediating susceptibility to this disease [287]. Other lncRNAs, such  
20  
21 916 as LINC01619, have been reported to influence DN by inducing oxidative stress and podocyte damage  
22  
23 917 via regulating miR-27a [276,288]. HIF1A-AS2 is another lncRNA that shows a potential role in DR  
24  
25 918 throughout its stages and its interplay with hypoxia, oxidative stress, and angiogenesis via a  
26  
27 919 MAPK/VEGF-dependent pathway [289].  
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30  
31 920 On the other hand, the prevalence of T2D has increased in line with the worldwide rise in obesity in  
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33 921 recent decades. lncRNAs specifically associated with T2D vascular complications have also been  
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35 922 reported. The levels of lncRNA-NR\_033515 were significantly upregulated in the serum of patients  
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37 923 with DN, compared with normal patients, and its expression was associated with the clinical stages of  
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39 924 this pathology [290]. A microarray-based study identified 303 differentially expressed lncRNAs in the  
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41 925 retinas of mice with DR compared with non-diabetic mice, and the results were further corroborated by  
42  
43 926 PCR analysis. These changes correlated with several processes that may be linked to the pathological  
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45 927 neovascularization seen in DR. The highly conserved lncRNA, MALAT1, was found to be upregulated  
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47 928 in the retinas of diabetic mice, suggesting that MALAT1 dysregulation may be associated with DR  
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49 929 occurrence [291]. Furthermore, lncRNA MALAT1 was upregulated in the serum of T2D patients with  
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51 930 diabetic kidney disease compared with those without diabetes and was correlated with specific markers  
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53 931 of diabetic kidney disease (urine beta-2-microglobulin, urine alpha-1-microglobulin, and albumin-to-  
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55 932 creatinine ratio) [292]. For example, the levels of lncRNAs such as HCG27-201 and LY86-AS1 were  
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57 933 downregulated in peripheral blood mononuclear cells isolated from T2D patients compared with  
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934 controls [293]. Similarly, the levels of circulating lncRNA GAS5 were downregulated in the serum of  
935 patients with diabetes and correlated with the onset of the disease; however, circulating lncRNA GAS5  
936 was also downregulated in patients with HbA1c levels between 5.9% and 6.4%, which is not considered  
937 clinically diabetic. These results suggested that other parameters besides conventional parameters, such  
938 as the measurement of circulating levels of specific lncRNAs, should be considered to predict the  
939 chances of developing diabetes [294].

940 Similarly, human lncRNA microarray analysis showed that lncRNA-p3134 was upregulated in the  
941 serum of patients with diabetes compared with those without diabetes [295]. The same study reported  
942 that lncRNA-p3134 was secreted by islet pancreatic beta-cells and further stored in exosomes in  
943 response to high glucose levels. Moreover, lncRNA-p3134 may mediate pancreatic beta-cell protection  
944 and promote insulin synthesis and secretion by enhancing specific regulators (Pdx-1, MafA, Tcf712,  
945 and GLUT2) in these cells [295].

946 More than 1,000 lncRNAs associated with beta-cell maturation and T2D have been identified to date in  
947 pancreatic beta-cells, such as lncRNAs KCNQ1OT1 and HI-LNC45, which were significantly  
948 upregulated in the islets isolated from patients with T2D compared with individuals without diabetes  
949 [296]. Furthermore, lncRNA HI-LNC25 is specifically found in human beta-cells and was also found  
950 to regulate the expression of the GLIS3, which is a key transcription factor containing several T2D risk  
951 variants [296,297].

952 Overall, different studies have reported altered levels of lncRNAs in patients with T2D [262],  
953 corroborating the potential relevance of ncRNAs in this disease. However, most studies focused on  
954 evaluating the differential expression patterns of these molecules; therefore, further validation to gain a  
955 better understanding of the exact mechanisms by which these molecules regulate diabetes  
956 pathophysiology is required.

## 957 958 **5. Future perspectives and therapeutic applications**

959 Since their discovery, many lncRNAs have been identified, and lncRNA research has become especially  
960 relevant due to the wide range of cellular functions in which they are involved. This functional variety

1 961 makes lncRNAs potential therapeutic targets since numerous lncRNAs are frequently altered in AT-  
2 962 related pathologies, such as obesity and diabetes.  
3

4 963 Although major advances in the study of lncRNAs have been achieved in recent years, their regulatory  
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6 964 role is still a relatively young and unknown field, especially in AT. Moreover, the expression of  
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8 965 lncRNAs affected by epigenetic alterations is potentially reversible, complicating the collection of  
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11 966 conclusive data and, at the same time, providing an attractive and promising strategy for its clinical  
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13 967 application. Most of the pharmacotherapy used in clinical practice have protein targets; therefore, these  
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15 968 drugs frequently have unwanted side effects due to their interactions with other proteins [298]. Nucleic  
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17 969 acid-targeting pharmaceuticals, such as lncRNAs, are a promising new field in the quest to identify new  
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19 970 therapies because they have fewer systemic adverse effects than current treatments [299]. The obstacles  
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21 971 currently present in the field of RNA therapies will, without a doubt, be conquered due to the promising  
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23 972 innovations currently emerging from valuable preclinical work. The present review summarizes recent  
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25 973 evidence for the possible roles of several lncRNAs in AT function, such as adipogenesis, lipid  
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27 974 metabolism, and thermogenesis. The findings demonstrate significantly different lncRNA expression  
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29 975 profiles between obese and normal-weight individuals *in vivo* and *in vitro*. Deregulation of lncRNA  
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31 976 expression demonstrates that these molecules are involved in the metabolism of both white and  
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33 977 brown/beige AT.  
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38 978 Future studies should focus on the potential application of lncRNA as biomarkers since lncRNAs can  
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40 979 be detected in both intracellular and extracellular environments. An extensive list of lncRNAs that  
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42 980 function as cancer biomarkers has been identified; however, the list is considerably shorter for diabetes  
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44 981 and obesity; thus, further studies are required. Validation, appropriate primer design, and normalization  
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46 982 are essential steps in developing lncRNA measurement as a promising biomarker. Despite current  
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48 983 limitations, the existence of these peripheral molecules in patients allows for early and non-invasive  
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50 984 diagnosis, prognosis, and monitoring of AT-related disorders. lncRNAs have three main advantages  
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52 985 for obesity treatment: (1) small-molecule drugs have been reported to regulate lncRNA expression and  
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54 986 thus may be a novel treatment method for human obesity [300]; (2) lncRNAs are expressed at relatively  
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56 987 low levels in tissues, indicating powerful regulation even at low doses; and (3) nucleic acid-based drugs  
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58 988 are an emerging class of therapeutics with fewer potential side effects than protein-based drugs that  
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989 could also interact with non-target proteins. Thus, future WAT and BAT lncRNA studies including *in*  
1 *vitro* and *in vivo* experiments may identify novel exciting targets to treat obesity.

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

#### 995 **CREDIT AUTHORSHIP CONTRIBUTION STATEMENT**

996 AC, MCD, and LH conceived the project. AC designed the figures. All the authors wrote and revised  
997 the final version of the manuscript. DS and LH provided funding.

#### 999 **DECLARATION OF COMPETING INTEREST**

1000 The authors declare no conflicts of interest.

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1972 **FIGURE LEGENDS**

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2 1973 **Graphical abstract:**

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4 1974 - LncRNAs are involved in a wide variety of metabolic pathways depending on their localization.  
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6 1975 - In recent years, a large number of lncRNAs have been identified as regulators of adipogenesis  
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8 in different organisms and may be key regulators of obesity.  
9 1976  
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11 1977 - Identification and measurement of circulating lncRNAs could be applied as a predictive  
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13 1978 technique to prevent the progression of diseases such as obesity and diabetes.  
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15 1979  
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18 1980 **Figure 1.** Adipose tissue distribution in humans and rodents. The adipose tissue depots are grouped in  
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20 1981 sWAT (subcutaneous white adipose tissue, colored light brown), gWAT (gonadal white adipose  
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22 1982 tissue, colored yellow) and BAT (brown adipose tissue, colored dark brown).  
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24 1983  
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27 1984 **Figure 2.** Transcriptome classification. The top blue box represents that only 1.5% of the RNA is  
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29 1985 translated into protein. The purple boxes show the main types of non-coding RNA (ncRNAs) based on  
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31 1986 the transcript length (small and long ncRNAs). Abbreviations: Circular RNA (circRNA), linear RNA  
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33 1987 (lncRNA), microRNA (miRNA), non-coding RNA (ncRNA), PIWI-interacting RNA (piRNA),  
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35 1988 ribosomal RNA (rRNA), small interfering RNA (siRNA), transfer RNA (tRNA).  
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37  
38 1989  
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40 1990 **Figure 3.** LncRNA functions based on their location. In the nucleus, DNA-related interactions are  
41  
42 1991 highlighted. In the cytoplasm, lncRNAs interact primarily with RNA and proteins and regulate  
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44 1992 metabolism at the post-translational and post-transcriptional levels. Finally, lncRNAs can be excreted  
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46 1993 into the bloodstream to target other tissues or organs, emerging as excellent candidates for being used  
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48 1994 as biomarkers.  
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51 1995  
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53 1996 **Figure 4.** Venn diagram showing the localization and distribution of lncRNAs in AT. Values in brackets  
54  
55 1997 represent the number of lncRNAs belonging to animals and humans or BAT and WAT. Common areas  
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57 1998 contain the numbers and names of the exclusive lncRNAs within the overlapping groups. The diagram  
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59 1999 includes all of the lncRNAs summarized in this review. The diagram is structured using the following  
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2000 groups: exclusive to human WAT (15 lncRNAs); exclusive to human BAT (4 lncRNAs) and human  
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22001 WAT and BAT (2 lncRNAs); exclusive to animal WAT (9 lncRNAs) and exclusive to animal BAT (5  
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42002 lncRNAs) and animal WAT and BAT (10 lncRNAs).  
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72003  
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92004 **Figure 5.** LncRNAs as biomarkers in obesity and diabetes. (A) Adipocytes release lncRNAs into the  
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112005 bloodstream to reach their targets. These lncRNAs are collected from a blood sample for further  
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132006 isolation and purification. (B) The expression of circulating lncRNAs is measured to detect variations  
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152007 related to diseases, such as obesity and diabetes, to identify the lncRNAs involved in these diseases and  
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172008 develop new therapeutic targets.  
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## 1 TABLES

2 **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, 3T3-L1 adipocytes	Binds and coactivates Ppar $\gamma$	Nucleus, cytoplasm	[158,159,162,301]
Adipoq-AS	WAT, BAT	Negative	3T3-L1 adipocytes	Binds to Adipoq mRNA and inhibits its translation	Unknown	[164,167]
AK079912	WAT, BAT	Positive	Primary BAT and WAT stromal vascular fraction cells	Promoter of mitochondrial biogenesis mediated by Pgc1 $\alpha$ and inducer of transcription of thermogenic genes mediated by Ppar $\gamma$	Unknown	[169]
Xist	BAT	Positive	3T3-L1 adipocytes	Binds C/ebp $\alpha$ to regulate brown differentiation	Nucleus	[157,158,170]
LncRNA-BATE1	BAT	Positive	Primary BAT stromal vascular fraction cells, 3T3-L1 adipocytes	Interacts with hnRNPU	Nucleus, cytoplasm	[158,172]
LncRNA-BATE10	WAT, BAT	Positive	Primary BAT and WAT stromal vascular fraction cells, 3T3-L1 adipocytes	Avoids Pgc1 $\alpha$ degradation by sequestering Celf1	Nucleus, cytoplasm	[158,172,173]
Ctcflos	WAT, BAT	Positive	Primary BAT and WAT stromal vascular fraction cells, 3T3-L1 adipocytes	Regulates transcription and alternative splicing of BAT key genes	Unknown	[174]
ADNCR	WAT	Negative	3T3-L1 adipocytes, ADSCs	Sponges miR-204, leaving free SIRT1, a repressor of Ppar $\gamma$	Unknown	[178]
PU.1-AS	WAT	Positive	Primary WAT stromal vascular fraction cells, 3T3-L1 adipocytes	Binds and blocks PU.1, an inhibitor of adipogenesis	Unknown	[181,182]
SlinRAD	WAT	Positive	3T3-L1 adipocytes	Epigenetic regulation of adipogenesis via DNMT1	Unknown	[184,185]
Lnc-U90926	WAT	Negative	3T3-L1 adipocytes	Inhibits the transactivation of PPAR $\gamma$ 2 or PPAR $\gamma$ .	Unknown	[186]
GM13133	WAT, BAT	Unknown	Primary BAT and WAT stromal vascular fraction cells	Involved in regulation of thermogenesis	Unknown	[187]
NEAT1	WAT	Positive	3T3-L1 adipocytes, ADSCs	Associates with SRp40 to regulates Ppar $\gamma$ splicing	Nucleus	[77,157,158,188]
Paral1	WAT	Positive	3T3-L1 and 3T3-442A adipocytes	Co-activates and upregulates Ppar $\gamma$ transcriptional activity	Unknown	[189]
Lnc-leptin	WAT	Positive	Primary WAT stromal vascular fraction cells	Mediates loop formation between genomic loci of lep and lnc-leptin	Unknown	[190]
Lnc-RAP-1 (FIRRE)	WAT, BAT	Positive	Primary BAT and WAT stromal vascular fraction cells	Interacts with hnRNPU	Nucleus	[157,158,191]
Plnc1	WAT	Positive	3T3-L1 adipocytes, C3H10T1/2 cells, stromal cells ST2, BMSCs	Reduces methylation Ppar $\gamma$ 2 promoter, enhancing its expression	Unknown	[194]
AK142386	WAT, BAT	Unknown	Primary BAT and WAT stromal vascular fraction cells	Targets Hoxa3 and regulates its transcription and expression	Unknown	[195]
AK133540	WAT, BAT	Unknown	Primary BAT and WAT stromal vascular fraction cells	Targets Acad10 and regulates its transcription and expression	Unknown	[195]

TCONS_00041960	WAT	Negative	Rat BMSCs	Inhibits adipogenesis by kidnapping miR- 125a- 3p, a regulator of GILZ, an inhibitor of PPAR $\gamma$	Unknown	[196]
Gm15051	BAT	Unknown	Primary BAT adipocytes	Targets Hoxa1	Unknown	[197]
Tmem189	BAT	Unknown	Primary BAT adipocytes	Targets CEBP $\beta$	Cytoplasm	[158,197]
Cebpd	BAT	Unknown	Primary BAT adipocytes	Targets CEBP $\delta$	Nucleus	[158,197]
LncRNA 2310069B03Rik	WAT, BAT	Unknown	Primary BAT, WAT stromal vascular fraction cells	Unknown	Unknown	[198]

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7 **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	[157,158,201,203–205]
Blnc1	BAT	Positive	C3H10T1/2 cells, Primary BAT adipocytes	Stabilizes the Blnc1/ Zbtb7b/hnRNPU/EBF2 ribonucleoprotein complex	Plasma membrane	[158,207–209,211]
Lnc-dPrdm16	WAT, BAT	Positive	Human fetal BAT	Prdm16 stabilization in WAT browning; unknown in BAT	Unknown	[212]
HOTAIR	WAT	Unknown	Primary WAT adipocytes, ASDCs, immortalized multipotent adipose-derived (iMAD) cells, 3T3-L1 cells	Acts via DNA methylation and has been associated with transcriptional regulation of adipogenic genes	Nucleus	[157,213,215–218]
UC.417	BAT	Negative	Primary BAT stromal vascular fraction cells	Reduces p38 MAPK phosphorylation	Unknown	[197,219]
Dio3os	BAT	Positive	Primary BAT stromal vascular fraction cells	Directly inhibits Dio3 expression. Potential inhibition of miRNA-122	Nucleus	[157,222]
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	[157,158,226]
HoxA-AS3	WAT	Positive	Human ADSCs, mouse ADSCs	Acts via EZH2, a switch for adipogenesis and osteogenic differentiation, promoting transcription of osteogenic genes	Cytoplasm	[157,230]
MIR31HG	WAT	Positive	Human ADSCs	Acts on the FABP4 gene, triggering histone methylation and acetylation, enhancing its expression	Cytoplasm	[157,233]
FoxC2-AS1	WAT	Unknown	Human primary WAT adipocytes	Unknown	Unknown	[235]
HOXA11-AS1	WAT	Positive	Human primary WAT adipocytes	Regulates adipogenesis by upregulating adipogenic-related genes	Nucleus	[158,236]
ADINR	WAT	Positive	Human ADSCs	ADINR induces C/EBP $\alpha$ gene expression during adipogenesis via MLL3/4	Unknown	[237]
MEG3	WAT	Unknown	Human ADSCs, 3T3-L1 adipocytes, rat primary BMSC lines	Inhibits adipogenesis via miR-140-5p in hADSCs and rat BMSCs. Promotes adipogenesis in 3T3-L1 via the miR-217/Dkk3 axis	Nuclear	[157,239,240,302]
ecCEBPA	Unknown	Positive	Leukemic cell lines HL-60 and U937	Avoids methylation of promoter C/EBP $\alpha$ and leads to its overexpression	Unknown	[241]
ASMER	WAT	Positive	Human primary WAT adipocytes	Unknown	Unknown	[242]
Gm15290	WAT	Positive	hMADS-2, hMADS-3	Sponges miR-27b, an inhibitor of PPAR $\gamma$ and C/EBP $\alpha$	Unknown	[243,244]
LncRNA RP11-20G13.3	WAT	Positive	Human primary WAT adipocytes	Unknown	Unknown	[245]
LINC00968	WAT	Unknown	Human primary WAT adipocytes	Unknown	Nucleus	[157,245]
AC011891.5	WAT	Unknown	Human primary WAT adipocytes	Unknown	Unknown	[245]
GYG2P1	WAT	Unknown	Human primary WAT adipocytes	Unknown	Unknown	[245]

RP11-529H2.1	WAT	Unknown	Human primary WAT adipocytes	Unknown	Unknown	[245]
OLMALINC	WAT	Unknown	Human primary WAT adipocytes	Unknown	Nucleus	[157,245]

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

<b>LncRNA</b>	<b>Disease</b>	<b>Circulating levels vs. control subjects</b>	<b>AT expression (LncBook or NONCODE ID)</b>	<b>References</b>
LncRNA-p5549	Obesity	downregulated	Yes (HSALNG0105664)	[252,254]
LncRNA-p21015	Obesity	downregulated	Yes (HSALNG0012350)	[253,254]
LncRNA-p19461	Obesity	downregulated	Yes (HSALNG0101515)	[252,254]
AP001429.1	Obesity, breast cancer	downregulated	Yes (HSALNG0132979)	[251,253,255]
LncRNA-SNHG9	Obesity	downregulated	Yes (HSALNG0108960)	[251,253,256]
LncRNA-SNHG12	Obesity	downregulated	Yes (HSALNG0002075)	[251,253,257]
MSTRG.63013	T1D	upregulated	Unknown (novel transcript)	[283,284]
PVT1	T1D	unknown	Yes (HSALNG0068477)	[251,252,287]
LINC01619	T1D	upregulated	Yes (HSALNG0093041)	[251,252,276,288]
HIF1A-AS2	T1D	upregulated	Yes (HSALNG0101776)	[251–253,289]
lncRNA-NR_033515	T2D	upregulated	Unknown	[290]
MALAT1	T2D	upregulated	Yes (HSALNG0084905)	[251–253,291]
HCG27-201	T2D	downregulated	Yes (HSALNG0049246)	[252,253,293]
LY86-AS1	T2D	downregulated	Yes (HSALNG0047822)	[251,252,293]
LncRNA GAS5	T2D	downregulated	Yes (HSALNG0008545)	[251–253,294]
LncRNA-p3134	T2D	upregulated	Yes (HSALNG0090364)	[251–253,295]
KCNQ1OT1	T2D	upregulated	Yes (HSALNG0082235)	[251–253,296]
HI-LNC45	T2D	upregulated	Yes (NONHSAG020377.2)	[296,303]

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

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**ABSTRACT**

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.

**KEYWORDS:** lncRNA, adipose tissue, biomarkers, obesity, diabetes, therapeutics.

**RUNNING TITLE:** long non-coding RNAs in adipose tissue

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**Figures:** 45

**Tables:** 3

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7 43 **ABBREVIATIONS**  
8  
9 44 AdipoQ, adiponectin  
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11 45 ADSC, adipocyte-derived stem cell  
12 46 ASAT, abdominal subcutaneous adipose tissue  
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14 47 ASMER, adipocyte-specific metabolic-related lncRNA  
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16 48 AT, adipose tissue  
17 49 BAT, brown adipose tissue  
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19 50 Blnc1, brown fat lncRNA 1  
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21 51 BMSC, bone marrow stem cells  
22 52 C/EBP, CCAAT enhancer binding protein  
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24 53 DIO3OS, DIO3 opposite strand  
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26 54 DN, diabetic nephropathy  
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28 55 DR, diabetic retinopathy  
29 56 D3, iodothyronine deiodinase 3  
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31 57 ecCEBPA, extra-coding CEBP $\alpha$   
32  
33 58 FABP4, fatty acid binding protein 4  
34 59 FFA, free fatty acids  
35  
36 60 FOXC2, forkhead box protein C2  
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38 61 GSAT, gluteofemoral subcutaneous white adipose tissue  
39 62 HFD, high-fat diet  
40  
41 63 hnRNPU, heterogeneous nuclear ribonucleoprotein U  
42  
43 64 HOTAIR, HOX antisense intergenic RNA  
44 65 lncRNA, long non-coding RNA  
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46 66 lnc-RAP, polyadenylated long non-coding RNA  
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48 67 miRNA, microRNA  
49 68 mRNA, messenger RNA  
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51 69 ncRNA, non-coding RNA  
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53 70 NEAT, nuclear enriched abundant transcript 1

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7 71 Para11, PPARG activating RBM14 associated lncRNA 1  
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9 72 PGC1, peroxisome proliferator-activated receptor gamma coactivator 1  
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11 73 PPAR, peroxisome proliferator-activated receptor  
12 74 PRDM16, PR domain containing 16  
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14 75 SAT, subcutaneous white adipose tissue  
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16 76 slincRAD, super-long intergenic ncRNA functioning in adipocyte differentiation  
17 77 SRA, steroid receptor RNA activator  
18  
19 78 T1D, type 1 diabetes mellitus  
20  
21 79 T2D, type 2 diabetes mellitus  
22  
23 80 UCP1, uncoupling protein 1  
24 81 VAT, visceral white adipose tissue  
25  
26 82 WAT, white adipose tissue  
27 83 Xist, X-inactive specific transcript  
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7 84 **TABLE OF CONTENTS**  
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**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 \(AT\). Adipose tissue \(AT\) is a metabolically active endocrine organ that releases various hormones that may exert their effects at the systemic or local level and can lead to several health problems in a chronic situation \[14\].](#) 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.

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**1.2. White and brown AT**

**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.

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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, and post-lactation.~~ After the lactation period concludes, they transdifferentiate to white or brown adipocytes again. In addition to being involved in ~~Besides~~ 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].

**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 (Figure 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 pericardial WAT) and subcutaneous adipose tissue (SAT) (Figure 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].

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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]. ~~Several studies have suggested that alterations in the growth of new adipocytes or enlargement of existing adipocytes regulate ASAT and GSAT differently in obese individuals.~~ 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]. ~~Changes in the number and size of adipocytes as well as infiltration of immune cells modulate the microenvironment within AT [34]. In addition to anatomical location and cellular changes, genetic and epigenetic~~ All these factors play a very important role in AT dysfunction, as will be discussed in the following section. ~~Indeed, AT biogenesis is regulated by specific and tightly regulated gene expression programs that have been extensively studied over the past 30 years [33].~~

### 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, ~~and increase in increment 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,

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7 hypoxia, impaired angiogenesis, inflammation, fibrosis, mitochondrial dysfunction, and oxidative  
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9 damage due to endoplasmic reticulum (ER) stress and oxidative stress.

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11 **Hyperplasia, hypertrophy, and impaired adipogenesis**

12 AT expansion has a limit, and when it is exceeded, adipocytes suffer from hypertrophy. Hypertrophy  
13  
14 leads to the tissue becoming inflamed and dysregulated, and fat begins to accumulate in the visceral and  
15  
16 peri-epicardial areas as well as ectopic sites, including liver, heart, and skeletal muscle [41–45]. Hence,  
17  
18 both hyperplasia and hypertrophy are mechanisms involved in AT remodeling. However, the  
19  
20 consequences of each are quite different. Hyperplasia plays a protective role since it has been associated  
21  
22 with improved glucose metabolism and insulin sensitivity [41]. Instead, hypertrophy is related to  
23  
24 different disorders, including insulin resistance, even in normal-weight individuals, and has become a  
25  
26 marker of T2D [46].

27 ASAT shows a hypertrophic response with limited capacity to recruit new adipocytes, whereas GSAT  
28  
29 demonstrates a proliferative response to weight gain [30,31,47,48]. Thus, GSAT is considered  
30  
31 protective against metabolic-related diseases, while the opposite has been described for ASAT [33]. A  
32  
33 greater accumulation of ASAT increases the risk of cardiovascular disease and T2D, similar to that of  
34  
35 VAT [49,50]. The mechanisms underlying these depot-specific differences are complex and not fully  
36  
37 understood. Several factors, including hormones, transcription factors, and cell signaling molecules,  
38  
39 that could influence these differences have been proposed [47].

40 Furthermore, hypertrophic adipocytes showed reduced expression of adipogenic markers and alterations  
41  
42 in the profile of secreted adipokines. Increased infiltration of proinflammatory macrophages has been  
43  
44 observed in expanded VAT [51,52]. Consequently, adipocytes release inflammatory cytokines, which  
45  
46 diminish the production of protective molecules such as adiponectin (Adipoq). Thus, normal  
47  
48 adipogenesis and differentiation are compromised, leading to dysfunctional AT [39,42,46].

49  
50 **Hypoxia and impaired angiogenesis**

51 The expansion of AT requires a larger number of blood vessels to supply oxygen, nutrients, and other  
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53 molecules for new and/or hypertrophic adipocytes. AT expansion and angiogenesis, which is the growth  
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55 of blood vessels from the existing vasculature, go hand in hand. However, it remains unclear whether  
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7 adipogenesis is under the control of angiogenesis or *vice versa*. Various processes regulate angiogenesis,  
8  
9 including adipocyte expansion [53], inflammation [54], and hypoxia [54].

10  
11 During hyperplasia, tissue grows healthily and develops new blood vessels to avoid hypoxia. However,  
12 this does not occur during hypertrophy, and severe hypoxia begins to emerge. The development of  
13  
14 hypoxia in adipocytes has been closely related to changes in the cell secretome [54–57]. Angiogenesis  
15  
16 depends on numerous factors and although, hypoxia itself does not seem to be sufficient to enhance  
17  
18 angiogenesis it is one of its triggering mediators both *in vitro* and *in vivo* [41].

19 **Inflammation and fibrosis**

20  
21 Various cytokines are released in response to normal AT expansion. However, in obesity, hypertrophic  
22  
23 adipocytes trigger signals that activate inflammation-related metabolic pathways. Inflammation causes  
24  
25 adaptive responses in adipocytes in order to attenuate its adverse effects. Nevertheless, when  
26  
27 inflammation becomes chronic, maladaptive responses emerge, leading to a pathological state. Some  
28  
29 mechanisms that lead to downstream inflammatory signaling include hypoxia, FFA accumulation, and  
30  
31 mechanical stress caused by expansion through the extracellular matrix [58].

32  
33 The secretome of hypertrophic adipocytes is altered and adipocytes begin to release proinflammatory  
34  
35 cytokines that promote immune cell infiltration, including macrophages, T cells, and mast cells [59].

36  
37 The cytokines secreted by adipocytes include tumor necrosis factor alpha (TNF $\alpha$ ), interleukin (IL) 6,  
38  
39 IL8, monocyte chemotactic protein 1, inducible nitric oxide synthase, transforming growth factor beta  
40  
41 1, C-reactive protein, and soluble intercellular adhesion molecule 1 [60,61]. An increase in adipocyte  
42  
43 size is closely related to macrophage infiltration into AT and adipocyte death. During obesity,  
44  
45 macrophages constitute up to 40% of all AT cells [61]. The proinflammatory molecules released by  
46  
47 macrophages and other molecules produced by different immune cells have direct effects on cellular  
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49 metabolism and block insulin action to limit energy accumulation and promote angiogenesis to prevent  
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51 hypoxia [58,62–64].

52  
53 Chronic inflammation is usually related to tissue remodeling and fibrosis, especially in pathological  
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55 states. During fibrosis there is an excessive deposition of extracellular matrix components which  
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57 negatively affects tissue function [65]. The relationship between fibrosis and obesity is unclear. Some  
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59 studies have shown a positive correlation between fibrosis and metabolic disease in murine models and  
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7 humans [66–68]. However, other studies have not supported this correlation and have reported the  
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9 involvement of other factors, such as BMI and hyperplastic expansion, and proposed that fibrosis limits  
10  
11 hypertrophy expansion and acts as an adaptative feature to preserve adipocyte function [69–72]. In  
12 parallel, unresolved inflammation triggers adipocyte fibrosis, metabolic inflexibility, dysregulation of  
13  
14 adipocyte function, and cell death [58].

### 15 16 **Mitochondrial dysfunction**

17 Mitochondria play a crucial role in fatty acid metabolism and, therefore, in adipogenesis [73,74]. A  
18  
19 sequence of disorders leads to mitochondrial dysfunction, which has severe consequences, including  
20  
21 insulin resistance and inflammation [75]. Obesity is strongly related to ER stress and reactive oxygen  
22 species production, which are two closely mitochondrial dysfunction-related processes. When fatty acid  
23  
24 oxidation and mitochondrial biogenesis rates are diminished, mitochondrial DNA is reduced, triggering  
25  
26 fibrosis, inflammation, and apoptosis [66,76]. Similar results have been found in humans [77–81] and  
27  
28 obese patients with T2D [82].

29 These mechanisms, including hypertrophy, hypoxia, inflammation, fibrosis, and mitochondrial  
30  
31 dysfunction, are some of the main drivers of the development of AT-related disorders.

## 32 33 34 **2. Non-coding RNA (ncRNA)**

### 35 36 **2.1. Types and functions**

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

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7 different types of ncRNA to fully understand the mechanisms involved in these disorders and propose  
8 highly effective treatments to improve AT-related disorders ([Figure 2](#)).

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10 Our understating of the different types of ncRNAs is increasing exponentially with the development of  
11 next-generation sequencing techniques and bioinformatics analysis. ncRNAs are classified as small  
12 ncRNAs (length <200 nucleotides), including ribosomal RNA, transfer RNA, microRNA (miRNA),  
13 small nuclear RNA, small interfering RNA, PIWI-interacting RNA, and long ncRNAs (~~lncRNAs~~; length  
14 >200 nucleotides) [95], which are further subdivided into circular (circRNA) and linear RNAs. Among  
15 these, the main groups of ncRNAs involved in AT metabolism and associated pathologies are miRNA  
16 and lncRNAs. The miRNAs are by far the most studied family of ncRNAs in this context. These  
17 molecules are small RNAs (18–22 nucleotides) that act as negative regulators of gene expression by  
18 binding to short complementary regions of target mRNAs [96–98]. All mRNAs are predicted to have  
19 more than 60% of their 3' untranslated region (UTR) target sites for miRNAs, indicating tight control  
20 and participation in both normal cell homeostasis and illness [99]. The circRNAs are another example  
21 of lncRNAs recently studied in AT. They are produced by alternative splicing of RNAs, act as miRNA  
22 sponges and contain RNA-binding protein (RBP) binding sites, regulating alternative splicing and gene  
23 expression. The roles of linear RNAs (from now on referred as lncRNAs) will be explained in depth in  
24 the next section in which we describe the recent findings in the field of lncRNAs, and their association  
25 with AT.

## 26 27 28 29 30 31 32 33 34 35 36 37 38 39 **2.2. LncRNAs**

40 In the 1990s, the pioneering discovery of the uncharacterized ncRNAs, H19 and X-inactive specific  
41 transcript (Xist) 1, led to the early belief that lncRNAs were transcriptional noise with little or no  
42 functional significance [100,101]. Although lncRNAs were discovered in the early 2000s, later studies  
43 showed that they were critical for a wide range of biological functions [86,102]. As mentioned  
44 previously, lncRNAs are a heterogeneous group of ncRNA that range in size from 200 nucleotides to  
45 20 kb. The nucleotide chains have the remarkable capacity to acquire various complex secondary and  
46 tertiary structures, enabling them to fulfill specialized roles required for survival [103]. Due to their  
47 structural diversity, lncRNAs can interact with DNA, RNA, and proteins and perform several regulatory  
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7 activities, as we will describe. A systematic integration of annotations of existing databases revealed  
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9 that there are almost 270,000 lncRNA transcripts annotated in humans [104–110]. Their nomenclature  
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11 and symbols have been certified by the HUGO Gene Nomenclature Committee [111].  
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13 Knowledge of the biosynthesis of lncRNAs is necessary to decode their functional significance,  
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15 relevance, and distinction from other types of RNAs. DNA elements, such as enhancers, promoters, and  
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17 intergenic regions, are responsible for the transcription of a wide range of lncRNAs. Like mRNAs,  
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19 lncRNAs are transcribed by RNA polymerase II, which requires the assembly of similar preinitiation  
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21 complex and transcription factors [112]. Overall, lncRNAs also present 5' ends with a 7-methyl  
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23 guanosine cap and 3' ends with a polyadenylated tail [113]. While, several lncRNA loci have been  
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25 shown to use non-canonical 3' end processing that results in non-polyadenylated RNAs [114,115], this  
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27 method of lncRNA stability involves ribonuclease P, which cleaves and generates a mature 3' end [113].  
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29 In general, lncRNAs are intracellular (and could be released into the circulation) and stable with  
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31 expression patterns that are unique to each cell type, tissue, and stage in the development and function  
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33 of each cell. They are expressed at a lower rate than mRNAs in a given cell type [116,117]. Therefore,  
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35 identifying the evolutionary conservation of functional sequences in the genome is one of the most solid  
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37 and accurate characteristics, highlighting their involvement as potential regulatory elements in essential  
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39 biological processes [118]. The skepticism concerning the evolutionary conservation of lncRNAs  
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41 extends to controversy about their functionality and biological relevance [119–123]. In 2015, a study  
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43 on the non-coding transcriptomes of 17 diverse species revealed that the bodies of the non-coding genes  
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45 are not conserved [124]. However, their 5' ends contained short conserved sequences [123], which  
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47 revealed a higher level of expression patterns in diverse tissues, particularly those involved in  
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49 development [125].  
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51 The structure, function, localization, and interaction with other biomolecules are applied to classify the  
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53 wide diversity of lncRNAs [126]. [The wide functions of lncRNAs are reviewed elsewhere](#) [127–131].  
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55 Regarding their location within the genome, lncRNAs are categorized into various types, including  
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57 sense lncRNAs, antisense lncRNAs, bidirectional lncRNAs, intronic lncRNAs, intergenic lncRNAs,  
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59 promoter-associated lncRNAs, and UTR-associated lncRNAs [116,132]. In addition, lncRNA  
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61 classification according to the intracellular location could be used to predict their mechanism of action.  
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Whereas mature mRNAs are only found in the cytoplasm, most lncRNAs are mainly located in the nucleus [116,133] 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 [134,135]. In the absence of an active *cis*-element, it is probable that capped and polyadenylated stable RNA serves as a nuclear export substrate [136]. Thus, the location of lncRNAs in the nucleus is coordinated at multiple levels (reviewed in [131]), 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 [130,131,137]). 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 [138].

A considerable proportion of lncRNAs are exported to the cytosol and are thought to use analogous processing and export pathways, similar to mRNAs [139]. 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 [140], protein activity [141], and levels through protein post-translational modifications [141,142]. Additionally, lncRNAs act as miRNA sponges by binding to complementary sites and influence gene expression by competing with endogenous RNAs [143,144].

Analysis of the human mitochondria transcriptome revealed that various lncRNAs are recruited into the mitochondria, indicating other subcellular localizations [145]. 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 [146,147]). Some other lncRNAs are sublocalized in exosomes by binding specific motifs via RBPs [148]. This sublocation may be related to their function as possible

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7 376 biomarkers, as described in section 4 “LncRNAs as biomarkers” of this review. In addition, high-  
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9 377 throughput sequencing of ribosome-protected fragments (Ribo-seq) analysis demonstrated that  
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11 378 lncRNAs interact with ribosomes [149–151]. Although this is controversial (reviewed in [131,152]),  
12 379 some studies have demonstrated that lncRNAs may encode small polypeptides (also known as  
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14 380 micropeptides) in certain circumstances [153], which raises the question whether lncRNAs are non-  
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16 381 coding molecules. However, other studies have revealed that lncRNA association with ribosomes does  
17 382 not always indicate that they are actively translated [154].  
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19 383 In summary, lncRNAs can regulate gene expression at the epigenetic (e.g., DNA methylation, histone  
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21 384 modification), transcriptional (e.g., recruitment of transcription factors), and post-transcriptional (e.g.,  
22 385 modulation of miRNA and mRNA integrity) level (Figure 23). Furthermore, lncRNAs may interact with  
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24 386 DNA, RNA, miRNA, and protein complexes in order to perform their role and control a variety of  
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26 387 physiological and pathological processes. ~~The wide functions of lncRNAs are reviewed elsewhere~~  
27 388 ~~[132,135,153–155].~~  
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### 30 31 390 **3. LncRNAs in AT**

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33 391 In the last few years, it has been postulated that lncRNAs act as coregulators in a wide range of  
34 392 processes, including AT development and function. As mentioned, numerous mechanisms are  
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36 393 responsible for proper adipogenesis and functioning of WAT. BAT has is a myriad of activators, co-  
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38 394 activators, transcription factors, and even miRNAs that have been described to play pivotal roles in the  
39 395 generation of adipocyte precursors (engrailed-1, myogenic factor 5), adipogenesis leading to mature  
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41 396 brown adipocytes [PR domain containing 16 (PRDM16), peroxisome proliferator-activated receptor  
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43 397 gamma (PPAR $\gamma$ ), and peroxisome proliferator-activated receptor gamma coactivator 1 (PGC1 $\gamma$ )], and  
44 398 transdifferentiation from white to beige adipocytes (irisin, meteorin-like protein) [155]. Thus, promoting  
45  
46 399 the thermogenic potential is a tightly regulated process in which new regulators are constantly being  
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48 400 discovered. Although these pathways have been studied extensively, it remains unclear how they are  
49 401 regulated by lncRNAs. Since most of these pathways have been described in animal models, it is crucial  
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51 402 to unequivocally identify those related to human lncRNAs in terms of genomic or splicing signal  
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53 403 sequence conservation, similar secondary structures, or syntenic transcription [156]. This would provide

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404 a strong background for the potential use of ncRNAs as therapeutic tools to treat metabolic diseases.  
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905 The following section describes some of the lncRNAs responsible for regulating AT expansion and  
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406 function that have been shown to be important in recent studies. The lncRNAs described in this section  
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407 are summarized in Tables 1 and 2. [The subcellular localization of each lncRNA has been collected](#)  
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408 [from the databases LncAtlas \[157\] and BioGPS \[158\] and their](#) tissue expression [of these](#)  
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409 [lncRNAs](#) is ~~described shown~~ in Figure 34.

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3.1. LncRNAs involved in AT in animal models

#### 412 **Steroid receptor RNA activator (SRA)**

413 The steroid receptor RNA activator 1 (*Sra1*) gene encodes lncRNAs of different lengths and mRNA by  
414 alternative splicing [159]. SRA lncRNA is involved in numerous metabolic processes, including  
415 mammary gland development and muscle differentiation, and is related to the development of cancers,  
416 such as ovarian cancer [160]. Furthermore, SRA was the first lncRNA reported to be present in  
417 adipocytes [161].

418 SRA is highly expressed in WAT and BAT [159] and increases twofold during adipocyte differentiation.  
419 Its overexpression in the stromal cell line, ST2, induces differentiation of adipocytes *in vitro*, whereas  
420 knockdown showed the opposite effects in 3T3-L1 white adipocytes [162]. In addition, SRA promotes  
421 glucose uptake and reduces insulin resistance and *Sra* knockdown in mature 3T3-L1 adipocytes led to  
422 a reduced number of insulin receptors [163]. Furthermore, *Sra* knockout in the WAT of mice led to  
423 resistance to high-fat diet (HFD)-induced obesity and a healthier phenotype with increased glucose  
424 tolerance, decreased fatty liver, decreased adipogenesis, reduced expression of inflammation-related  
425 genes, reduced plasma TNF- $\alpha$  levels, and improved insulin sensitivity [159]. Regarding its molecular  
426 mechanism, SRA binds to and coactivates *Ppar $\gamma$* , which is the master transcriptional regulator of  
427 adipogenesis [162]. These results indicate that SRA is an essential regulator of obesity, fatty liver, and  
428 glucose homeostasis *in vivo* and may be a potential therapeutic target.

#### 429 **Adiponectin antisense (Adipoq-AS)**

430 Within the *Adipoq* locus, Adipoq-AS is transcribed from the opposite strand to the *Adipoq* mRNA in  
431 mice and humans, presenting an overlapping sequence [164]. Like *Adipoq* mRNA, Adipoq-AS is

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expressed in AT and increases during differentiation of 3T3-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 [164].

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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 3T3-L1 cells and enhance cell proliferation. [165]. *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 [166]. 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*, *Pgc1a*, and *Prdm16* was increased in the epididymal and inguinal WAT and in BAT. Circulating 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 [164]. 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 [167].

#### AK079912

Uc009csb.1, also known as AK079912, is a lncRNA that was initially related to white adipogenesis [168]. 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 [169].

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 [169]. 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

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7<sup>459</sup> regulation of mitochondrial biogenesis via PGC1 $\alpha$  and as a mediator of PPAR $\gamma$ -induced transcriptional  
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9<sup>460</sup> activation of thermogenic genes [169].

#### 10 11<sup>461</sup> **Xist**

12<sup>462</sup> Wu *et al.* recently proposed Xist as a potential regulator of BAT differentiation [170]. This lncRNA has  
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14<sup>463</sup> been widely related to pathological conditions, such as cancer, fibrosis, and inflammation [171]. The  
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16<sup>464</sup> authors reported that Xist levels increased during brown adipocyte differentiation *in vitro*.  
17<sup>465</sup> Overexpression of Xist during differentiation increased the expression of BAT marker genes, such as  
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19<sup>466</sup> *Ucp1*, CCAAT enhancer binding protein (*Cebp*)  $\alpha$ , and *Ppar $\gamma$*  [170]. Conversely, the expression of  
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21<sup>467</sup> these genes was reduced after Xist silencing during differentiation. However, by *Xist* silencing in mature  
22<sup>468</sup> brown adipocytes showed no effects. Moreover, RNA immunoprecipitation assays demonstrated that  
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24<sup>469</sup> Xist may directly bind *Cebpa* to regulate brown differentiation [170]. Although there is no evidence of  
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26<sup>470</sup> a potential adipogenic role in human BAT, if confirmed, this could provide new insight into the  
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28<sup>471</sup> biological differences of BAT between men and women beyond hormonal control.

#### 29<sup>472</sup> **LncRNA-BATE1 and LncRNA-BATE10**

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31<sup>473</sup> In 2015, murine transcriptome profiling analysis revealed that 40 lncRNAs were upregulated during  
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33<sup>474</sup> BAT adipogenesis [172]. Both lnc-BATE1 and lnc-BATE10 were found to be specifically highly  
34<sup>475</sup> expressed in murine brown adipocytes both *in vivo* and *in vitro*. Knockdown of these lncRNAs did not  
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36<sup>476</sup> cause a significant impact on lipid accumulation during brown adipogenesis but reduced the expression  
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38<sup>477</sup> of common BAT marker genes, such as *Ucp1* and *Pgc1 $\alpha$* . Furthermore, ablation of these regulatory  
39<sup>478</sup> RNAs reduced the expression of *Ucp1* and *Pgc1 $\alpha$*  during the transdifferentiation of white adipocytes  
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41<sup>479</sup> into beige adipocytes, suggesting a pivotal role of lnc-BATE1 and lnc-BATE10 in browning [172,173].  
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43<sup>480</sup> Knockdown of *lnc-BATE1* resulted in lower mitochondrial oxygen consumption [172], whereas  
44<sup>481</sup> suppression of *lnc-BATE10* hindered norepinephrine-mediated thermogenesis in brown adipocytes  
45  
46<sup>482</sup> [173].

47  
48<sup>483</sup> It was shown that lnc-BATE1 can act *in trans* to regulate brown adipogenesis by controlling the  
49<sup>484</sup> expression of BAT-specific genes (including *Dio2*, *Ucp1*, and *Ppara*) and adipogenic genes (such as  
50  
51<sup>485</sup> *Cebpa* and *Ppar $\gamma$* ). RNA immunoprecipitation analysis revealed that lnc-BATE1 interacts with  
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53<sup>486</sup> heterogeneous nuclear ribonucleoprotein U (hnRNP) to form a functional ribonucleoprotein [172].

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Meanwhile, lnc-BATE10 competitively binds Celf1, which is an RNA-binding protein that targets *Pgc1a* mRNA, causing its degradation [173].

#### **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 [174] 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 [174].

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 [175]. 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 [175].

#### **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 [176,177]. 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 3T3-L1 cells [178–180]. SIRT1 overexpression decreased adipogenesis in 3T3-L1 cells, whereas silencing of SIRT1 via RNA interference enhanced adipogenesis [179]. 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 PPAR $\gamma$ , C/EBP $\alpha$ , and fatty acid binding protein 4 (FABP4), whereas ADNCR knockdown increased PPAR $\gamma$  and FABP4 expression [178].

#### **PU.1 antisense (PU.1-AS) lncRNA**

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7 515 PU.1 regulates a wide range of pathways, including adipogenesis. *PU.1* is strongly related to insulin  
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9 516 resistance and inhibition of adipocyte differentiation in 3T3-L1 cells. PU.1-AS lncRNA is transcribed  
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11 517 from the opposite DNA strand and overlaps with sense *PU.1* mRNA [181]. Several studies have  
12 518 confirmed the inhibitory role of PU.1-AS in different animal models, including murine [182] and  
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14 519 porcine [183] adipocytes. PU.1-AS knockdown inhibits adipogenesis and promotes the expression of  
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16 520 PU.1 protein in both preadipocytes and adipocytes. Furthermore, repression of PU.1-AS led to  
17 521 decreased *Adipoq* expression and secretion in mature adipocytes of C57BL/6 male mice [182]. These  
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19 522 results indicate that PU.1 is an inhibitor of preadipocyte differentiation and is blocked by PU.1-AS to  
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21 523 promote adipogenesis.

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#### 30 **Super-long intergenic ncRNA functioning in adipocyte differentiation (slincRAD)**

31 529 SlincRAD is an essential lncRNA for AT expansion. Its expression is upregulated in the early stages of  
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33 530 3T3-L1 differentiation and decreases to remain stable during the later stages [184]. Zhang *et al.*  
34 531 demonstrated that slincRAD knockdown in 3T3-L1 cells led to impaired expression of adipogenic  
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36 532 markers and an imbalanced AT development, with smaller adipocytes, decreased lipid accumulation,  
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38 533 and decreased *Pparγ* and *Fabp4* expression. Furthermore, these adipocytes showed unregulated glucose  
39 534 and lipid metabolism, defective epigenetic regulation, and impaired adipogenesis [185]. Although the  
40  
41 535 mechanisms of slincRAD remain unclear, it appears to be involved in clonal expansion together with  
42  
43 536 DNA methyltransferase 1 (DNMT1), regulating adipogenesis via epigenetic processes [184].

#### 44 537 **Lnc-U90926**

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46 538 Lnc-U90926 is an adipogenesis regulator whose expression is negatively correlated with adipocyte  
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48 539 differentiation in 3T3-L1 cells [186]. It is mainly expressed in WAT and its levels are lower in obese  
49 540 mice. Overexpression of lnc-U90926 impaired adipogenesis, decreased lipid accumulation, decreased  
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51 541 mRNA levels of *Pparγ2*, *Fabp4*, and *Adipoq* (but not *C/ebpa*), and reduced protein levels of PPARγ2  
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53 542 and FABP4. In contrast, knockdown of lnc-U90926 showed the opposite effects and enhanced

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7 adipogenesis, with significant increases in *Pparγ2*, *C/ebpa*, *Fabp4*, and *Adipoq* mRNA levels, PPAR $\gamma$   
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9 and FABP4 protein levels, and lipid accumulation [186]. These results suggest that lnc-U90926 inhibits  
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11 *Pparγ2* promoter transactivation. However, further studies are needed to determine its mechanism of  
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13 action since lnc-U90926 is located in the cytoplasm and it does not seem to interact directly with the  
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15 *Pparγ2* promoter [186].

### 16 **GM13133**

17 You *et al.* published novel data about GM13133, a 736-bp lncRNA transcribed in the opposite direction  
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19 from the first intron of PRDM16 in mice; however, no homology or synteny has been observed in  
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21 humans. It was found to be predominantly expressed in BAT, although its expression is not modified  
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23 by cold or  $\beta$ 3-adrenergic agonist treatment [187]. Overexpression of GM13133 *in vitro* increased the  
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25 expression of BAT markers and mitochondrial DNA, although there is not enough evidence to show  
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27 whether it impacts thermogenic activity. Although oxygen consumption rates were measured, the results  
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29 showed no differences in basal respiration or proton leak compared with control cells and the lack of a  
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31 normalization method may invalidate these results. In addition, no evidence of *Gm13133* ablation *in*  
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33 *vitro* was presented [187]; therefore, further *in vivo* studies should be carried out to evaluate the potential  
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35 of this lncRNA.

### 36 **Nuclear enriched abundant transcript 1 (NEAT1)**

37 NEAT1 is a lncRNA that is highly abundant in nuclei, essential for paraspeckles, and involved in  
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39 adipogenesis [188]. NEAT1 expression presents a variable profile during adipocyte differentiation and  
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41 regulates *Pparγ2* splicing during adipogenic differentiation of 3T3-L1 cells. Furthermore,  
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43 downregulation of NEAT1 decreases lipid accumulation and reduces the expression of *C/ebpa* and  
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45 *Pparγ* but re-expression of NEAT1 rescues the adipogenic phenotype [77,188]. The published  
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47 information on its mechanism of action is minimal. It appears that NEAT1 regulates *Pparγ* splicing  
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49 during adipogenesis via SRp40, which is a protein responsible for regulating the alternative splicing of  
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51 pre-mRNA [188].

### 52 **PPARG activating RBM14 associated lncRNA 1 (Paral1)**

53 Paral1 is exclusive to mature adipocytes. Its expression is positively correlated with PPAR $\gamma$  expression  
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55 and a decrease in diet-induced obesity or genetic mouse models of obesity [189]. Little is known about

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7 571 its mechanism, except that Par11 acts by co-activating and upregulating *Pparγ* transcriptional activity.  
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9 572 In 3T3-L1 cells, Par11 downregulation significantly decreased lipid accumulation and adipogenic gene  
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11 573 expression *in vitro*. Surprisingly, overexpression of Par11 did not reverse this effect, demonstrating  
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13 574 that Par11 is necessary but not sufficient for adipogenesis [189].

#### 14 575 **Lnc-leptin**

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16 576 Lnc-leptin plays a regulatory role in *leptin* expression and is necessary to maintain *leptin* levels. Its  
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18 577 expression is closely correlated with *leptin* expression in adipocytes from mouse inguinal and  
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20 578 epididymal WAT [190]. Moreover, knockdown of lnc-leptin showed impaired adipogenesis, whereas  
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22 579 overexpression of lnc-leptin did not affect *leptin* or other adipocyte markers. These results provide  
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24 580 evidence that lnc-leptin is necessary but not sufficient to regulate *leptin* expression and its effects on  
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26 581 adipogenesis [190]. Although its mechanisms remain unclear, the authors proposed that lnc-leptin forms  
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28 582 a loop with the *lep* loci to enhance its expression.

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#### 28 584 **Polyadenylated lncRNA**

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31 585 Polyadenylated lncRNA (lnc-RAP-n) is a group of 10 lnc-RNAs that are required for the differentiation  
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33 586 and maturation of adipocytes and were identified in a study on primary adipocytes from mouse WAT  
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35 587 and BAT. Twenty lnc-RAPs were upregulated during adipocyte differentiation and knockdown using  
36  
37 588 RNA interference impaired white preadipocyte differentiation and reduced the expression of *Adipoq*,  
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39 589 *C/ebpa*, *Fabp4*, and *Pparγ* [191]. Among the 20 lnc-RAPs, lnc-RAP-1, also known as Functional  
40  
41 590 Intergenic Repeating RNA Element (Firre), was localized on the X-chromosome. Firre mediates the  
42  
43 591 expression of indispensable adipogenic factors binding to hnRNPU *in trans* [192,193].

#### 42 592 **Plnc1**

44 593 Zhu *et al.* identified Plnc1 as a regulator of adipogenesis as it is transcribed ~25,000 bp upstream of the  
45  
46 594 *Pparγ2* gene. They reported that Plnc1 was upregulated in obese mice and its knockdown inhibited  
47  
48 595 adipocyte differentiation in ST2 cells and bone marrow stem cells (BMSCs) and diminished the  
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50 596 expression of adipocytes markers, such as *Pparγ2*, *C/ebpa*, and adipocyte protein 2 (*Ap2*), whereas  
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52 597 Plnc1 overexpression showed the opposite results [194].

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Plnc1 decreases *Pparγ* promoter methylation of the CpG region and promotes its expression, enhancing adipocyte differentiation and, consequently, adipogenesis [194].

**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 [195].

**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 [196]. However, there is insufficient information on this lncRNA and further studies are required.

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**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 [197].

**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 [198]. 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 [198].

**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](#)

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7 626 ~~been found in humans in recent years.~~ However, their implementation in human therapy ~~of these in~~  
8 ~~humans as a therapy~~ still has many limitations due to the ~~little limited~~ available information of lncRNAs  
9 627 ~~in humans that is available on them,~~ and due to the fact that obtaining human samples is sometimes  
10 628 ~~complicated, especially for~~ in BAT. Because of this, many of these lncRNAs have been more extensively  
11 629 ~~studied in animals than in humans.~~ In this section we focus specifically on those that have been ~~but were~~  
12 630 ~~reviewed separately from the previous section since they were~~ isolated from human samples.  
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## 632 H19

19 633 LncRNA H19 is a maternal imprinted gene located on human chromosome 11 whose regulatory roles  
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21 634 in diseases, such as cancer [199] and diabetes [200], have been widely described. In addition to this  
22 635 myriad of roles, Schmidt *et al.* reported that its expression changed in BAT from mice exposed to cold  
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24 636 or fed an HFD. The authors used gain and loss-of-function approaches in primary brown preadipocytes  
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26 637 to describe a regulatory role of H19 in brown adipogenesis and oxidative metabolism [201]. *In vivo*, the  
27 638 ubiquitous overexpression of H19 in HFD-fed mice prevented weight gain by increasing energy  
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29 639 expenditure, whereas selective knockdown of H19 in fat made HFD-fed mice more prone to obesity. In  
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31 640 lean and obese humans, H19 expression was shown to be inversely correlated with BMI in subcutaneous  
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33 641 and visceral WAT and positively related to *UCPI* mRNA levels [201].

34 642 Concerning gene expression, H19 acts as a *trans* regulator to bind the methylated binding factor,  
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36 643 downregulate the expression of paternally inherited genes that predispose to obesity, and reduce  
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38 644 mitochondrial biogenesis exclusively in BAT [201]. Although Schmidt *et al.* showed no impact of H19  
39 645 on WAT, Huang *et al.* proposed a different mechanism. H19 has been shown to drive the fate of BMSCs  
40  
41 646 toward an osteogenic program [202]. It appears to play an inhibitory role in adipogenic differentiation  
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43 647 of BMSCs via epigenetic modification along with miR-675, which targets histone deacetylases  
44 648 (essential molecules in adipogenesis). H19 and miR-675 are downregulated during adipogenic  
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46 649 differentiation and knockdown of H19 increases the expression of PPAR $\gamma$ , C/EBP $\alpha$ , and FABP4,  
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48 650 whereas overexpression of H19 and miR-675 compromises adipogenesis [203,204]. Furthermore, the  
49 651 expression levels of H19 are negatively correlated with miR-188. Downregulation of H19 leads to  
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51 652 overexpression of miR-188, inhibits the effect of ligand-dependent corepressor, and promotes  
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53 653 adipogenesis in WAT [205,206]. Thus, the observations by Schmidt *et al.* who found that H19 had no



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7 654 impact on white adipogenesis may be explained by the early role of H19 selecting an osteogenic fate of  
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9 655 precursor cells to the detriment of preadipocytes.

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11 656 **Brown fat lncRNA 1 (Blnc1)**

12 657 Zhao *et al.* used transcriptional profiling arrays to identify 21 lncRNAs that were overexpressed in BAT  
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14 658 and  $\beta$ 3 adrenergic-stimulated WAT, and during brown adipocyte differentiation. Among these, three  
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16 659 were highly conserved intergenic lncRNAs, but only one affected adipogenesis when silenced. This  
17 660 lncRNA, identified as AK038898, was then renamed Blnc1 [207].  
18

19 661 *In vitro* gain and loss-of-function studies revealed Blnc1 as a key factor during thermogenic adipocyte  
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21 662 development in brown and beige adipocytes. A full-length human transcript of Blnc1 was created and  
22 663 different truncated mutants were transfected into mouse brown preadipocytes [208]. This allowed  
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24 664 identification of the conserved region that is required to promote the thermogenic program by stabilizing  
25  
26 665 the Blnc1/Zbtb7b/hnRNPU/EBF2 ribonucleoprotein complex [208,209]. Early B-cell factor 2 (EBF2)  
27 666 collaborates with PPAR $\gamma$  to enhance the expression of crucial BAT markers, such as PRDM16, which  
28  
29 667 are critical for the development of the thermogenic phenotype [210].  
30

31 668 Finally, an *in vivo* approach in which fat-specific Blnc1 transgenic mouse and conditional knockouts  
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33 669 were fed an HFD demonstrated that Blnc1 is also critical for maintaining adaptive thermogenesis [211].

34 670 **Lnc-dPrdm16**

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36 671 In 2018, a *de novo* reconstruction of the transcriptome of human fetal BAT, subcutaneous WAT, and  
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38 672 omental WAT using deep RNA-seq yielded two main improvements to the preexisting lncRNA  
39 673 database, GENCODE. First, it revealed more than 2,000 new unannotated lncRNAs and second, it  
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41 674 showed that lncRNAs are almost 25 times more tissue-specific than mRNAs [212]. This *in silico*  
42  
43 675 analysis also revealed 54 pairs of conserved lncRNA–mRNA between mice and humans related to  
44 676 canonical pathways in AT. Among these, the authors focused on lnc-dPrdm16, which is located  
45  
46 677 divergently from Prdm16. *In vitro*, knockdown of lnc-dPrdm16 reduced lipid accumulation and  
47  
48 678 expression of BAT markers during differentiation of white and brown adipocytes [212].

49 679 In addition, lnc-dPrdm16 silencing via shRNA-associated adenovirus reduced the expression of BAT  
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51 680 markers when injected into WAT and BAT after browning and cold-induced thermogenesis,  
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53 681 respectively [212]. Although the regulatory mechanisms have not yet been elucidated, it is interesting

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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.

### **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, ~~and exclusively~~, subcutaneous preadipocyte differentiation in human gluteal fat ~~and~~. Its ectopic expression upregulated the adipogenic markers *PPAR $\gamma$* , lipoprotein lipase, and *FABP4* but did not increase the proliferation rate [213,214]. 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 [215,216]. Furthermore, the results in human cells were similar. HOTAIR knockout in AT resulted in gluteal–femoral fat defects [217] 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 [218]. These findings indicate that HOTAIR may play an important role in the epigenetic regulation of adipogenesis, although further studies are required.

### **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 [197]. 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 [219]. 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 [219]; however, further studies are required since different isoforms of p38 may exhibit opposite roles in brown fat differentiation [220].

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7 **DIO3 opposite strand upstream RNA (DIO3OS)**  
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9 DIO3 encodes type 3 iodothyronine deiodinase (D3), which inactivates the thyroid hormones, T4 and  
10  
11 T3, converting them into inactive metabolites. T3 has been shown to play a crucial role in brown  
12 adipocyte differentiation during embryogenesis [221]. Knockout of BAT-specific *Dio3* triggered early  
13 exposure of embryonic BAT to T3, resulting in a long-term upregulation of thermogenic genes [221].  
14  
15 Mouse and human DIO3OS, which show around 25% homology, overlap with the DIO3 gene, although  
16 they are transcribed in opposite directions. *In vitro*, CRISPR–Cas9 knockdown of *Dio3os* in mouse  
17 embryonic fibroblasts activated DIO3 expression, which reduced T3 levels and PRDM16 expression  
18 and thus, inhibited brown adipogenesis. Conversely, *Dio3os* overexpression promoted brown  
19 adipogenesis and thermogenesis, although this was ablated when *Dio3* was also overexpressed,  
20 suggesting *Dio3* inhibition as the primary mechanism involved in DIO3OS-induced adipogenesis. These  
21 results were also reproduced *in vivo* by injecting a *Dio3os* adeno-associated virus into the interscapular  
22 BAT of mice neonates. Five weeks later, lower body weight gain, increased BAT mass, and reduced D3  
23 content were observed [222].

24  
25 In addition to direct inhibition of *Dio3* expression, other mechanisms may explain the regulatory roles  
26 of *Dio3os* lncRNA. Specifically, *Dio3os* binds and inhibits miRNA-328 in hepatocellular carcinoma  
27 [223] and miRNA-122, which suppresses cell proliferation in pancreatic cancer cells [224]. It is  
28 attractive to speculate that the latter mechanism may also be involved in *Dio3os*-mediated adipogenesis  
29 since miRNA-122 has been negatively associated with BAT activity in humans [225].

30  
31 **LINC00473**

32 In 2020, Tran *et al.* investigated the potential role of LINC00473 as a regulator of thermogenesis in  
33 human adipocytes [226]. LINC00473 is located on chromosome 6 and has been classified as an  
34 oncogenic lncRNA as it has been shown to promote cell proliferation, migration, and invasion in several  
35 types of cancer cells [227,228].

36 RNA-seq analysis of norepinephrine-stimulated adipocytes from abdominal subcutaneous fat and  
37 supraclavicular AT revealed that LINC00473 was among the most upregulated genes following  
38 thermogenic induction and adipogenesis [226]. Although initially there is a low abundance of this  
39 lncRNA in the nuclei of the cells, it may regulate thermogenesis via activation of the *Ucp1* promoter in

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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 [226]. 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 [229].

**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 [230]. Furthermore, *in vitro*, knockdown of *HoxA-AS3* showed impaired adipogenesis and decreased the expression of adipogenic markers *PPAR $\gamma$* , *C/EBP $\alpha$* , *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 [230].

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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 [230]. These results demonstrate that HoxA-AS3 is required to inhibit osteogenic differentiation and promote adipogenesis.

**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 [175,231,232] 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 [233].

MIR31HG acts directly on the *FABP4* gene, triggering histone methylation and acetylation, enhancing its expression. Depletion of MIR31HG by gene silencing compromises adipogenesis [233]. In addition,

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MIR31HG promotes inflammation via nuclear factor- $\kappa$ B (NF- $\kappa$ B), which promotes osteogenic differentiation of human ADSCs [234].

**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 [235]. FoxC2-AS1 is located on chromosome 16 and transcribed from the negative strand of FOXC2 [235]. 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 [235]. 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.

**HOXA11-AS1**

Nuermainmaiti *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/EBP $\alpha$* , *CIDEA*, *Perilipin*, and *Diacylglycerol acyltransferase 2* [236]. 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 [236].

**Adipogenic differentiation-induced noncoding RNA (ADINR)**

ADINR is located ~450 bp upstream of the *C/EBP $\alpha$*  gene and is co-expressed with *C/EBP $\alpha$*  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/EBP $\alpha$*  and *PPAR $\gamma$*  expression and leads to defects in adipogenesis that is not reversible through the expression of ADINR *in trans* [237]. Although its mechanism of action remains unclear, the authors propose a model in which ADINR

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7 794 promotes *C/EBPα* transcription activity in *cis* through PA1, which is a subunit of the histone methylation  
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9 995 complex MLL3/4, although further studies are needed to corroborate this hypothesis [237].

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11 1796 **Maternally expressed gene 3 (MEG3)**

12 297 MEG3 is an imprinted gene located on chromosome 14 in humans and chromosome 12 in mice [238].  
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14 498 This lncRNA is involved in the adipogenic and osteogenic differentiation of human ADSCs [196].  
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16 799 Numerous studies have identified the effect of MEG3 on adipogenesis but there is controversy  
17 800 concerning its mechanism. MEG3 inhibits adipogenic differentiation sponging miR-140-5p, which  
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19 801 promotes adipogenesis, and its expression is downregulated during adipogenic differentiation in rat  
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21 802 BMSCs [239] and human ADSCs [240].

22 803 **Extra-coding *C/EBPα* (ecCEBPA)**

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24 404 EcCEBPA was discovered by Di Ruscio *et al.* in the HL-60 and U937 leukemic cell lines. It is encoded  
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26 605 from the upstream *C/EBPα* gene on chromosome 19 and interacts with DNMT1. Consequently, the  
27 806 *C/EBPα* promoter is prevented from being methylated, leading to its overexpression. This mechanism  
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29 807 could promote adipogenesis epigenetically but there is still very little information about its role in AT  
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31 808 [241].

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34 810 **Adipocyte-specific metabolic related lncRNA (ASMER)**

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36 611 Gao *et al.* found that adipocyte-specific metabolic-related lncRNAs (ASMER) 1 and 2 were upregulated  
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38 812 in the AT of obese humans and mice, suggesting that they play a significant role in adipogenesis,  
39 813 lipolysis, and obesity. Knockdown of both ASMERS led to a significant decrease in Adipoq release,  
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41 814 PPAR $\gamma$  expression, and lipid accumulation [242].

42 815  
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44 817 **Gm15290**

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46 818 Gm15290 promotes adipogenesis in *ob/ob* mouse adipocytes by sponging miR-27b, which is associated  
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48 819 with human obesity and T2D [243]. Overexpression of Gm15290 enhances *C/EBPα*, PPAR $\gamma$ , and AP2  
49 820 expression in human multipotent adipose-derived stem cells 2 and 3, whereas decreased miR-27b levels  
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and Gm15290 knockdown had the opposite effect, leading to a decrease in lipid accumulation and body weight *in vivo* [244].

#### **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 [245]. In addition, knockdown of RP11-20G13.3 in SW872 adipocytes reduced lipid accumulation and PPAR $\gamma$ , C/EBP $\alpha$ , 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 [245].

#### **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 [246]. Therefore, they may contribute to intercellular communication as autocrine, endocrine, or paracrine molecules [246,247], 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 [248]. 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 [249]. 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 (Figure 4A5A). Furthermore, lncRNAs may be released in an exosome-independent

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mechanism into bodily fluids, where they may form complexes with high-density lipoprotein or protein argonaute-Argonaute 2, similar to miRNAs [250]. Therefore, circulating lncRNAs ~~se~~ molecules have been identified as highly sensitive, specific, and reproducible biomarkers for severe diseases, and they have been. Hence, lncRNAs have been suggested as promising markers for some AT-related disorders, including diabetes and obesity (Table 3, Figure 4B5B), as will be reviewed in the next section. ~~Therefore, circulating lncRNAs have emerged as biomarkers for all their characteristics.~~ ~~However~~ Despite the fact that ~~many published studies fail to study~~ identify the lncRNAs' tissue of origin of lncRNAs, due to the lack of biopsies or their difficult access, ~~Therefore, we can use~~ bioinformatic tools ~~that can alternatively give~~ provide us information about the cell types and tissues where they are usually expressed, demonstrating their relevance to disease mechanisms and developmental processes (Tables 1-3) [251–253]. Thus, circulating lncRNAs are very useful as biomarkers in these pathologies, and they are not only detected in serum, but their expression in AT has been demonstrated by means of bioinformatic tools. (Yo pondría aquí Tabla 3)

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**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.

**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-



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8 weight individuals. LncRNA-p5549, LncRNA-p21015, and LncRNA-p19461 were significantly  
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10 downregulated in obese individuals. These analyses were repeated after the participants consumed a  
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12 very low-calorie diet for 12 weeks and no significant changes were observed except for LncRNA-  
13  
14 p19461, which showed significantly increased expression [254].

#### 15 16 **AP001429.1**

17  
18 A direct relationship has been established between obesity and various types of cancer, especially breast  
19  
20 cancer. AP001429.1 has recently become a biomarker of breast cancer in obese patients. AP001429.1  
21  
22 is a lncRNA that may have a protective role against breast cancer. Its expression was measured in obese  
23  
24 and non-obese individuals with breast cancer and it was found that AP001429.1 is downregulated in  
25  
26 obese patients with breast cancer compared with non-obese individuals with breast cancer [255].

#### 27 28 **LncRNA-small nucleolar RNA host gene 9 (LncRNA-SNHG9)**

29  
30 LncRNA-SHNG9 was recently shown to be released by exosomes and its expression was diminished in  
31  
32 blood samples of obese patients with endothelial dysfunction [256]. These results may indicate that  
33  
34 LncRNA-SHNG9 promotes lipid metabolism; however, the mechanism is unclear and further studies are  
35  
36 required to understand the mechanisms of LncRNA-SNHG9.

#### 37 38 **LncRNA-SNHG12**

39  
40 Childhood obesity is a significant emerging problem due to its association with related severe metabolic  
41  
42 diseases. LncRNA-SNHG12 was isolated from plasma samples from adolescents and its expression was  
43  
44 shown to be downregulated in obese compared with non-obese individuals, although there is still limited  
45  
46 information about this molecule and its mechanism of action [257].

## 47 48 **4.2. Circulating lncRNA in diabetes**

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50 The rising prevalence of diabetes is a significant public health concern in the modern era, highlighting  
51  
52 the need for the development of novel diagnostic methods to identify early metabolic abnormalities,  
53  
54 such as insulin resistance. Accumulating evidence suggests that lncRNAs appear to be dysregulated in  
55  
56 diabetes, DM, and they may play a role in type 1 diabetes mellitus (T1D) and T2D,  $\beta$ -cell function, and  
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58 glucose homeostasis [258–260]. Differential expression patterns of lncRNAs have been reported  
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60 between healthy individuals without diabetes and patients with both types of diabetes [261,262]. Given

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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 [263,264].

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 [66,265,266], 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 [66,267–272]. 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  $\beta$ -cell function, contributing to its pathogenesis. More importantly, dysregulated lncRNA expression is associated with the development of T1D [273,274], suggesting that these molecules could be used as biomarkers to assess the risk of this pathology [275,276]. 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 [277–281]. Inflammation of the pancreas triggers  $\beta$ -cell apoptosis and the absence of insulin production and secretion [282]. 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* [283] and *CYCS* [284], 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

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modulate the risk for complications in diabetes [285,286], 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 [287]. Other lncRNAs, such as LINC01619, have been reported to influence DN by inducing oxidative stress and podocyte damage via regulating miR-27a [276,288]. 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 [289].

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, which is one of the most severe microvascular diabetic complications,~~ compared with normal patients, and its expression was associated with the clinical stages of this pathology [290]. 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 [291]. 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) [292]. For example, the levels of lncRNAs such as HCG27-201 and LY86-AS1 were downregulated in peripheral blood mononuclear cells isolated from T2D patients compared with controls [293]. Similarly, ~~the levels of circulating lncRNA GASS were downregulated in the serum of patients with diabetes and correlated~~

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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 [294].

Similarly, human lncRNA microarray analysis showed that lncRNA-p3134 was upregulated in the serum of patients with diabetes compared with those without diabetes [295]. 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 [295].

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 [296]. 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 [296,297].

Overall, different studies have reported altered levels of lncRNAs in patients with T2D [262], 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

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7 Since their discovery, many lncRNAs have been identified, and lncRNA research has become especially  
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9 relevant due to the wide range of cellular functions in which they are involved. This functional variety  
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11 makes lncRNAs potential therapeutic targets since numerous lncRNAs are frequently altered in AT-  
12  
13 related pathologies, such as obesity and diabetes.

14 Although major advances in the study of lncRNAs have been achieved in recent years, their regulatory  
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16 role is still a relatively young and unknown field, especially in AT. Moreover, the expression of  
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18 lncRNAs affected by epigenetic alterations is potentially reversible, complicating the collection of  
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20 conclusive data and, at the same time, providing an attractive and promising strategy for its clinical  
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22 application. Most of the pharmacotherapy used in clinical practice have protein targets; therefore, these  
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24 drugs frequently have unwanted side effects due to their interactions with other proteins [298]. Nucleic  
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26 acid-targeting pharmaceuticals, such as lncRNAs, are a promising new field in the quest to identify new  
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28 therapies because they have fewer systemic adverse effects than current treatments [299]. The obstacles  
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30 currently present in the field of RNA therapies will, without a doubt, be conquered due to the promising  
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32 innovations currently emerging from valuable preclinical work. The present review summarizes recent  
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34 evidence for the possible roles of several lncRNAs in AT function, such as adipogenesis, lipid  
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36 metabolism, and thermogenesis. The findings demonstrate significantly different lncRNA expression  
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38 profiles between obese and normal-weight individuals *in vivo* and *in vitro*. Deregulation of lncRNA  
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40 expression demonstrates that these molecules are involved in the metabolism of both white and  
41  
42 brown/beige AT.

43 Future studies should focus on the potential application of lncRNA as biomarkers since lncRNAs can  
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45 be detected in both intracellular and extracellular environments. An extensive list of lncRNAs that  
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47 function as cancer biomarkers has been identified; however, the list is considerably shorter for diabetes  
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49 and obesity; thus, further studies are required. Validation, appropriate primer design, and normalization  
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51 are essential steps in developing lncRNA measurement as a promising biomarker. Despite current  
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53 limitations, the existence of these peripheral molecules in patients allows for early and non-invasive  
54  
55 diagnosis, prognosis, and monitoring of AT-related disorders. lncRNAs have three main advantages  
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57 for obesity treatment: (1) small-molecule drugs have been reported to regulate lncRNA expression and  
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59 thus may be a novel treatment method for human obesity [300]; (2) lncRNAs are expressed at relatively  
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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.

**CREDIT AUTHORSHIP CONTRIBUTION STATEMENT**

AC, MCD, and LH conceived the project. AC designed the figures. All the authors wrote and revised the final version of the manuscript. DS and LH provided funding.

**DECLARATION OF COMPETING INTEREST**

The authors declare no conflicts of interest.

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## FIGURE LEGENDS

### **Graphical abstract:**

- ~~LncRNAs are involved in a wide variety of metabolic pathways depending on in which~~  
~~lncRNAs can affect are highly diverse and depend on their localization.~~
- In recent years, a large number of lncRNAs have been identified as regulators of adipogenesis in different organisms and may be a key regulators of obesity.
- Identification and measurement of circulating lncRNAs could be applied as a predictive technique to prevent the progression of diseases such as obesity and diabetes.

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

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**Figure 2.** Transcriptome classification. The top blue box represents ~~that only 1.5% of that 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).

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**Figure 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.

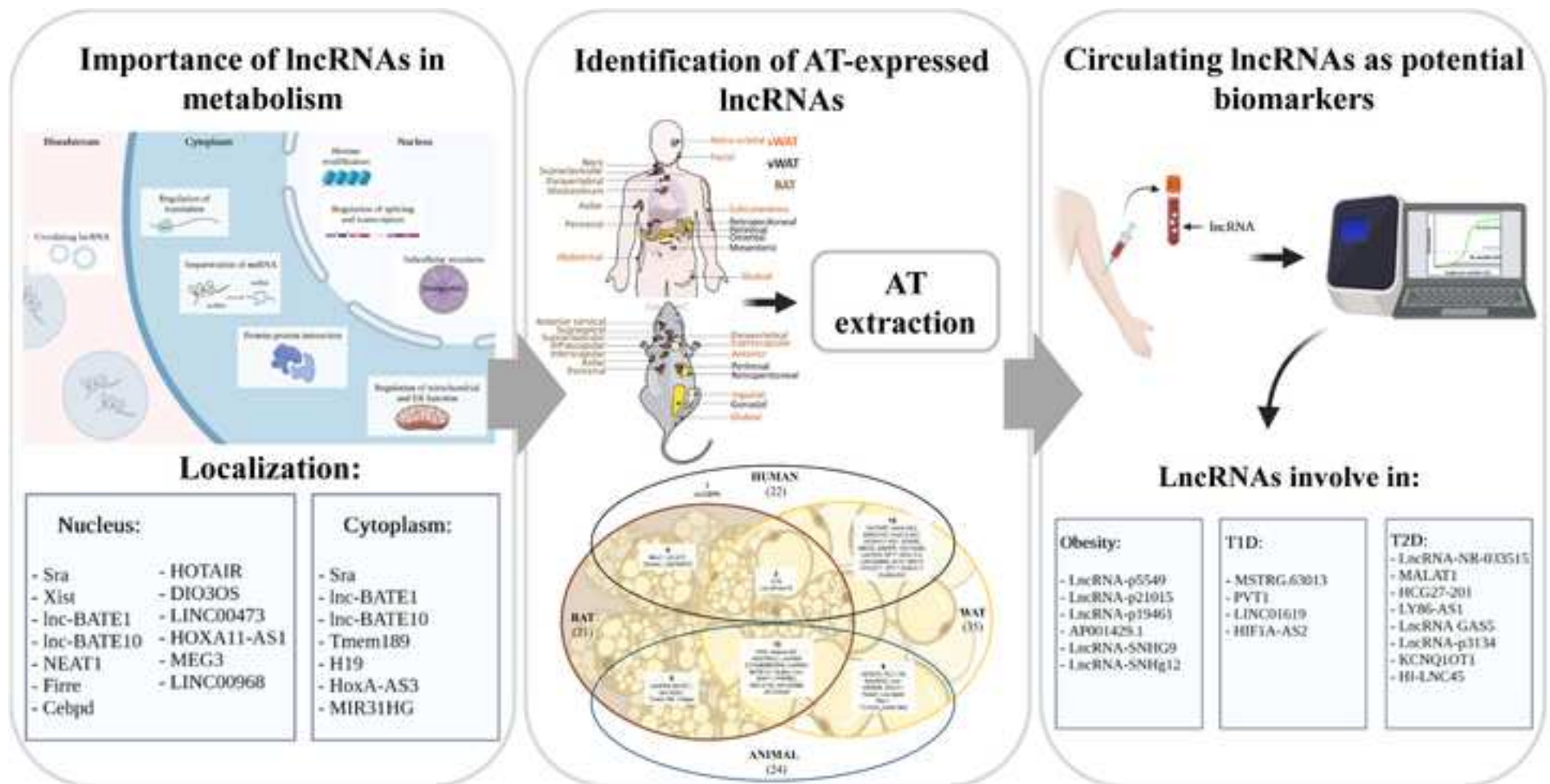
**Figure 4.** Venn diagram showing the localization and distribution of lncRNAs in AT. Values in brackets represent the number of lncRNAs belonging to animals and humans or BAT and WAT.

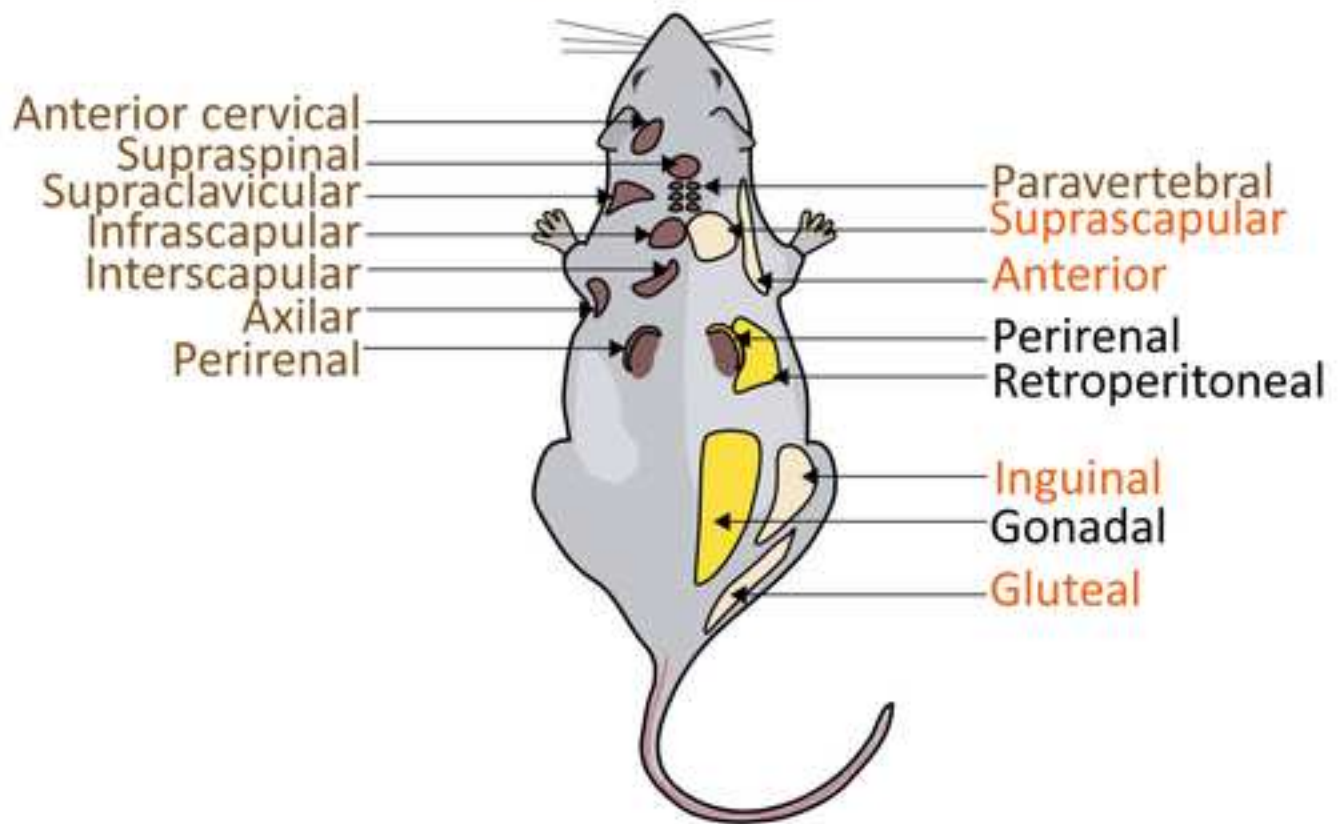
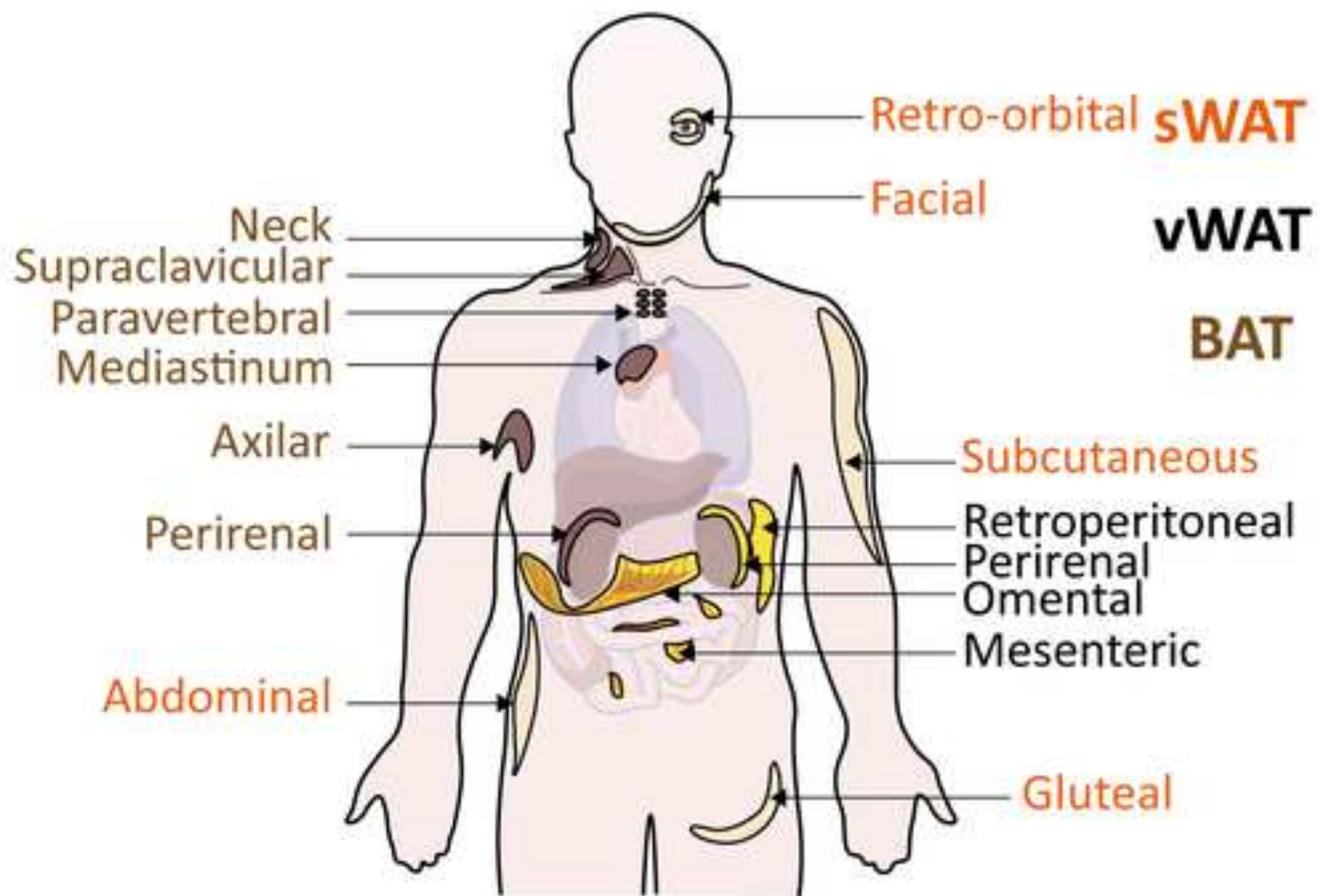
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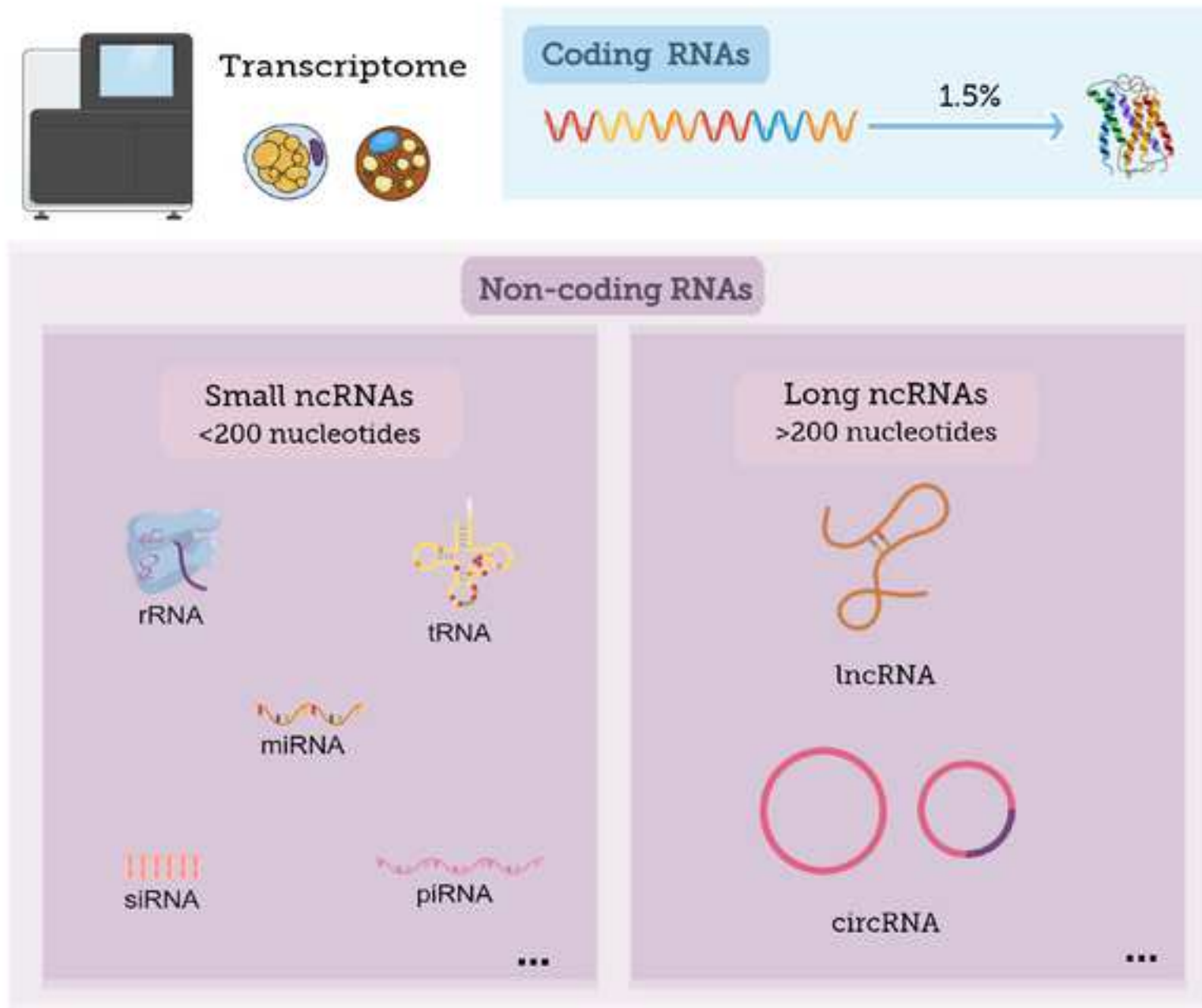
Common areas contain the numbers and names of the exclusive lncRNAs within the overlapping groups.

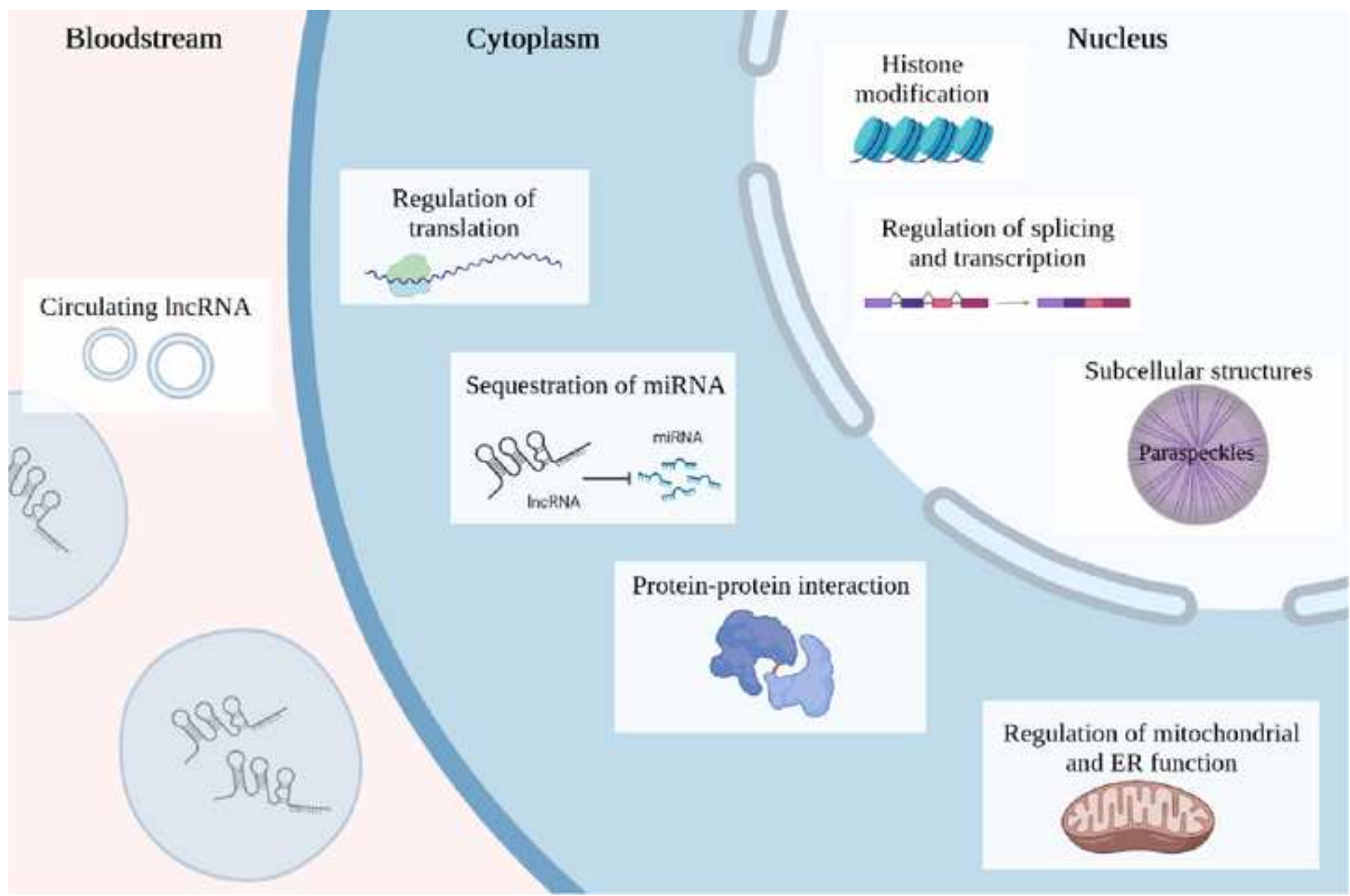
The diagram includes all of the lncRNAs summarized in this review. The diagram is structured using the following groups: exclusive to human WAT (15 lncRNAs); exclusive to human BAT (4 lncRNAs) and human WAT and BAT (2 lncRNAs); exclusive to animal WAT (9 lncRNAs) and exclusive to animal BAT (5 lncRNAs) and animal WAT and BAT (10 lncRNAs).

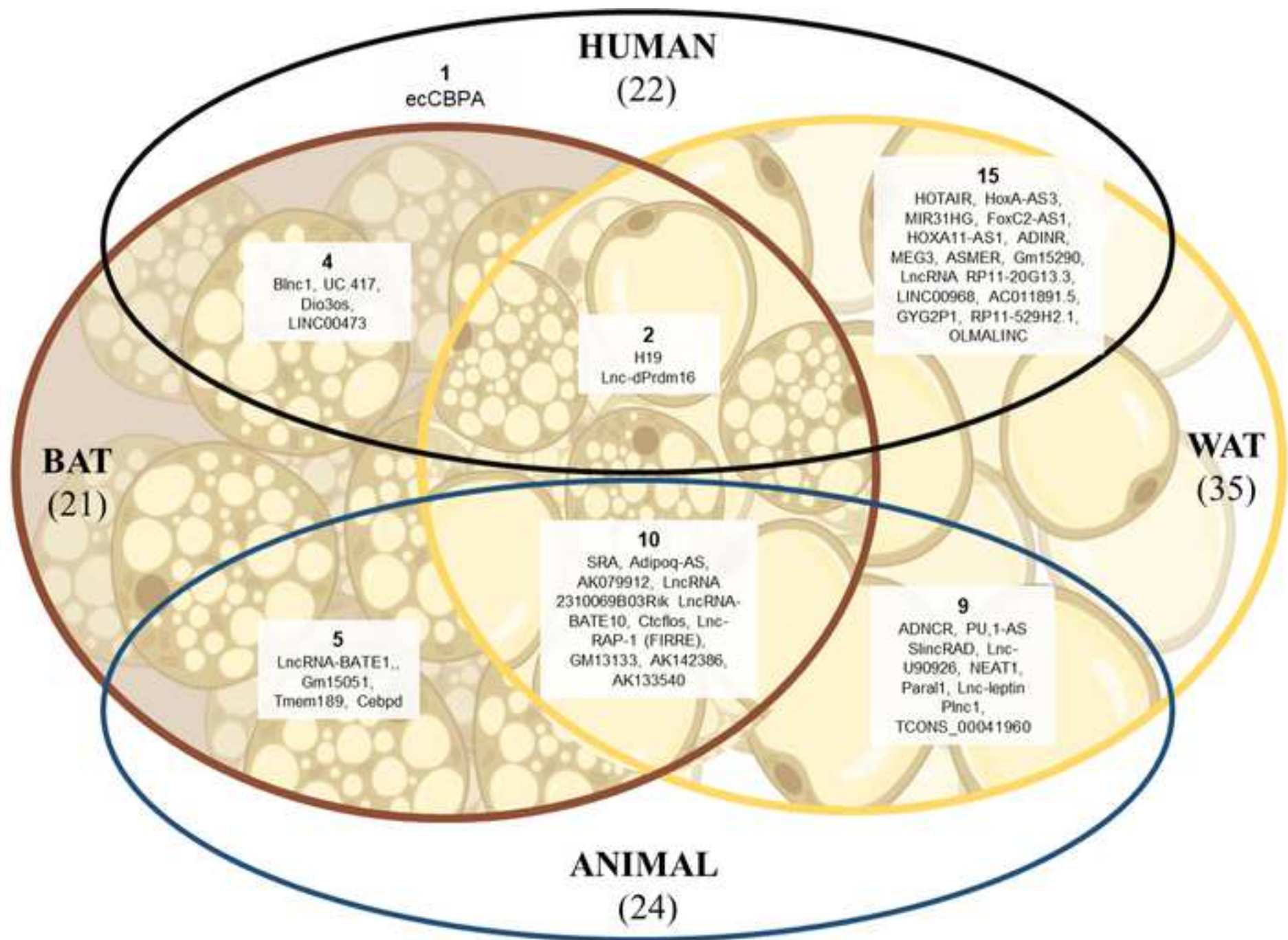
**Figure 54. LncRNAs as biomarkers in obesity and diabetes.** (A) Adipocytes release lncRNAs into the bloodstream to reach their targets. These lncRNAs are collected from a blood sample for further isolation and purification. (B) The expression of circulating lncRNAs is measured to detect variations related to diseases, such as obesity and diabetes, to identify the lncRNAs involved in these diseases and develop new therapeutic targets.





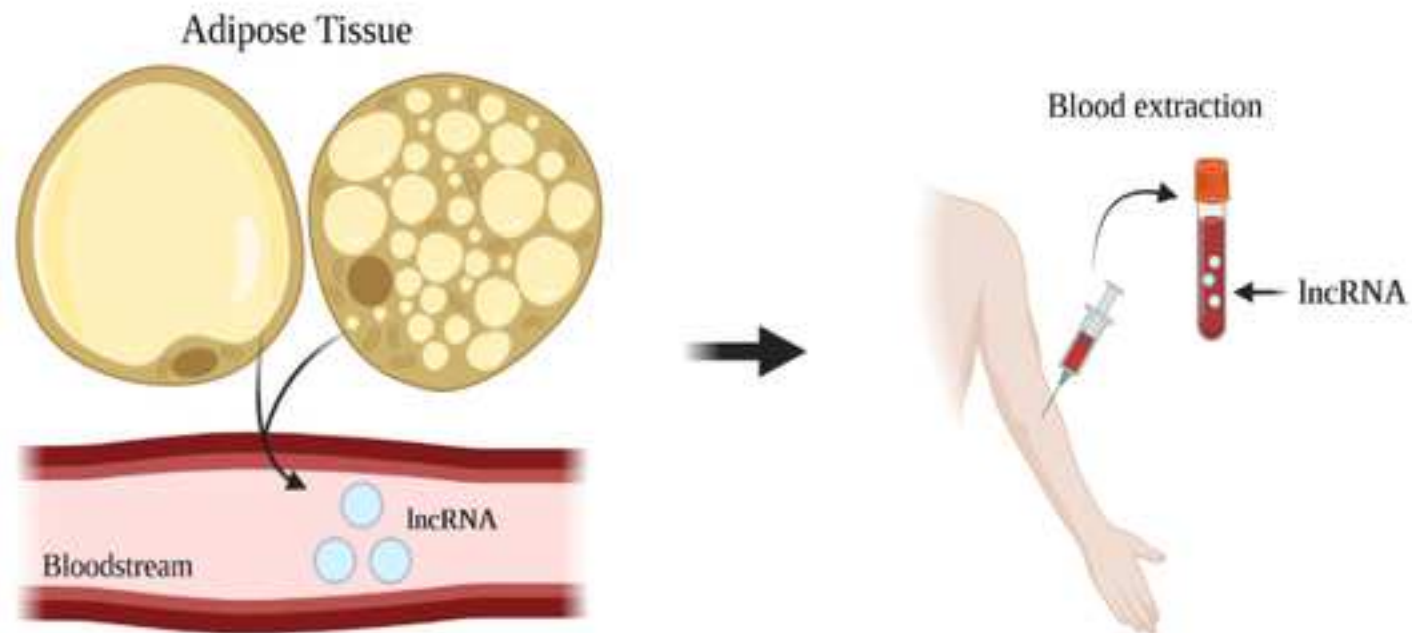




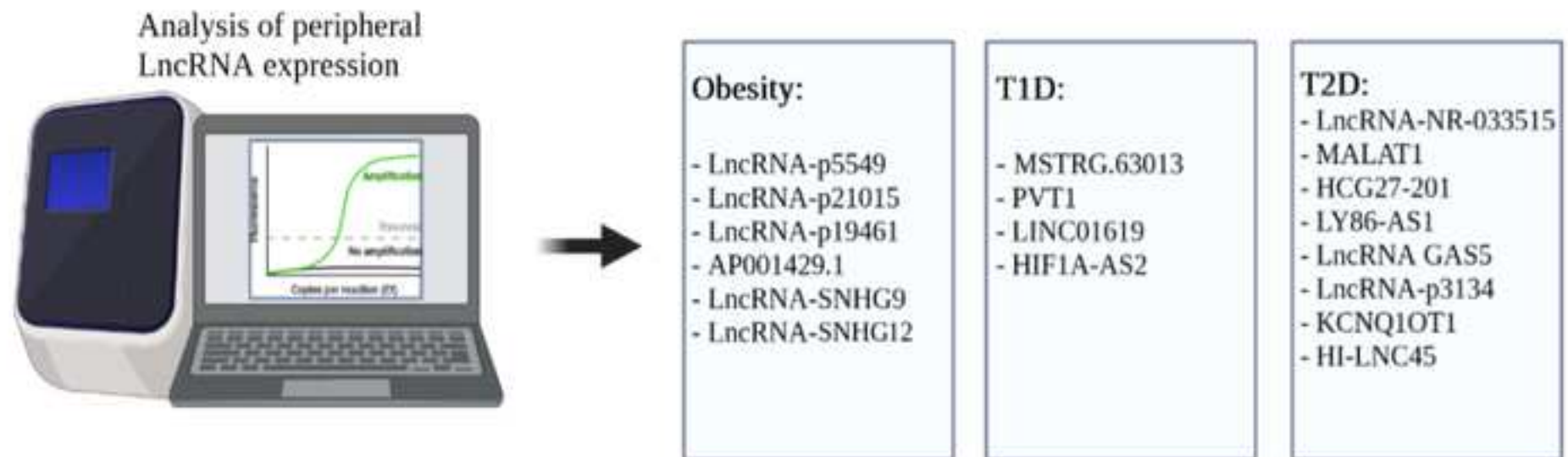




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**DECLARATION OF COMPETING INTEREST**

The authors declare no conflicts of interest.

**CREDIT AUTHORSHIP CONTRIBUTION STATEMENT**

AC, MCD, and LH conceived the project. AC designed the figures. All the authors wrote and revised the final version of the manuscript. DS and LH provided funding.