

# Involvements of long noncoding RNAs in obesity-associated inflammatory diseases

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## Summary

Obesity is associated with chronic low-grade inflammation that affects the phenotype of multiple tissues and therefore is implicated in the development and progression of several age-related chronic inflammatory disorders. Importantly, a new family of noncoding RNAs, termed long noncoding RNAs (lncRNAs), have been identified as key regulators of inflammatory signalling pathways that can mediate both pretranscriptional and posttranscriptional gene regulation. Furthermore, several lncRNAs have been identified, which are differentially expressed in multiple tissue types in individuals who are obese or in preclinical models of obesity. In this review, we examine the evidence for the role of several of the most well-studied lncRNAs in the regulation of inflammatory pathways associated with obesity. We highlight the evidence for their differential expression in the obese state and in age-related conditions including insulin resistance, type 2 diabetes (T2D), sarcopenia, osteoarthritis and rheumatoid arthritis, where obesity plays a significant role. Determining the expression and functional role of lncRNAs in mediating obesity-associated chronic inflammation will advance our understanding of the epigenetic regulatory pathways that underlie age-related inflammatory diseases and may also ultimately identify new targets for therapeutic intervention.

## KEYWORDS

inflammation, lncRNAs, long noncoding RNAs, obesity

**Abbreviations:** AKT, protein kinase B; ANRL, antisense noncoding RNA in the INK4 locus; APEX1, apurinic/aprimidinic endodeoxyribonuclease 1; ASMER, adipocyte-specific metabolic-related lncRNAs; AT, adipose tissue; AtroInc-1, atrophy-related long noncoding RNA-1; BAT, brown adipose tissue; Blnc1, brown fat lncRNA 1; BMI, body mass index; C/EBP, CCAAT-enhancer binding protein; CCL2/5, C-C motif chemokine ligand 2/5; Chronos, Gm17281; CoREST, REST corepressor 1; DNMT1, DNA-methyltransferase 1; EZH2, enhancer of zeste homolog 2; FOXO, forkhead box o; GA, guanine and adenine; GOF, gain of function; H3K27me3, histone H3 lysine 27 trimethylation; HDAC1, histone deacetylase 1; HFD, high-fat diet; HOTAIR, HOX transcript antisense RNA; IL-1 $\beta$ , interleukin 1-beta; IL-6, interleukin 6; IL-8, interleukin 8; INK4, inhibitors of CDK4; JNK, c-Jun N-terminal kinases; lncASIR, adipose-specific insulin responsive lncRNAs; lnc-dPRM16, long noncoding RNA divergent from PR domain containing 16; lncRNAs, long noncoding RNA; LOF, loss of function; LSD1, lysine-specific histone demethylase 1A; MALAT1, metastasis associated lung adenocarcinoma transcript 1; MAR1, muscle anabolic regulator 1; miRNA, microRNA; MIST, macrophage inflammation-suppressing transcript; OA, osteoarthritis; OASF, OA synovial fibroblasts; PCA3, prostate cancer antigen 2; PI3K, phosphatidylinositol-3 kinase; PPAR, peroxisome proliferator-activated receptor; PRCs, polycomb repressive complexes; RA, rheumatoid arthritis; REST, RE1-silencing transcription factor; ROCK1, Regulatory of Cytokines and Inflammation; SRA1, steroid receptor RNA activator 1; T2D, type 2 diabetes; TNF $\alpha$ , tumour necrosis factor alpha; WAT, white adipose tissue; XIST, X-inactive specific transcript.

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## 1 | INTRODUCTION

With the understanding that much of the human genome is transcribed into noncoding transcripts, it comes as no surprise that long noncoding RNAs (lncRNAs) have been linked to multiple diseases including developmental disorders and many cancers. Characterized as noncoding transcripts larger than 200 nucleotides,<sup>1</sup> they are the largest and most heterogeneous group of noncoding RNAs involved in several cellular processes.<sup>2,3</sup> Generally transcribed by RNA polymerase II, lncRNA transcripts undergo splicing events to remove introns and form alternatively spliced isoforms, are 5' capped and can even be polyadenylated. lncRNAs can exhibit tissue and cell-specific expression<sup>4,5</sup> and can impact gene regulation at every level, from manipulating epigenetic marks and chromatin folding to transcriptional initiation, activation and silencing, RNA splicing, editing, translation and RNA and protein turnover.<sup>6</sup>

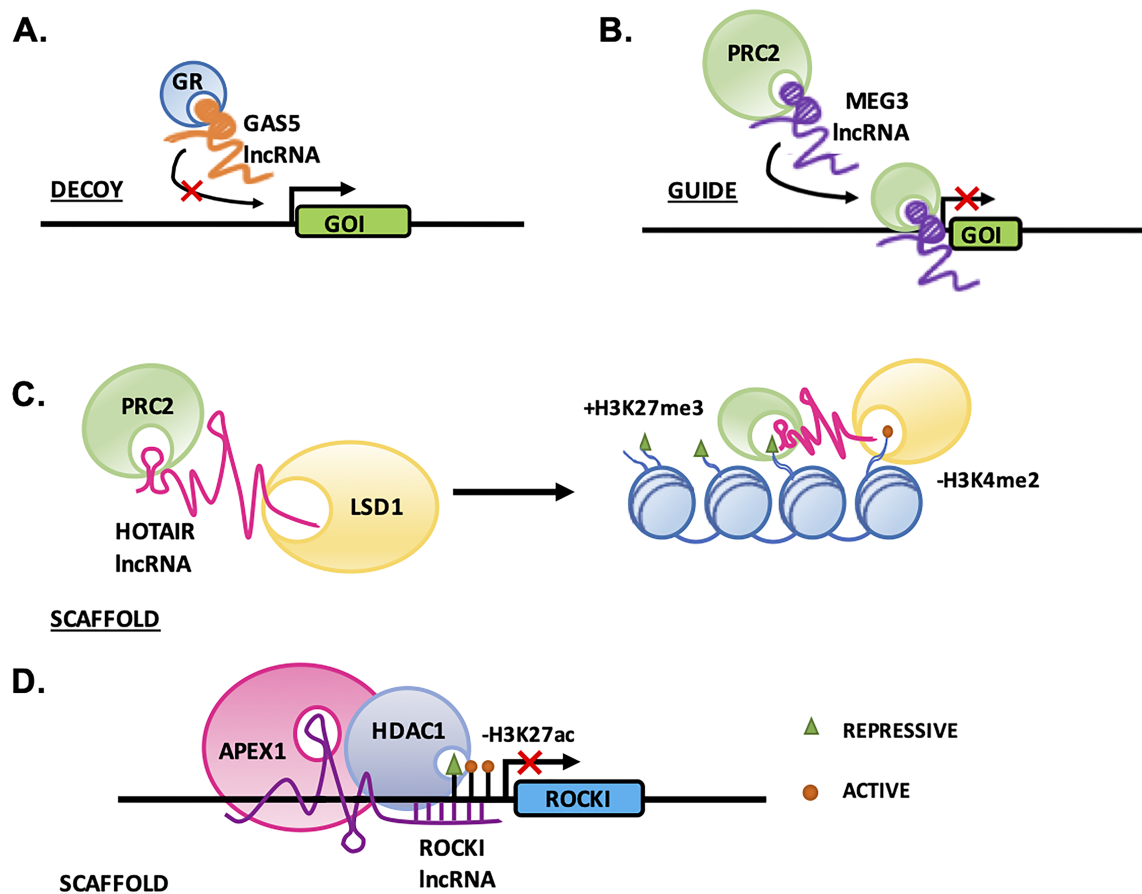
The lncRNA and Disease Database (lncRNADisease: <http://www.cuilab.cn/lncrnadisease>) has seen entries surge from 63 disease-associated lncRNAs to 2,947 experimentally verified disease-associated lncRNAs in as little as 5 years.<sup>7</sup> With the development in deep-sequencing technologies, studies have been able to uncover genome-wide mutations associated with disease. Remarkably, Calin et al. found that many ultra-conserved noncoding regions that give rise to ncRNAs harbour mutations in cancers that lead to their dysregulation.<sup>8,9</sup> Currently, the function and mechanism of action of the vast majority of lncRNAs remain unclear. However, there are a small number of well-characterized lncRNAs, which have provided evidence of several mechanisms by which lncRNAs can exert their diverse functions. A strong argument for the physiological importance of lncRNAs as molecular signals lies in their variable expression observed between different cell types and tissues, in response to numerous stimuli and timely expression at specific developmental cues.<sup>10</sup> The process of initiation, elongation or termination at a lncRNA gene alone can suffice to elicit a regulatory response.<sup>10</sup> Additionally, transcripts are thought to recruit chromatin-remodelling complexes to modulate epigenetic regulation leading to either the repression or activation of specific genes. This holds true in the case of the X-inactive specific transcript (XIST), the antisense of insulin growth factor 2 receptor lncRNA and HOX transcript antisense RNA (HOTAIR) known to interact with several histone-modifying complexes. XIST is thought to recruit the PRC2 complex, which is essential for catalysing the repressive histone modification, trimethylation of histone H3 lysine 27 (H3K27me3), leading to X-chromosome inactivation.<sup>11</sup> As such, XIST influences chromatin compaction and silencing of the future inactive X-chromosome. Similarly, HOTAIR is also known to selectively bind components of the PRC2 complex including the histone methyltransferase EZH2.<sup>12</sup> Whereas the 5' region of HOTAIR associates with PRC2 proteins, the 3' domain also has been found to interact with the histone demethylase complex LSD1/CoREST/REST.<sup>13</sup>

Decoy lncRNAs can act as a sponge or 'molecular sink' for RNA-binding proteins or as guides to specifically localize bound proteins to target genes, allowing for greater coordination of transcription factors and chromatin modifiers (Figure 1A,B).<sup>10</sup> GAS5 is a well-studied decoy

lncRNA that competitively binds the DNA-binding domain of the glucocorticoid receptor (GR) suppressing the activation of GR target genes (Figure 1A),<sup>14</sup> whereas MEG3 lncRNA acts as a guide for the PRC2 complex to specific chromatin sites due to a triplex forming GA-rich sequence at MEG3 binding sites that enable an RNA-DNA triplex formation (Figure 1B).<sup>15</sup> Similarly, CCDC26 lncRNA regulates global DNA methylation in myeloid cells by coordinating the subcellular locations of DNA-methyltransferase 1 (DNMT1).<sup>16</sup> lncRNAs can also act as scaffolds forming functional ribonucleoprotein complexes providing a platform for the assembly of multiple proteins onto chromatin through sequence complementarity, stem loops, affinity and various tertiary structures (Figure 1C,D).<sup>17</sup> HOTAIR is cited as such owing to its ability to simultaneously bind the PRC2 and LSD1 complex bridging the two to form the gene suppressive HOTAIR/PRC2/LSD1 complex (Figure 1C).<sup>10,18</sup> Similarly, lncRNA ROCK1 forms a ribonucleic complex at the MARCKS promoter with the endonuclease APEX1, which recruits HDAC1, a histone deacetylase to silence its own transcription (Figure 1D).<sup>19</sup> These are the key mechanisms by which lncRNAs can epigenetically influence chromatin state and gene regulation. As such, lncRNAs are directly and indirectly significant for coordinating the activation or repression of target genes, and thus, it is important to gain an understanding of these integral regulators in the context of obesity-associated chronic inflammation on age-related conditions (Table 1).

## 2 | lncRNAs AND OBESITY

Obesity is the accumulation of excessive body fat, which can severely impact health and currently affects 650 million adults worldwide. Transcriptional analyses by both next-generation sequencing and microarray have identified several lncRNAs that are differentially expressed in body fat or adipose tissue (AT) in individuals who are obese. The human body consists of the insulating, energy-storing white AT (WAT) and thermogenic brown AT (BAT). Visceral WAT around the intra-abdominal organs and subcutaneous WAT under the skin are fundamental in energy homeostasis, whereas energy-burning and heat-generating BAT is found around the shoulders and ribs.<sup>20</sup> In obesity, BAT undergoes molecular and morphological changes effectively 'whitening' to resemble WAT, thus impacting on metabolic dysfunction and inflammation.<sup>21</sup> Brown fat lncRNA 1 (Blnc1) is a conserved BAT-enriched nuclear lncRNA that acts as a scaffold to form ribonucleoprotein complexes with several transcription factors. In BAT, Blnc1 interacts with thermogenic transcription factors including EBF2 and ZBTB7B.<sup>21-23</sup> Zhao et al. found high expression of Blnc1 in high-fat diet (HFD)-fed obese mice, which on conditional inactivation accelerated BAT whitening, fibrosis and tissue inflammation.<sup>21</sup> Transgenic expression of Blnc1 rescues these effects by silencing pro-inflammatory cytokines interleukin 6 (IL-6) and CCL5 and promoting lipid metabolism through a ribonucleoprotein complex with ZBTB7B.<sup>21</sup> Additionally, Tang et al. find that not only is overexpression of Blnc1 in WAT protective against HFD-induced obesity but through remodelling of mitochondrial biogenesis is able to



**FIGURE 1** LncRNA mechanisms of action. (A) Decoy: by binding the glucocorticoid receptor (GR), GAS5 lncRNA prevents GR from binding its DNA target. (B) Guide: RNA-binding PRC2 complex is directed to specific targets through interactions with specific lncRNAs such as MEG3. (C) Scaffold: HOTAIR lncRNA acting as a scaffold brings together groups of proteins (PRC2 and LSD1 complexes), which may otherwise not be able to interact and work together as part of a ribonucleoprotein complex. (D) Scaffold lncRNAs like ROCK1 can also interact with DNA at specific promoters; in this case, ROCK1 binds its own promoter, allowing for the assembly of chromatin-modifying ribonucleoprotein complexes to activate the downstream gene by changing the epigenetic marks at the promoter. The figure is not to scale. LncRNA examples are discussed in detail in Section 1. HOTAIR, HOX transcript antisense RNA; lncRNA, long noncoding RNA; ROCK1, Regulatory of Cytokines and Inflammation

improve insulin sensitivity.<sup>24</sup> There is increasing interest in the lipid oxidation-mediated thermoregulatory properties of BAT, and understanding the role of lncRNAs in this process may be key in harnessing this potential for therapeutic treatment of obesity.<sup>20,24</sup>

RNA-sequencing analysis of human AT has provided a catalogue of over 3,000 lncRNAs, of which approximately 900 were specifically detected in BAT, which in humans is associated with improved metabolic health. Of these BAT-specific lncRNAs, the expression of lnc-PRM16 was associated with the expression of BAT-selected markers in vivo and its knockdown impaired differentiation of brown adipocytes.<sup>25</sup> Furthermore, BAT H19 expression, which in the mouse decreases with obesity, has been reported to be inversely correlated with body mass index (BMI) in humans.<sup>26</sup> H19 is implicated in several obesity-associated inflammatory conditions. H19 expression is reduced in adipocytes from individuals with obesity, and its overexpression in mice was found to have a protective effect against diet-induced obesity and improved insulin sensitivity in BAT but not WAT tissue.<sup>26</sup> As BAT 'whitening' in obesity impacts on metabolic dysfunction and inflammation,<sup>21</sup> there is increasing interest in the

thermoregulatory properties of BAT, and understanding the role of lncRNAs may be key in tackling obesity and obesity-associated conditions.

In abdominal subcutaneous WAT, 1,268 lncRNAs were found to be differentially expressed in children with obesity, compared with age- and gender-matched children without obesity. Of these, the expression level of lncRNA RP11-20G13.3 was positively associated with BMI, waist circumference, waist-to-hip ratio, fasting insulin, low-density lipoprotein cholesterol, high-sensitivity C-reactive protein and leptin. On the contrary, the expression level of the lncRNA GYG2P1 was negatively associated with BMI, waist circumference, fasting insulin and triglycerides.<sup>27</sup> In a separate study, lncRNA u001kfc.1 was identified as differentially downregulated in visceral WAT from individuals with obesity, compared with those without,<sup>28</sup> and was predicted to be a potential *cis*-regulator for phosphatase and tensin or PTEN homolog.

In addition to AT, differential expression of lncRNAs has been reported in the blood of individuals classed as obese, suggesting that the obesity-associated differences in lncRNA expression will affect

**TABLE 1** Summary of lncRNAs and associated conditions

Disease/biological process	lncRNA	Mechanism	Reference
Adiposity	GYG2P1	Expression is negatively associated with BMI, waist circumference, fasting insulin and triglycerides.	Liu et al. <sup>27</sup>
	lnc-dPrm16	Loss of function markedly represses brown adipogenesis whereas in WAT results in reduced expression of pan-adipogenic markers and BAT-selective markers. Also reduces expression of Prdm16 in WAT but not in BAT.	Ding et al. <sup>25</sup>
	lncRNA-p21015	lncRNA expression is negatively correlated with BMI, waist circumference, waist-to-hip ratio and fasting insulin.	Sun et al. <sup>29</sup>
	lncRNA-p5549	lncRNA expression is negatively correlated with BMI, waist circumference, waist-to-hip ratio and fasting insulin.	Sun et al. <sup>29</sup>
	MIST	Knockdown in adipose tissue macrophages increases M1-associated genes, whereas gain of function reduces genes associated with inflammation and lipid metabolism. Epigenetically regulates pro-inflammatory genes through an interaction with PARP1.	Stapleton et al. <sup>63</sup>
	RP11-20G13.3	Knockdown prevents adipocyte differentiation and reduces the mRNA levels of PPAR $\gamma$ , C/EBP $\alpha$ and adiponectin during adipocyte differentiation.	Liu et al. <sup>27</sup>
Diabetes	ANRIL	Methylation of ANRIL promoter is reduced in subcutaneous adipose; ANRIL expression is induced by high glucose and diabetes and is positively correlated with pro-inflammatory factors. ANRIL is also transcriptionally regulated by NF- $\kappa$ B-mediated TNF $\alpha$ .	Lillicrop et al., <sup>52</sup> Thomas et al., <sup>55</sup> and Zhou et al. <sup>56</sup>
	H19	Decreased in muscle of individuals with obesity and type 2 diabetes resulting in impaired insulin signalling and decreased glucose uptake through the PI3K/AKT pathway induced by Let-7 miRNA.	Gao et al. <sup>64</sup>
Insulin resistance	ASMER1	Expression correlated with increased lipid metabolism. Silencing reduces adiponectin release, impacts lipolysis, fatty acid and energy metabolism leading to reduced triglyceride accumulation.	Gao et al. <sup>45</sup>
	ASMER2	Expression correlated with inflammatory pathways. Silencing reduces adiponectin release, impacts lipolysis, fatty acid and energy metabolism leading to reduced triglyceride accumulation.	Gao et al. <sup>45</sup>
	MIST	MIST expression in human adipose tissue macrophages is downregulated in individuals with obesity and negatively correlated with insulin resistance. This maybe through transcriptional regulation of the <i>FABP5</i> gene.	Stapleton et al. <sup>63</sup>
	lncRNA-p19461	Negatively associated with insulin resistance and upregulated by 12-week diet-induced weight loss.	Sun et al. <sup>29</sup>
	Blnc1	Transgenic expression silences pro-inflammatory cytokines and promotes lipid metabolism, whereas silencing accelerated	Zhao et al. <sup>21</sup> and Tang et al. <sup>24</sup>

**TABLE 1** (Continued)

Disease/biological process	LncRNA	Mechanism	Reference
		BAT fibrosis and tissue inflammation. Overexpression in WAT is protective against HFD-induced obesity and improves insulin sensitivity.	
	H19	H19 expression reduces with adiposity. Overexpression in mice has a protective effect against diet-induced obesity and improves insulin sensitivity in BAT. H19 recruits PEG-inactivating H19-MBD1 complexes and acts as BAT-selective PEG gatekeeper.	Schmidt et al. <sup>26</sup>
	LncASIR	Silencing downregulates metabolic pathways downstream of insulin signalling including PPAR and adipocytokine signalling.	Degirmenci et al. <sup>57</sup>
	SRA1	Overexpression increases insulin-stimulated uptake of glucose and represses pro-inflammatory chemokine CCL2; however, SRA <sup>-/-</sup> mice are protected from diet-induced obesity, are more sensitive to insulin and are less inflammatory with reduced expression of TNF $\alpha$ , CCL2 and IL-6.	Xu et al. <sup>49</sup> and Liu et al. <sup>50</sup>
	u001kfc.1	Downregulated in WAT of individuals with obesity and associated with enhanced insulin sensitivity in WAT by <i>cis</i> -regulating PTEN.	Yang et al. <sup>28</sup>
Myogenesis	H19	Promotes myoblast differentiation by suppression of Sirt1/FOXO1 expression. Also, increases miR-675-3p and miR-675-5p, in turn suppressing BMP/TGF- $\beta$ signalling.	Dey et al. <sup>78</sup>
	MALAT1	Evidence of both promoting myogenesis via upregulation of muscle specific gene expression and suppressing myogenesis by inhibiting MyoD.	Chen et al. <sup>82</sup>
Osteoarthritis	MALAT1	Knockdown reduces proliferation of obese OASF and expression of IL-6 and CXCL8.	Nanus et al. <sup>98</sup>
Rheumatoid arthritis	MALAT1	Silencing results in an increase in IL-6, IL-10 and TNF $\alpha$ secretion and elevated proliferation. MALAT1 binds to the promoter of CTNNB1 regulating DNA methylation to inhibit $\beta$ -catenin and thus the Wnt-signalling pathway.	Li et al. <sup>111</sup>
Rheumatoid arthritis and osteoarthritis	H19	Serum starvation and stimulation with or without IL-1 $\beta$ , TNF $\alpha$ or PDGF-BB induce H19 expression in synovial fibroblasts via the MAP-kinase ERK-1/2 and phosphatidylinositol-3 kinase pathways.	Pearson et al. <sup>100</sup>
	HOTAIR	Exosomal HOTAIR contributes to the migration and activation of macrophages as well as the production of MMPs in individuals with obesity.	Lu et al. <sup>112</sup> and Song et al. <sup>113</sup>
Skeletal muscle atrophy	Atrolnc1	Binds and represses ABIN1, an endogenous inhibitor of NF- $\kappa$ B, in turn facilitating increased NF- $\kappa$ B-mediated transcription of the ubiquitin E3 ligase MuRF-1	Sun et al. <sup>87</sup>
	Chronos	Represses Bmp7, a positive regulator of hypertrophic gene expression. Increased expression with age is associated with skeletal muscle atrophy.	Neppl et al. <sup>84</sup>

(Continues)

**TABLE 1** (Continued)

Disease/biological process	LncRNA	Mechanism	Reference
	MAR1	Acts as a sponge for mir-487b in C <sub>2</sub> C <sub>12</sub> cells, in turn preventing a reduction in Wnt5a expression, promoting myogenesis. Expression decreases with age and muscle unloading in mice.	Zhang et al. <sup>85</sup>

Abbreviations: AKT, protein kinase B; ANRIL, antisense noncoding RNA in the INK4 locus; ASMER, adipocyte-specific metabolic-related lncRNAs; AtroInc-1, atrophy-related long noncoding RNA-1; BAT, brown adipose tissue; Blnc1, brown fat lncRNA 1; BMI, body mass index; C/EBP, CCAAT-enhancer binding protein; CCL2, C–C motif chemokine ligand 2; Chronos, Gm17281; FOXO, forkhead box o; HFD, high-fat diet; HOTAIR, HOX transcript antisense RNA; IL-1 $\beta$ , interleukin 1-beta; IL-6, interleukin 6; lncASIR, adipose-specific insulin responsive lncRNAs; lnc-dPRM16, long noncoding RNA divergent from PR domain containing 16; lncRNA, long noncoding RNA; MALAT1, metastasis associated lung adenocarcinoma transcript 1; MAR1, muscle anabolic regulator 1; miRNA, microRNA; MIS, macrophage inflammation-suppressing transcript; NF- $\kappa$ B; OASF, osteoarthritis synovial fibroblasts; PI3K, phosphatidylinositol-3 kinase; PPAR, peroxisome proliferator-activated receptor; SRA1, steroid receptor RNA activator 1; TNF $\alpha$ , tumour necrosis factor alpha; WAT, white adipose tissue.

distal tissues. With the use of an lncRNA array, a total of 249 lncRNAs were found to be differentially expressed (213 upregulated and 36 downregulated) in the blood of those individuals with obesity, compared with healthy control individuals. Of these, the circulatory expression of three lncRNAs, namely, lncRNA-p5549, lncRNA-p21015 and lncRNA-p19461, was negatively correlated with BMI, waist circumference, waist-to-hip ratio and fasting insulin.<sup>29</sup> Furthermore, the circulatory expression of lncRNA-p19461 was significantly increased in eight individuals with obesity following a 12-week diet-induced weight loss programme.<sup>29</sup> These findings support the notion that the effect of obesity on lncRNA expression may extend to peripheral tissues with implications for age-related conditions influenced by obesity-associated chronic inflammation.

### 3 | LncRNAs AND OBESITY-ASSOCIATED CHRONIC INFLAMMATORY DISEASE

Obesity-associated chronic inflammation largely features the energy-storing endocrine organ AT. AT is not only recognized for its endocrine role in regulating energy homeostasis but also in the regulation of immunity and inflammation.<sup>30</sup> AT is largely composed of fat cells known as adipocytes, which store energy as fat. Increased adiposity directly impacts AT remodelling as adipocytes overaccumulate to accommodate an increased demand for lipid storage. This can have severe effects on lipogenesis, lipolysis and AT adipokine responses leading to metabolic stress, adipocyte cell death and hypoxia. These events culminate in the activation of JNK and NF- $\kappa$ B signalling pathways, which regulate the production and release of pro-inflammatory signalling molecules known as cytokines, contributing to an inflammatory AT microenvironment and their accumulation in multiple tissues including skeletal muscle.<sup>30–32</sup> lncRNAs are now being recognized as contributing intermediates in obesity and inflammation, although the exact molecular processes involving lncRNAs in obesity-associated inflammatory conditions is still unclear. Here, with the focus on obesity-associated chronic inflammatory diseases, this section will highlight the fundamental lncRNAs involved in AT remodelling and those that may contribute to obesity-associated inflammation.

#### 3.1 | Insulin resistance and type 2 diabetes (mellitus)

Obesity-linked insulin resistance leads to increased lipolysis, elevated plasma fatty acid levels and reduced tissue glucose transport, which, coupled with simultaneous dysfunction of pancreatic  $\beta$ -cells, may result in the development of type 2 diabetes (T2D).<sup>33</sup> AT becomes less responsive to insulin during obesity as adipocytes become enlarged (hypertrophic) and more inflammatory. However, the mechanism linking insulin resistance to inflammation remain unclear. There is evidence that low-grade inflammation may play a role in the development of insulin resistance and pathogenesis of T2D and its co-morbidities,<sup>34,35</sup> but a reverse causation has also been suggested whereby insulin resistance and dysregulation of metabolic control can lead to low-grade inflammation and contribute to pancreatic  $\beta$ -cell dysfunction, and hence glycaemic control, in T2D.<sup>36,37</sup> However, the use of anti-inflammatory compounds (salicylic acid, salsalate and specific antagonists against pro-inflammatory molecules such as IL-1 and TNF $\alpha$ ) as potential antidiabetic treatments in human clinical trials has produced small or modest fasting glucose and HbA1c-lowering effects, which were a consequence of improved  $\beta$ -cell function (possibly as a result of a decrease in islet inflammation), but had no effect on peripheral insulin resistance.<sup>38–44</sup> As such, lncRNAs are now gathering interest as potential alternative therapeutic targets.

Gao et al. identified 86 differentially expressed lncRNAs between obese and nonobese individuals and 44 lncRNAs that were differentially expressed in individuals who were insulin resistant versus insulin sensitive and obese.<sup>45</sup> The adipocyte-specific metabolic-related lncRNAs, ASMER-1 and ASMER-2, were identified in RNA sequencing and microarray analysis of human WAT from 108 female participants with obesity and insulin sensitivity. Bioinformatics analysis revealed that ASMER-1 increased lipid metabolism whereas ASMER-2 expression correlated with inflammatory pathways.<sup>45</sup> Silencing of both ASMER-lncRNAs resulted in reduced adiponectin release and impacted lipolysis, fatty acid and energy metabolism leading to reduced triglyceride accumulation.<sup>45,46</sup> Adiponectin has a role in insulin sensitizing and is found to be reduced in obesity-linked insulin resistance.<sup>47</sup> An interesting therapeutic strategy for obesity-

associated insulin resistance has involved increasing expression of adiponectin and its receptors.<sup>47</sup> Further work is required to fully understand the mechanisms by which these ASMER-lncRNAs impact upon adiponectin, and it remains yet to be seen whether these may have a therapeutic potential in obesity and insulin resistance.

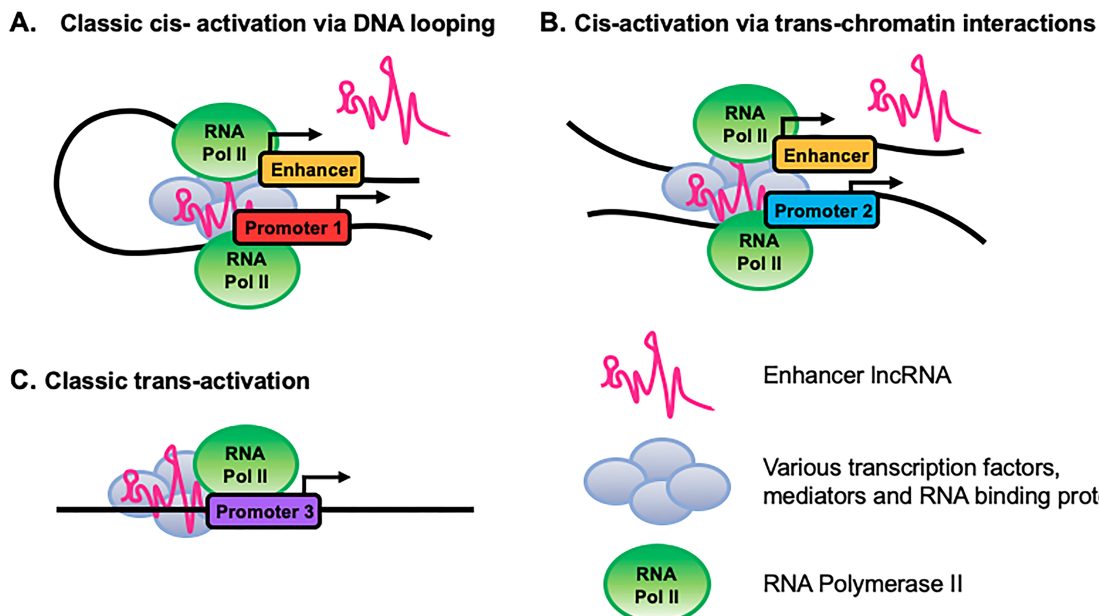
The steroid receptor RNA activator 1 (SRA1) was the first steroid receptor coactivator lncRNA discovered over 20 years ago.<sup>48</sup> The *SRA1* gene is transcribed into four transcripts, two protein-coding and two noncoding transcripts including an intergenic lncRNA. The intergenic lncRNA *SRA1* is highly expressed in WAT and is reported to promote adipocyte differentiation. *SRA1* binding of the adipogenic master transcriptional regulator, PPAR $\gamma$ , enhances its transcriptional activity and upregulates the expression of several adipocyte genes including key adipogenesis regulators, such as *C/EBP $\alpha$* , and PPAR $\gamma$  itself.<sup>49,50</sup> Overexpression of the *SRA1* gene upregulated genes involved in insulin-related signal transduction pathways as well as inflammation. *in vitro* analysis of glucose uptake found that *SRA1* overexpression resulted in increased insulin-stimulated uptake of glucose. This was consistent with phosphorylation of protein kinase B (AKT) and FOXO1. Additionally, Xu et al. found that inflammatory genes were strongly repressed upon *SRA1* overexpression including the macrophage-attracting chemokine *CCL2*. Further investigation confirmed that *SRA1* knockdown, with short-hairpin RNAs, had the opposite effect to overexpression, including inhibition of AKT and FOXO2 phosphorylation, inhibition of glucose uptake and upregulation of tumour necrosis factor alpha (TNF $\alpha$ )-induced JNK phosphorylation.<sup>49</sup> Together, these data suggest both anti-inflammatory and insulin sensitivity-enhancing properties of *SRA1*. More recently, the Xu group found that HFD-fed mice highly expressed the *SRA1* gene in WAT and generated a *SRA1* gene knock-out mice (*SRA*-/-) with a lean phenotype.<sup>50</sup> In contrast to their previous study, *SRA*-/- mice protected from diet-induced obesity were more sensitive to insulin and less inflammatory with reduced expression of TNF $\alpha$ , *CCL2* and IL-6. There are number of discrepancies between these two studies regarding insulin sensitivity and whether *SRA* is pro-inflammatory or anti-inflammatory. Importantly, as mentioned above, the *SRA1* gene encodes both coding and noncoding transcripts. Therefore, it is unclear whether the effects of these *in vitro* and *in vivo* loss of function (LOF) and gain of function (GOF) studies were mediated by the lncRNA alone. These contradictions highlight the challenges of replicating *in vitro* effects within *in vivo* models, and certainly, more research is required to tease out the specific functionality of the lncRNA. Despite this, it is evident in both studies that *SRA1* has a fundamental role in insulin-regulated glucose metabolism and inflammation. Additionally, *SRA1* has great therapeutic potential with strategies already being investigated within the cancer and cardiovascular field.<sup>48</sup>

The antisense noncoding RNA in the *INK4* locus, *ANRIL*, is expressed from the 9p21 locus, which is frequently mutated containing several diabetes-associated and age-related disease polymorphisms.<sup>51,52</sup> *ANRIL* interacts with both polycomb repressive complexes (PRCs) binding the PRC2 component *SUZ12* and PRC1 through polycomb component chromobox 7 (*CBX7*) forming

ribonucleoprotein complexes, which are required for epigenetic gene regulation through trimethylation of histone H3 on lysine 27.<sup>53,54</sup> Regulation of CpG methylation sites within the promoter of *ANRIL* is reported to influence adiposity. Lillycrop et al. discovered that lower CpG methylation marks in the *ANRIL* promoter in umbilical cord tissue at birth was a predictor of increased adiposity in childhood.<sup>52</sup> The *ANRIL* promoter in subcutaneous AT of adults with obesity also has reduced methylation, compared with those who are lean.<sup>52</sup> Additionally, *ANRIL* is reportedly induced by high glucose and diabetes in retinal endothelial cell lines.<sup>55</sup> Although there is limited knowledge in the context of adiposity, *ANRIL*'s role in inflammation is well developed, and its expression is positively correlated with pro-inflammatory factors. In human endothelial cells, *ANRIL* is regulated by NF- $\kappa$ B-mediated TNF $\alpha$ , which induces *ANRIL* expression. Inflammatory markers were dysregulated on silencing of *ANRIL*, which was shown to be necessary in YY1 transcriptional regulation at the IL-6 and IL-8 promoters.<sup>56</sup> Given that *ANRIL* expression correlates with obesity and diabetes, as well as its sensitivity to glucose and TNF $\alpha$ , together with its influence on downstream inflammatory factors, *ANRIL* may also have a contributing role in obesity-associated inflammation, which remains to be fully investigated.

Degirmenci et al. identified 343 lncRNAs in adipocytes that responded to insulin stimulation of which 80 were superenhancer lncRNAs involved in energy metabolism.<sup>57</sup> Enhancer RNAs are thought to be important for recruitment of RNA polymerases to the promoter of neighbouring genes and to influence the three-dimensional architecture of DNA and chromatin-chromatin interactions (Figure 2).<sup>58</sup> It is believed these enhancer RNAs may facilitate and stabilize chromatin loops acting as tethers that allow them to influence genes *in cis* on the same chromosome as well as on other chromosomes *in trans* (Figure 2A,B). The adipose-specific insulin responsive lncRNA (*lncASIR*) was identified as one such superenhancer lncRNA containing several binding sites for PPAR $\gamma$ , an adipogenesis master regulator. CRISPRi-mediated silencing of *lncASIR* resulted in the downregulation of several metabolic pathways downstream of insulin signalling including PPAR and adipocytokine signalling as well as lipolysis. Overexpression of this lncRNA was unable to rescue these effects, suggesting that *lncASIR* transcription from its endogenous locus drives its functionality.<sup>57</sup> Unfortunately, the study does not mention the genes under adipocytokine signalling, although unsurprisingly supplementary data find that leptin is particularly responsive to insulin, which is important for lipolysis and is also reportedly regulated by the PPAR $\gamma$  signalling pathway.<sup>59</sup>

Adiposity-associated inflammation in AT is well correlated with increased macrophage infiltration. Under lean body conditions or transient changes in body fat mass, these specialized immune cells or AT resident macrophages function to regulate tissue homeostasis and are involved in energy production, adipogenesis and lipid metabolism.<sup>60,61</sup> With obesity, the chronic expansion in AT mass results in the accumulation of macrophages through monocyte recruitment as well as proliferation leading to macrophages adopting a pro-inflammatory activation state that is typically associated with the development of insulin resistance and accumulation of pro-



**FIGURE 2** Enhancer lncRNAs in *cis*- and *trans*-activation of coding gene expression. (A) Enhancer lncRNAs can activate proximal genes in *cis* by enhancing and stabilizing DNA looping with neighbouring and remote promoters on the same chromosome. (B) Similarly, spatial organization of chromosomes within a cell brings together enhancers and *trans*-located promoters on different chromosomes leading to *cis*-activation. (C) Enhancer lncRNAs can also activate coding genes in *trans* by recruiting transcriptional machinery at distal promoters. lncRNA, long noncoding RNA

inflammatory cytokines in multiple tissues including the adipose tissue, pancreas, liver and skeletal muscle.<sup>60,62</sup> Stapleton et al. found that AT macrophages from HFD-fed mice suppress the lncRNA macrophage inflammation-suppressing transcript (MIST). MIST is located downstream of a lipid chaperon encoded by *FABP5* gene, which has been linked to insulin sensitivity and inflammation.<sup>63</sup> LOF studies reduced *FABP5* expression and increased M1-associated genes, whereas GOF studies found reduction in genes associated with inflammation and lipid metabolism. RNA pull-down experiments found that MIST epigenetically regulates pro-inflammatory genes *TNF $\alpha$* , *IL-6*, *IL-10*, *IL-1 $\beta$*  and *CCL2* through an interaction with PARP1. Expression of MIST lncRNA was analysed in human AT macrophages and was found to be downregulated in individuals with obesity and negatively correlated with insulin resistance.<sup>63</sup>

Finally, glucose uptake into skeletal muscle accounts for a substantial amount of insulin-stimulated glucose uptake from the blood. To this end, the expression of lncRNAs in skeletal muscle in individuals with increased adiposity and with or without T2D has been examined, as well as their functional role in mediating skeletal muscle glucose utilization. H19 is significantly decreased in muscle of human subjects with obesity and T2D, compared with those who are lean healthy and have no T2D. Furthermore, H19 depletion results in impaired insulin signalling and decreased glucose uptake through phosphatidylinositol-3 kinase (PI3K)/AKT-induced Let-7 miRNA.<sup>64</sup> More recently, RNA-seq analysis of skeletal muscle cells has identified 147 differentially expressed lncRNAs that potentially contribute to palmitic acid-induced insulin resistance.<sup>65</sup> Given the importance of skeletal muscle tissue in glucose utilization and insulin sensitivity, lncRNAs that have been implicated in mediating changes to skeletal

muscle mass (Section 3.2) may also play important roles in regulating muscle metabolic function and in turn insulin sensitivity.

### 3.2 | Sarcopenia and skeletal muscle atrophy

Sarcopenia is the decline of skeletal muscle mass and strength with age, which is often associated with increased muscle atrophy and accompanied by an increased systemic inflammatory burden<sup>66</sup> and accumulation of AT.<sup>67</sup> Furthermore, it is known that sarcopenia is more prevalent in persons with increased adiposity.<sup>68</sup> This is believed to be due to the antimyogenic and muscle atrophic activity of several obesity-associated cytokines and adipokines. Indeed, it has been shown that obese, but not normal-weight, subcutaneous AT secretome impairs the myogenesis of old myoblasts.<sup>69</sup> Also, AT in older individuals with increased adiposity secretes differential amounts of adipokines that can impact the metabolic health and insulin sensitivity of older skeletal muscle tissue.<sup>70</sup> Furthermore, circulatory levels of *TNF $\alpha$*  and *IL-6* have been shown to be negatively correlated to muscle mass and strength in older individuals,<sup>71</sup> and their muscle atrophic actions have been demonstrated in both *in vitro* and *in vivo* studies.<sup>72,73</sup> Therefore, the aforementioned lncRNAs that regulate adiposity and inflammatory cytokines likely play important roles in mediating obesity-associated sarcopenia. In addition, several lncRNAs have been directly implicated in the regulation of skeletal muscle mass.

Currently, no study has investigated the impact of obesity on human skeletal muscle lncRNA expression. However, evidence that lncRNA expression can be either influenced by or regulated skeletal



muscle inflammation with increased adiposity may be inferred from patients with myositis, a collection of diseases associated with chronic skeletal muscle inflammation. Using next-generation sequencing, Hamman et al. identified 1,056 lncRNAs in human skeletal muscle, of which 55 and 46 lncRNAs were differentially expressed in inclusion body and Jo-1 myositis, respectively, compared with skeletal muscle from healthy individuals.<sup>74</sup> These differentially expressed lncRNAs included H19 as well as previously characterized skeletal muscle lncRNAs such as MALAT1, lncMyoD, PVT1 and MEG3.<sup>74–77</sup>

In a study by Dey et al., H19 increased miR-675-3p and miR-675-5p expression in C<sub>2</sub>C<sub>12</sub> cells (a murine myoblast cell line), which in turn suppressed BMP/TGF- $\beta$  signalling, promoting differentiation.<sup>78</sup> Similar positive regulation of myogenesis has since been observed in bovine myoblasts, by H19-mediated inhibition of Sirt1/FOXO1 signalling.<sup>79</sup> Whether H19 expression is downregulated in human skeletal muscle from individuals with obesity, as seen in other tissues,<sup>64</sup> and in turn reduces myoblast differentiation has not been investigated, highlighting the need for further studies to determine the potential role of H19 in sarcopenia.

Evidence for MALAT1's role in the regulation of skeletal muscle is conflicting. On the one hand, MALAT1 expression has been demonstrated to increase during human primary myotube differentiation, remaining elevated up to Day 6.<sup>80</sup> Additionally, MALAT1 knockdown in C<sub>2</sub>C<sub>12</sub> cells has been associated with a small reduction in myogenin and reduced proliferation, suggesting that MALAT1 may positively regulate myogenesis.<sup>80–82</sup> In support of this, myostatin, a negative regulator of muscle mass, was shown to suppress MALAT1 expression.<sup>80</sup> Additionally, in a comprehensive set of experiments, Han et al. reported that MALAT1 may act as a competitive RNA for miR133. By binding miRNAs, competitive RNAs can de-repress miRNA target genes, thus regulating the miRNA activity. Here, this interaction prevented miR133 from downregulating the transcription factor SRF in the cytoplasm of C<sub>2</sub>C<sub>12</sub> myoblasts, enabling SRF translocation to the nucleus and subsequently upregulation of muscle specific gene expression.<sup>81</sup> In contrast, Chen et al. reported that MALAT1 is downregulated during the first 24 h of myogenesis and negatively regulated differentiation, potentially by influencing the transcriptional activity of MyoD.<sup>82</sup> This was demonstrated both in C<sub>2</sub>C<sub>12</sub> and critically in vivo utilizing MALAT1 knockout mice. However, the potential impact of increased skeletal muscle MALAT1 expression and its role in regulating myogenesis in human skeletal muscle linked to increased adiposity has not been studied. Similarly, numerous other lncRNAs have also been shown to be directly involved in the regulation of skeletal muscle myogenesis and have recently been reviewed by Sweta et al.<sup>83</sup> Future studies investigating the role of such lncRNAs with increased adiposity and inflammation will also be important in identifying their potential roles in the regulation of sarcopenia.

Of the lncRNAs that have been associated with muscle ageing, Gm17281 (also referred to as Chronos) was found to be significantly increased with age in the skeletal muscle of mice, promoting atrophy mediated by repression of Bmp7, a positive regulator of hypertrophic gene expression.<sup>84</sup> Critically, a mean 42% increase in myofiber cross

sectional area was observed in vivo following 14 days of siRNA treatment, an effect similar to that seen following myostatin inhibition.<sup>84</sup>

In contrast, the expression of muscle anabolic regulator 1 (MAR1) in skeletal muscle declines with age in mice.<sup>85</sup> MAR1 was found to be a sponge for microRNA-487b, identified as a negative regulator of Wnt5a expression. Lentiviral-mediated overexpression of MAR1 in C<sub>2</sub>C<sub>12</sub> myoblasts increased expression of Wnt5a and in turn the myogenic transcription factors, MyoD, MyoG, Mef2c and Myf5, promoting differentiation, whereas the reverse was observed following MAR1 knockdown. Similar effects were observed in vivo following the upregulation or downregulation of MAR1 in adult mice, whereas MAR1 upregulation in aged (22 months) mice protected against muscular atrophy. Therefore, a decline in MAR1 with age may result in reduced inhibition of microRNA-487b, negatively impacting myoblast differentiation and skeletal muscle mass. Together, these studies identify the potential of age associated lncRNAs as drivers of muscular atrophy in sarcopenic obesity.

In addition to age, MAR1 was regulated by other external stimuli; its expression decreased with muscle unloading and was restored with reloading.<sup>85</sup> Other lncRNAs have also been demonstrated to respond to alterations in load. In a comprehensive study, Hitachi et al. utilized eight different animal models to investigate the impact of both hypertrophy and atrophy on skeletal muscle lncRNA expression.<sup>86</sup> Of note, this study highlighted the varied regulation of lncRNA expression depending on the type of model used, in addition to identifying Gtl2, IG-DMR and DUM1 as potentially important lncRNAs mediating hypertrophy.<sup>86</sup> In a similar study, the novel atrophy-related lncRNA-1 (AtroInc-1) was upregulated in the skeletal muscle of murine models of muscle wasting.<sup>87</sup> Furthermore, AtroInc-1 was demonstrated to bind A20 binding inhibitor of NF- $\kappa$ B-1 (ABIN-1) in the cytoplasm of C<sub>2</sub>C<sub>12</sub> myotubes, impairing its function as an inhibitor of NF- $\kappa$ B. As a result, AtroInc-1 appears to facilitate an NF- $\kappa$ B-mediated upregulation of MuRF-1 expression, resulting in increased proteolysis. In support of these in vitro findings, AtroInc-1 knockout mice exhibit skeletal muscle hypertrophy, whereas overexpression results in atrophy, again associated with upregulated MuRF-1 expression.<sup>87</sup> As sarcopenia is associated with skeletal muscle unloading, understanding the regulation of human skeletal muscle lncRNA expression in this setting is critical.<sup>88</sup>

It is also important to consider that human skeletal muscle is composed of multiple different fibre types that can be classified as either type I (slow twitch) or type II (fast twitch) based, in part, on their myosin heavy chain (MHC) expression. Owing to the plastic nature of skeletal muscle, fibre types can shift in response to regular training and disease. For example, elderly individuals with sarcopenia primarily present with a loss of type II fibres, whereas chronic obesity is primarily associated with type I fibre atrophy. Recently, a number of studies have investigated the potential role of lncRNAs in the regulation of muscle fibre type<sup>89–92</sup> and have been associated with a switch in MHC expression from IIx to IIa in humans following a 5-week exercise protocol.<sup>92</sup> Thus, it will be important to identify if similar lncRNA-mediated changes in fibre type occur in the obese state.

### 3.3 | Osteoarthritis

Obesity-mediated chronic low-grade inflammation is associated with dysregulated innate immune system activity. The innate immune system is the first line of defence utilizing leukocytes, which recognize pathogen or damage-associated molecular patterns and activate a cascade of pro-inflammatory pathways through pattern-recognition receptors.<sup>93,94</sup> Leukocytes secrete pro-inflammatory cytokines, which further promotes the pro-inflammatory secretory environment leading to increases in TNF $\alpha$ , IL-1 $\beta$ , IL-6, IL-8, leptin and growth hormone.<sup>95</sup> Critically, there is now increasing evidence that lncRNAs are central mediators of the innate immune response, and therefore, their role in adiposity-related inflammatory conditions such as osteoarthritis (OA) and rheumatoid arthritis (RA)<sup>94–96</sup> is being further studied.

Low-grade inflammatory assaults in OA are central to joint deterioration, with synovial fluid leukocyte counts in knee osteoarthritis correlating with synovial membrane inflammation (synovitis).<sup>97</sup> Additionally, synovitis is exacerbated in patients with OA and increased adiposity, where obese OA synovial fibroblasts (OASF) secrete greater amounts of IL-6 and IL-8 adding to the local inflammatory joint environment.<sup>98</sup> These obese OASFs are highly proliferative and exhibit an inflammatory phenotype that consists of several long intergenic noncoding RNAs. Nanus et al. reported 19 differentially expressed lncRNAs in OA synovial fibroblasts isolated from end-stage OA patients with obesity compared with those who were lean and without OA.<sup>98</sup> Expression of seven lncRNAs, MALAT1, CARMN, AF131217.1, miR155HG, LINC01705, RP11-863p13.3 and RP11-367F23.2, was induced in OASF in response to stimulation with obesity-associated cytokines including IL-1 $\beta$ , TNF $\alpha$ , leptin and visfatin. Interestingly, proliferation of obese OASF and the expression of IL-6 and IL-8 were reduced in MALAT1 LOF studies. Other studies have found that this lncRNA specifically interacts with and influences the distribution of pre-mRNA splicing factors to nuclear speckles, and its depletion results in cell cycle arrest and activation of p53 and its targets.<sup>99</sup> Similarly, pathway analysis of RNA-sequencing data following MALAT1 knockdown in OASF confirmed downregulation of cell proliferation and inflammatory genes, also supporting the therapeutic potential of MALAT1.<sup>98</sup> PACER, CILinc01 and CILinc02 (IL7-AS) are another three lncRNAs reported by the same group, which respond to pro-inflammatory cytokine stimuli in OA chondrocytes. Pearson et al. reported that CILinc01 and CILinc02 knockdown followed by IL-1 $\beta$  induction resulted in increased expression of IL-6, IL-8 and TNF $\alpha$ .<sup>100</sup> Additionally, Roux et al. identified 242 novel lncRNAs in chondrocytes, including IL7-AS, whose expression changed following the induction of the innate immune response.<sup>94</sup> Interestingly, H19 is prominently expressed in both OA and RA synovial tissue fibroblasts and macrophages. Serum starvation and stimulation with or without IL-1 $\beta$ , TNF $\alpha$  or PDGF-BB reportedly induce H19 expression in synovial fibroblasts via the MAPK/ERK/PI3K pathways.<sup>101</sup> H19 sensitivity to cytokine stimulation and serum starvation is thought to be important for synovial tissue dedifferentiation, ongoing

inflammation and oxidative stress. Several studies in the last 2 years report inflammation-associated lncRNAs in osteoarthritis including PVT1,<sup>102</sup> DANCER,<sup>103</sup> XIST,<sup>104</sup> H19,<sup>105</sup> FOXD2-AS1<sup>106</sup> and MF12-AS1.<sup>107</sup> Although these studies do not focus on adiposity, the implication of lncRNAs in OA is clear, and given that the majority of OA patients have significantly increased levels of adiposity, further investigations may help stratify patients for specific diagnostics and therapies.

### 3.4 | Rheumatoid arthritis

RA is a chronic inflammatory autoimmune disease where abdominal adiposity is prevalent amongst 20%–50% of patients.<sup>108</sup> Immune dysfunction in RA leads to destruction of bone and cartilage, immune cell infiltration and inflammation.<sup>109</sup> Several lncRNAs have been recognized to influence inflammatory pathways such as NF- $\kappa$ B signaling, p38 MAPK and toll-like receptor pathways in RA.<sup>109</sup> Although the precise mechanisms are poorly defined, especially in the context of obesity, the epigenetic regulation of the synovial RA fibroblast phenotype is considered to be central in mediating the inflammatory and autoimmunity RA joint pathology.<sup>110</sup>

Unsurprisingly, MALAT1 has also been identified to regulate synovial fibroblast proliferation and inflammation in RA. In RA synovial tissue, MALAT1 expression is found to be downregulated. Additionally, in contrast to the previously detailed findings in OA, silencing of MALAT1 in RA fibroblast-like synoviocytes (FLSs) results in an increase in IL-6, IL-10 and TNF $\alpha$  secretion and elevated proliferation.<sup>111</sup> Li et al. found that MALAT1 binds to the promoter of CTNNB1 regulating DNA methylation to inhibit  $\beta$ -catenin and thus the Wnt-signalling pathway.

The pro-adipogenic lncRNAs HOTAIR has also been implicated in RA. HOTAIR is expressed from the *HoxC* gene cluster on chromosome 12 and selectively binds components of the PRC2 complex including the histone methyltransferase EZH2.<sup>12</sup> Whereas the 5' region of HOTAIR associates with PRC2 proteins, the 3' domain also has been found to interact with the histone demethylase complex LSD1/CoREST/REST.<sup>13</sup> HOTAIR expression is elevated in adipose-derived exosomes in individuals with obesity and is also reported in RA serum exosomes.<sup>112,113</sup> In RA, profiling of exosomal lncRNAs identified several differentially expressed lncRNAs including HOTAIR, MEG9, SNHG4, TUG1, NEAT1, MALAT1 and SNHG1. HOTAIR expression was found to be increased fourfold in obese RA exosomes, compared with healthy controls. Exosomal HOTAIR contributed to the migration and activation of macrophages as well as the production of matrix metalloproteinases.<sup>113</sup> Exosomes from adipose-derived mesenchymal stem cells are also of therapeutic interest in OA.<sup>114</sup> Exosomes isolated from serum and synovial fluid of patients with OA contain HOTAIR, GAS5 and PCGEM1 lncRNA transcripts, although HOTAIR and GAS5 were not significantly different compared to prearthritic controls.<sup>115</sup> However, as those patients who were prearthritic controls had also presented with incidental knee pain, it is difficult to dissect the functional significance of HOTAIR in the

context of OA. The exact implications of HOTAIR in adipose-derived exosomes in both RA and OA have yet to be fully explored especially with the added complexity of obesity.

## 4 | LncRNA CHALLENGES AND CLINICAL PROSPECTS

In the context of obesity-associated inflammation, it will be important to distinguish between lncRNAs that are simply associated with increased adiposity and those that are implicated in mediating a chronic low-grade inflammatory obese state, particularly as lncRNAs have the potential to be the next generation of biomarkers and therapeutic targets owing to their tissue-specific nature of expression.<sup>116</sup> However, the functional study of lncRNAs is not without its challenges. Owing to their poor primary sequence conservation across species, in vivo GOF and LOF studies can be nonpredictive. However, in some cases, it is thought that lncRNA functional conservation is geared towards the maintenance of genomic position (synteny) rather than the transcript itself.<sup>94,117,118</sup> Importantly, it has been reported that around 10% of human lncRNAs associated with the innate immune inflammatory response have syntenic versions in the mouse.<sup>74</sup> Therefore, a future focus on syntenic lncRNAs, such as the aforementioned IL7-AS,<sup>94</sup> would give the greatest opportunity for in vivo validation studies to translate to humans, alongside LOF studies in primary human cells.

Clinical trials involving lncRNAs are largely diagnostic and predominantly in the cancer field, where lncRNAs are being examined as biomarkers of disease state or prognostic markers. To date, PCA3 is the only lncRNA to have gained biomarker approval from the Food and Drug Administration for detecting human prostate cancer.<sup>119,120</sup> The length of lncRNA sequences and their complex secondary and tertiary structures have added complexity to pharmacological approaches where much is yet to be determined.<sup>121</sup> However, in recent years, drug classes have broadened to include RNAi-based therapeutics, many of which show great promise having reached pre-clinical stages for some cancer lncRNA-targeted therapeutics.<sup>120</sup> Many of these RNAi approaches have been demonstrated in animal models against protein-coding targets and include locked nucleic acid GapmeRs (LNA) and antisense oligonucleotides (ASO) technologies, although siRNA approaches have proven to be most successful owing to their gene targeting efficacy in cancer preclinical trials.<sup>122</sup> Therefore, many of the lncRNAs mentioned in this review could provide a new class of targets for RNAi-based therapeutics.

Additionally, lifestyle changes including dietary interventions and exercise have long been advocated as measures to tackle the effects of adiposity on age-related inflammatory conditions. Indeed, lncRNAs linked to weight loss, which show promising mechanistic relevance, have been identified such as lncRNA-p19461.<sup>29</sup> Coupling both lifestyle changes and targeting of lncRNAs in various obesity-associated inflammatory conditions may be of therapeutic benefit. Furthermore, determining their mode of action and understanding the lncRNA commonalities that regulate obesity-related inflammatory processes

across different conditions could identify lncRNA-mediated targets that are suitable for therapeutic intervention.

## 5 | CONCLUSION

Our understanding of the role of lncRNAs in mediating obesity-associated inflammatory disease is very much in its infancy. However, a growing number of lncRNAs have been identified as differentially expressed in the obese state, and several have been implicated as regulators of AT and skeletal muscle mass and obesity-associated inflammatory pathways. Therefore, determining the mode of action of these disease-associated lncRNAs will be insightful and potentially clinically relevant, as will more extensive tissue expression profiling in humans to fully determine their functional roles.

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### CONFLICT OF INTEREST

No conflict of interest was declared.

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