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REVIEW ARTICLE

Long noncoding RNAs in cardiometabolic disorders

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The advancement of medical technology has led not only to an increase in life expectancy but also to a rise in aging-related diseases. Aging promotes metabolic disorders, in turn affecting cardiovascular health. Derailment of biological processes in the pancreas, liver, adipose tissue, and skeletal muscle impairs glucose and lipid metabolism, and mitochondrial function, triggering the development of diabetes and lipid-related disorders that inflict damage on cardiac and vascular tissues. Long noncoding RNAs (lncRNAs) regulate a wide range of biological process and are one of the key factors controlling metabolism and mitochondria. Here, we discuss the versatile function of lncRNAs involved in the metabolic regulation of glucose and lipid, and mitochondrial function, and how the dysregulation of lncRNAs induces the development of various metabolic disorders and their cardiovascular consequences.

Keywords: aging; cardiovascular system; glucose and lipid metabolism; LncRNA; mitochondria

Abbreviations
AF, atrial fibrillation; ApoE, apolipoprotein E; ATP, adenosine triphosphate; BAT, brown adipose tissue; BMI, body mass index; CAD, coronary artery disease; ceRNA, competing endogenous RNA; circRNA, circular RNA; CVD, cardiovascular disease; DDR, DNA damage response; EZH, enhancer of zeste homologue; GCK, glucokinase; HDL, high-density lipoprotein; HF, heart failure; HUVEC, human umbilical vein endothelial cell; LDL, low-density lipoprotein; lncRNAs, long noncoding RNAs; LV, left ventricular; miRNA, microRNA; mRNA, messenger RNA; mtDNA, mitochondrial DNA; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PBMC, peripheral blood mononuclear cell; PEG, paternally expressed gene; ROS, reactive oxygen species; rRNA, ribosomal RNA; snRNA, small nucleolar RNA; STZ, streptozotocin; TAC, transverse aortic constriction; tRNA, transfer RNA.

The increase in life expectancy over the past decades has led to a fast growth of the aged population, prompting a rise in the prevalence of cardiovascular diseases (CVD) and a 3-fold increase in treatment costs [1,2]. Aging promotes the development of metabolic disorders, such as obesity, diabetes mellitus, insulin resistance, and dyslipidemia, as it deranges biological processes that lead to an adverse metabolic profile [3–5]. In turn, metabolic disorders promote premature aging of the cardiovascular system, leading to various pathologies, including the reduced regenerative capacity of cardiomyocytes (from 1% per year at age 20 to 0.4% at 75 years) [6], myocardial hypertrophy and fibrosis [7,8], diastolic dysfunction, endothelial dysfunction, reduced vascular elasticity, and chronic vascular inflammation [9–12].

Metabolic impairment in tissues, such as the liver, skeletal muscle, pancreas, and adipose tissue, is a key element that can derail cardiovascular health by promoting the development of the metabolic syndrome [13]. The liver, for instance, plays a vital role in the systemic and local metabolism of lipids and glucose and is one of the main peripheral organs prone to insulin resistance [14,15]. The pancreas is involved in central and peripheral glucose metabolism by secreting insulin and maintaining normal blood glucose levels [16]. Skeletal muscle plays an important role in systemic glucose homeostasis [17], and adipose tissue acts not only on lipid storage and thermogenesis but also on releasing factors regulating the overall body metabolism [18]. Fine-tuning of these physiological processes ensures their proper function. In this review, we discuss the role of long noncoding RNAs (lncRNAs) in maintaining the homeostasis of metabolic processes and mitochondrial function (Table 1, Table S1) and how dysregulation of this noncoding nucleic acid impairs metabolism in various organs, increasing the risk of developing CVD.

Evolutionary conservation, structure, and function of long noncoding RNAs

The advancement of sequencing technologies has led to the discovery that the human genome is largely transcribed into RNA, but only a minor fraction of it (~ 3%) is translated into protein, while the majority (~ 97%) represents a variety of ncRNAs, including lncRNA, microRNA (miRNA), circular RNA (circRNA), small nucleolar RNA (snRNA), ribosomal RNA (rRNA), and transfer RNA (tRNA) (Fig. 1). lncRNAs are defined as nonprotein-coding RNA transcripts longer than 200 nucleotides and their role in metabolism-related cardiovascular disease is increasingly recognized [19–21]. It is estimated that the human genome contains approximately 100 000 lncRNAs [22,23]. However, only less than 5% of human lncRNAs have been functionally characterized, partly due to poor genomic sequence conservation between species [24,25] and to functional heterogeneity, which cannot yet be entirely assessed using currently available methodologies [26–28]. Nevertheless, lncRNAs have been identified across species in syntenic genomic regions. These so-called locus conserved lncRNAs usually display conserved function [29,30]. It is plausible that the 3D structure of lncRNAs be evolutionarily conserved. Interestingly, there is an increasing number of lncRNA transcripts in the more complex species and lncRNA expression is highly tissue-specific, suggesting that lncRNAs promote species-specific features and organ complexity and play a crucial role in the evolution towards more complex organisms [31,32].

Similar to mRNAs, lncRNAs are transcribed by RNA polymerase II from genomic loci with similar chromatin states and are often 5′-capped, spliced, and polyadenylated [33]. lncRNAs can be transcribed from a different genomic location relative to protein-coding genes: intergenic regions (lincRNA), intronic regions, overlapping with a specific gene on the same or the opposite strand, opposite strand of the promoter region, and enhancer region [29,34]. In contrast to mRNA, lncRNAs tend to be shorter, have fewer but longer exons, are expressed at relatively lower levels, and lack a translated open reading frame [33]. Nevertheless, some RNAs that were previously identified as lncRNAs turn out to have open reading frames allowing them to be translated into so-called micropeptides [27,35,36]. These transcripts are by definition no longer bona fide ncRNAs. Nevertheless, they are still categorized as a specific class of lncRNAs as they may play bifunctional roles as RNA and peptide [35,37].

The majority of lncRNAs are localized in the nucleus and associated with chromatin, while some fractions localize to the cytoplasm [33,38]. The function of lncRNAs is dependent on their subcellular localization. lncRNAs form lncRNA-DNA, lncRNA-protein, and lncRNA-RNA complexes and can organize chromosomal architecture [39–41], facilitate the formation of ribonucleoprotein complexes, and mediate gene transcription and post-transcriptional modification [24]. Nuclear lncRNAs can regulate gene transcription by mobilizing transcription factors [42–44], guiding chromatin remodeling complexes to the correct locations to promote histone modifications [45–47], acting as an enhancer [48,49], regulating translocation of transcription factors between nucleus and cytoplasm [50], and controlling splicing of

Table 1. LncRNAs involved in glucose and lipid metabolism and mitochondrial function.

lncRNA	lncRNA function	Mechanism of action	Main target	Model	Pathology	Ref.
Adipogenesis						
Plnc1	Chromatin modification	Promotes adipocyte differentiation	PPARγ-2	ob/ob mice	Obesity	[127]
uc.417	Chromatin modification	Impairs adipogenesis	p38/Mapk	Cold stimulated mice	Obesity	[146]
lncBATE10	Decoy	Promotes full brown fat differentiation	Celf1	Browning-treated mice	Obesity	[145]
Hoxa11-as	Induces transcription	Promotes adipogenesis	C/EBP-α	human primary ADSCs	Obesity	[133]
AC092159.2	Induces transcription	Promotes adipogenesis	TMEM18	Human visceral preadipocytes	Obesity	[134]
Sra1	Induces transcription of PPARγ-dependent gene expression	Promotes adipocyte differentiation	PPARγ	Mice fed with HFD	T2D, obesity	[86]
Paral1	Induces transcription of PPARγ-dependent gene expression	Promotes adipogenesis	RBM12/CoAA/ PPARγ	ob/ob mice/ human WAT	Obesity	[131]
lnc-U90926	Inhibits transcription	Inhibits adipogenesis	PPARγ, FABP4, adiponectin	ob/ob mice	Obesity	[137]
PU.1as	Inhibits translation	Inhibits adipogenesis	PU.1	Mouse AT/3T3-L1 cells	Hyperlipidemia, IR, T2D	[130]
AdipoQ-AS	Inhibits translation	Inhibits adipogenesis	Adiponectin	Mice fed with HFD	Obesity	[136]
Tincr	miRNA sponging/ ceRNA	Promotes adipocyte differentiation	miR-31	Human primary ADSCs	Obesity	[128]
TCONS_ 00041960	miRNA sponging/ ceRNA	Inhibits adipogenesis	miR-204-5p/miR-125a-3p	Rat bone marrow mesenchymal stem cells	Osteogenic differentiation	[135]
lncBATE1	Protein binding	Promotes formation and maintenance of brown adipocytes capable of thermogenesis	hnRNP U	Mouse preadipocytes	Obesity	[144]
Cholesterol metabolism						
Lexis	Enhancer	Inhibits cholesterol biosynthesis	Ribonucleoprotein Raly	High-fat and cholesterol diet-fed mice	Atherosclerosis	[110]
Chrome	MiRNA interaction	Promotes cholesterol efflux	miR-27b, miR-33a, miR-33b and miR-128	High-fat diet-fed macaque/human primary hepatocytes	Atherosclerosis, CAD	[116]
ARSR	Unknown	Promotes cholesterol biosynthesis	Akt/SREBF2/ HMGCR	High cholesterol diet-fed mice	NAFLD, NASH	[100,101]
Neat1	Unknown	Promotes adipogenesis	miR-342-3p	THP-1 cells	Atherosclerosis	[122]
lnc-HC	Unknown	Inhibits cholesterol metabolism	SREBP1c/PPARγ/ miR-130b-3p	High-fat and cholesterol diet-fed mice	Lipid disorders and NAFLD	[113]
Glucose metabolism						
lncLGR	Binding to repressor	Supresses glucokinase activity	Ribonucleoprotein L	Fasted mice	Fasting	[84]
Meg3	ceRNA	Promotes insulin production	miR-214/EZH2	Obese mice, diabetic mice	T2D	[76–80]

Table 1. (Continued).

lncRNA	lncRNA function	Mechanism of action	Main target	Model	Pathology	Ref.
Pluto	Chromatin modification	Regulates β-cell development	PDX1	Human β-cells	T2D	[68]
Uc.322	Induce transcription	Promotes insulin secretion	PDX1/FOXO1	Mouse β-cells	T2D	[82]
Miat	MiRNA sponging	Promotes insulin resistance	miR-139	Obese mice	T2D, obesity	[83]
Nonratt021972	Unknown	Interacts with phospho-Akt	p-AKT	Diabetic rats	T2D	[85]
Dreh	Unknown	KD impairs glucose metabolism	GLUT4	Mouse myotubes	T2D	[89]
Tug1	Unknown	Mediates glucose metabolism	PDX1/GLUT2	NOD mice	T2D	[81]
H19	MiRNA sponging	Promotes β-cell development	Let-7	Islets of new-born and adult rats	Diabetes	[69]
H19	Decoy/inhibit transcription	Improves glucose metabolism	p53	Hep2G cells, H19 silencing in mice	Diabetes	[70]
H19	MiRNA sponging	Improves insulin sensitivity	Let-7	Insulin resistant mice, patients with diabetes	Diabetes	[72]
MALAT1	Unknown	Induces capillary degeneration, microvascular leakage, and retinal inflammation	p38/MAPK	STZ-induced diabetic rats and db/db mice	Diabetes	[93,94]
Gas5	Riborepressor/ Inhibits transcription	Promotes wound healing and negative regulation of cholesterol efflux	TAF15/Abca1	HUVECS/diabetic foot ulcers mice/ ApoE−/− mice	T2D,DFU, hyperglycemia, CAD	[95,96]
Anril	Scaffold	Regulation of glucose and fatty acid metabolism	PRC2/ADIPOR1/ TMEM258/VAMP3	Peripheral blood from patients, T-Rex 293 (HEK 293) cell	MI, CAD	[90–92]
slincRAD	Unknown	KD impairs adipocyte development	Unknown	Mice	Obesity	[88]
Lipid efflux and lipid metabolism						
Mexis	Enhancer	Promotes cholesterol efflux	Abca1	LXR KO mice	Atherosclerosis, CAD	[114]
APOA1-AS	Inhibits transcription	Negative regulation of HDL biosynthesis	ApoA1	HepG2 cells/ African Green Monkeys	Atherosclerosis	[119]
Dynlrb2-2	Unknown	Promotes cholesterol efflux	Abca1/GPR119	ApoE−/− mice	Atherosclerosis	[115]
AC096664.3	Unknown	mediates LDL-induced cholesterol accumulation	PPARγ/Abcg1	VSMC/THP-1/ HUVEC cells	Atherosclerosis	[117]
H19	Induce transcription, regulation of mRNA stability	Induces high-fat and high-sucrose diet-induced steatosis	PTBP1	Primary hepatocytes, H19 KO mice	NAFLD	[105]
H19	MiRNA sponging	Attenuate high-fat diet-induced myocardial injury	miR-29a	Mouse model of obesity, palmitic acid-treated cardiomyocyte cell line	Obesity	[106]

Table 1. (Continued).

lncRNA	lncRNA function	Mechanism of action	Main target	Model	Pathology	Ref.
H19	Chromatin modification	BAT differentiation, protects against diet-induced obesity and improves insulin sensitivity and mitochondrial biogenesis	MBD1	H19 KO and transgenic mice fed with HFD	Obesity	[141]
MALAT1	Regulation of protein stability	Promoted hepatic steatosis and insulin resistance	SREBP1c	HepG2 cells, ob/ob mice	Steatosis	[103]
BM450697	Inhibits transcription	Control LDL uptake	LDLR/SREBP1a	HepG2 cells/ primary hepatocytes	Familial hypercholesterolemia	[121]
lncLSTR	Enhancer	Maintain lipid homeostasis	TDP-43	ApoE−/− mice	Hyperlipidemia	[124]
Mitochondrial function						
Plscr4	MiRNA sponging	Promotes MFN2 expression	miR-214	Mouse CM, TAC mice	Hypertrophy	[153]
CARL	MiRNA sponging	Inhibits mitochondrial fission	PHB2	Mouse CM, I/R injury mice	Cardiotoxicity	[154]
Cmdl-1	Phosphorylation	Inhibits mitochondrial fission	DRP1	H9c2 cells	Cardiotoxicity after DOX treatment	[119]
Cerox1	MiRNA sponging	Promotes mitochondrial respiration	miR-488-3p	N2A cells, HEK293T cells		[155]
Caren	Unknown	Impairs mitochondrial respiration	Hint1	Mouse CM, TAC mice	Heart failure	[157]
AsncmtRNA-2	Unknown	Promotes senescence	hsa-miR-4485/hsa-miR-1973	Aged mice/ HUVECS	Aging	[162]
Lipcar	Unknown	Upregulates TGF-β pathway	TGF-β/Smad	Human atrial fibroblasts	Atrial fibrillation	[158–160]
Triglyceride metabolism						
B4GALT1-AS1/ lncSHGL	Enhancer	Reduces triglyceride content	hnRNPA1/CALM	Obese mice/ NAFLD mice	Obesity, NAFLD, T2D	[112]
APOA4-AS	mRNA stability	Positively regulates serum triglyceride content	HuR/APOA4	ob/ob mice/ human liver	Fatty liver disease, obesity	[120]
lncHR1	Unknown	Reduces triglyceride synthesis	SREBP1c	Mice fed with HFD		[109]
Blnc1	Scaffold	Increases triglyceride synthesis	EDF1	Mice fed with HFD/obese mice	Obesity, NAFLD, T2D	[102,142]

pre-mRNAs [51,52]. Cytoplasmic lncRNAs can regulate mRNA stability and control their translation [53,54], act as a scaffold and stabilize ribonucleoprotein complexes [55,56], mediate protein phosphorylation and activate signaling pathways [57,58]. lncRNAs have also been shown to be able to sponge miRNAs (competing endogenous RNA, ceRNA) (Fig. 2) [59,60]. A similar function is also displayed by circRNAs, which are not classified as lncRNAs due to several differentiating characteristics, such as the circular shape, exon-originated, and the lack of 5′–3′ polarization, capping, and polyadenylation [61–63]. In addition, lncRNAs can be secreted in extracellular vesicles, potentially facilitating cell-to-cell communication [14] and play an essential role as structural elements of nuclear bodies, in particular paraspeckles and nuclear stress bodies [64–66]. Interestingly, lncRNA molecules may not by themselves regulate the expression of their downstream target. lncRNA *upperhand* (*Uph*), for instance, does not affect the level of its host and target gene *Hand2* in its mature form. However, inhibition of *Uph* transcription reduces *Hand2* expression *via* reducing chromatin acetylation state at *Hand2* enhancer region [28].

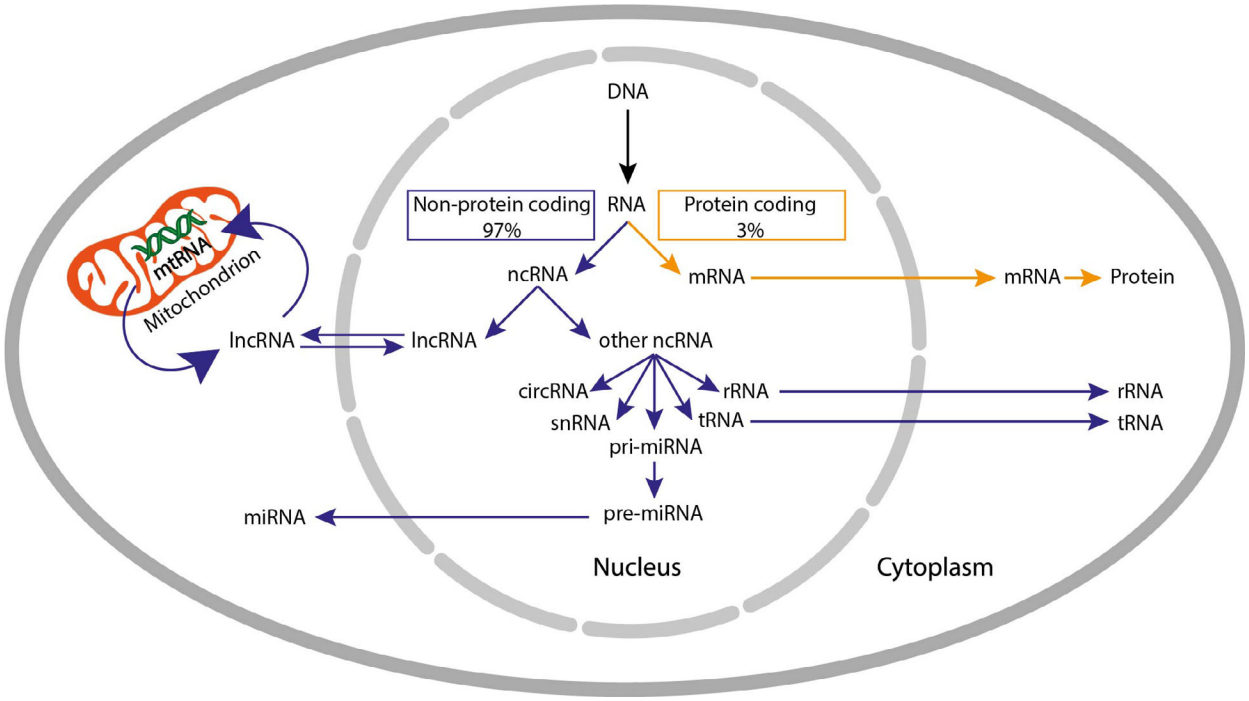

Fig. 1. Noncoding RNA family. The majority (~ 97%) of the genome is noncoding. Noncoding RNA (ncRNA) family can be classified into ribosomal RNA (rRNA), transfer RNA (tRNA), microRNA (miRNA), small nucleolar RNA (snRNA), long noncoding RNA (lncRNA), circular RNA (circRNA), and many other ncRNAs. LncRNAs can act in the nucleus, in the cytoplasm, and in mitochondria, upon being transferred into them. The majority of lncRNAs are transcribed within the nucleus, whereas a fraction of them originates from the mitochondrial genome.

Long noncoding RNAs in glucose metabolism

Abnormal glucose metabolism plays an important role in the development of diabetes. Several lncRNAs have been shown to regulate glucose metabolism and are associated with the pathology of type 2 diabetes by targeting pancreatic β-cell development, insulin synthesis and secretion, and insulin signaling in various tissues [20]. The pancreas maintains blood glucose level by the secretion of insulin from β-cells. Defects in the development of β-cells predispose individuals to abnormal glucose metabolism and associated disease such as diabetes [67]. lncRNA pancreatic and duodenal homeobox (*PDX1*) locus upstream transcript (*PLUTO*) has been shown to regulate β-cell development. Expression of *PLUTO* is lower in the islets of patients with type 2 diabetes and with impaired glucose tolerance. *PLUTO* affects 3D chromatin structure and promotes interactions between the promoter of *PDX1*, and its upstream enhancer cluster, enhancing the transcription of this gene [68]. Another lncRNA implicated in β-cell differentiation is *H19*, one of the first identified lncRNAs, which is paternally imprinted and maternally expressed. *H19* is highly expressed during embryonic development and repressed after birth. *H19* promotes the proliferation of β-cells through inhibition of miRNA *let*-7, leading to activation of the *Akt* signaling pathway [69]. In the liver, *H19* inhibition *in vivo* induces insulin resistance, with subsequent hyperglycemia and impaired glucose and pyruvate tolerance. Mechanistically, *H19* silencing increases the occupancy of *p53* on the *FoxO1* promoter, leading to increased *FoxO1* transcription levels in the nucleus and upregulation of gluconeogenic gene expression [70]. In contrast, *H19* level was elevated in diet-induced diabetic mice. *H19* knockdown in hepatocytes reduces promoter methylation, and consequently, induces the expression of *Hnf4a*, a master regulator of gluconeogenic enzyme transcription, promoting excessive hepatic glucose production, hyperglycemia, and insulin resistance [71]. The reason behind the seemingly opposite role of *H19* in the liver is unclear. *H19* also regulates insulin signaling in the skeletal muscle. *H19* was significantly lower in the muscle tissue of diabetic patients and rodents with insulin resistance. Here, *H19* acts as a molecular sponge to inhibit *let-7* miRNA. The reduction of *H19* level increases *let-7* bioavailability with subsequent reduction in expression of *let-7* target genes, resulting in impaired insulin sensitivity

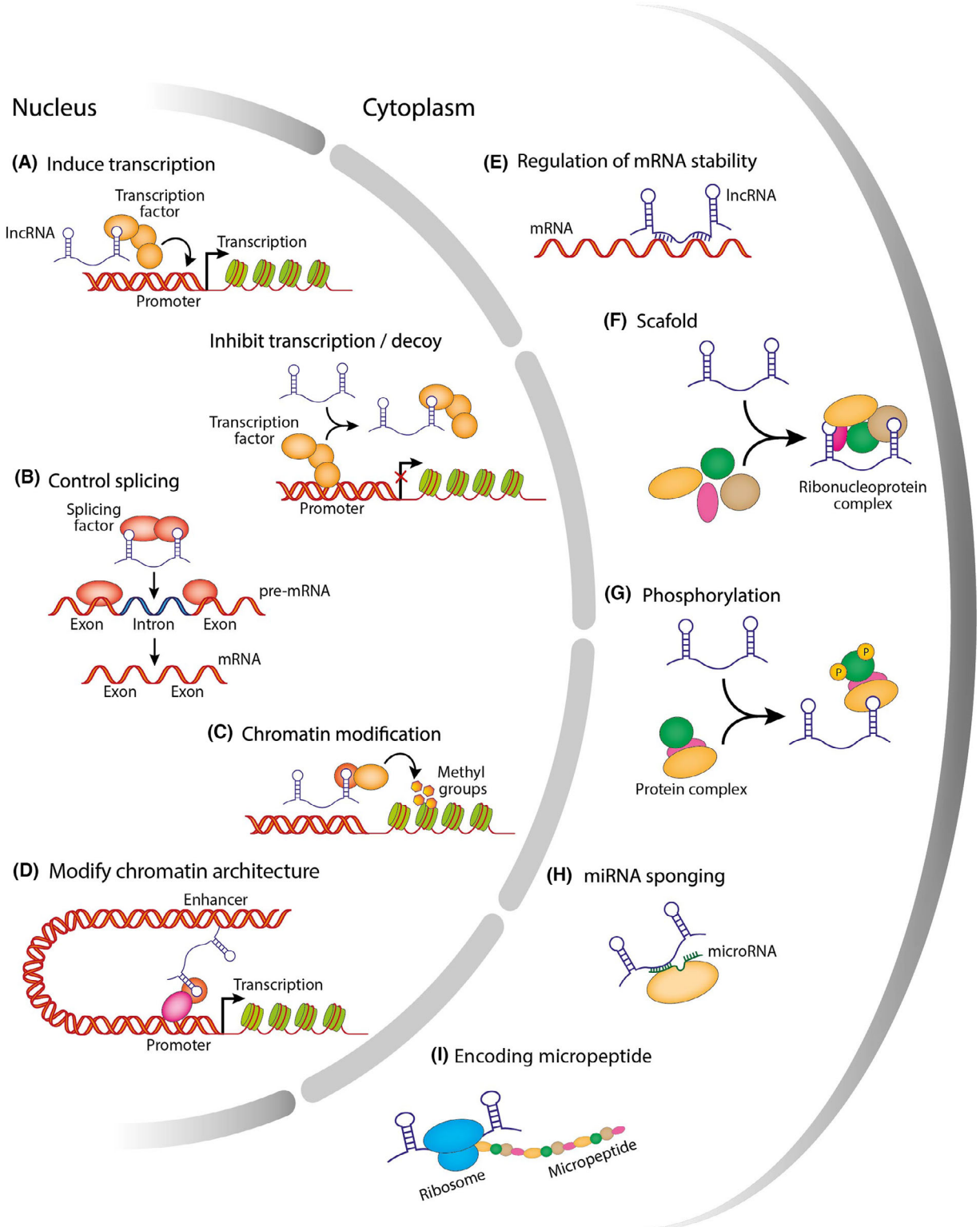

Fig. 2. The mode of action of lncRNAs. LncRNAs exert their effects depending on their subcellular localization. In the nucleus lncRNAs can induce or inhibit gene transcription by (A) guiding transcription factors, (B) controlling splicing of pre-mRNAs, (C) mediating chromatin/histone modifications, and (D) modifying chromatin architecture. Cytoplasmic lncRNAs can (E) regulate mRNA stability, (F) act as a scaffold for ribonucleoprotein complexes, (G) mediate protein phosphorylation, (H) act as a miRNA sponge, and (I) encode micropeptides.

and increased blood glucose level [72]. Furthermore, *H19* enhances insulin sensitivity by activating the adenosine monophosphate-activated protein kinase (*AMPK*) signaling pathway, which increases glucose uptake and mitochondrial biogenesis. The atypical dual-specificity phosphatase *DUSP27*/*DUPD1* acts as a downstream effector of *H19* to interact and activate *AMPK* in muscle cells (Fig. 3) [73]. Interestingly, extracellular vesicle-mimetic nanovesicle-containing *H19* was effective in the treatment of diabetes-associated chronic wounds. *H19*-containing nanovesicle displays the ability to counteract the inhibiting effect of hyperglycemia on angiogenesis *in vitro* and *in vivo* [74].

The expression of another lncRNA maternally expressed gene 3 (*Meg3*) is increased in the peripheral

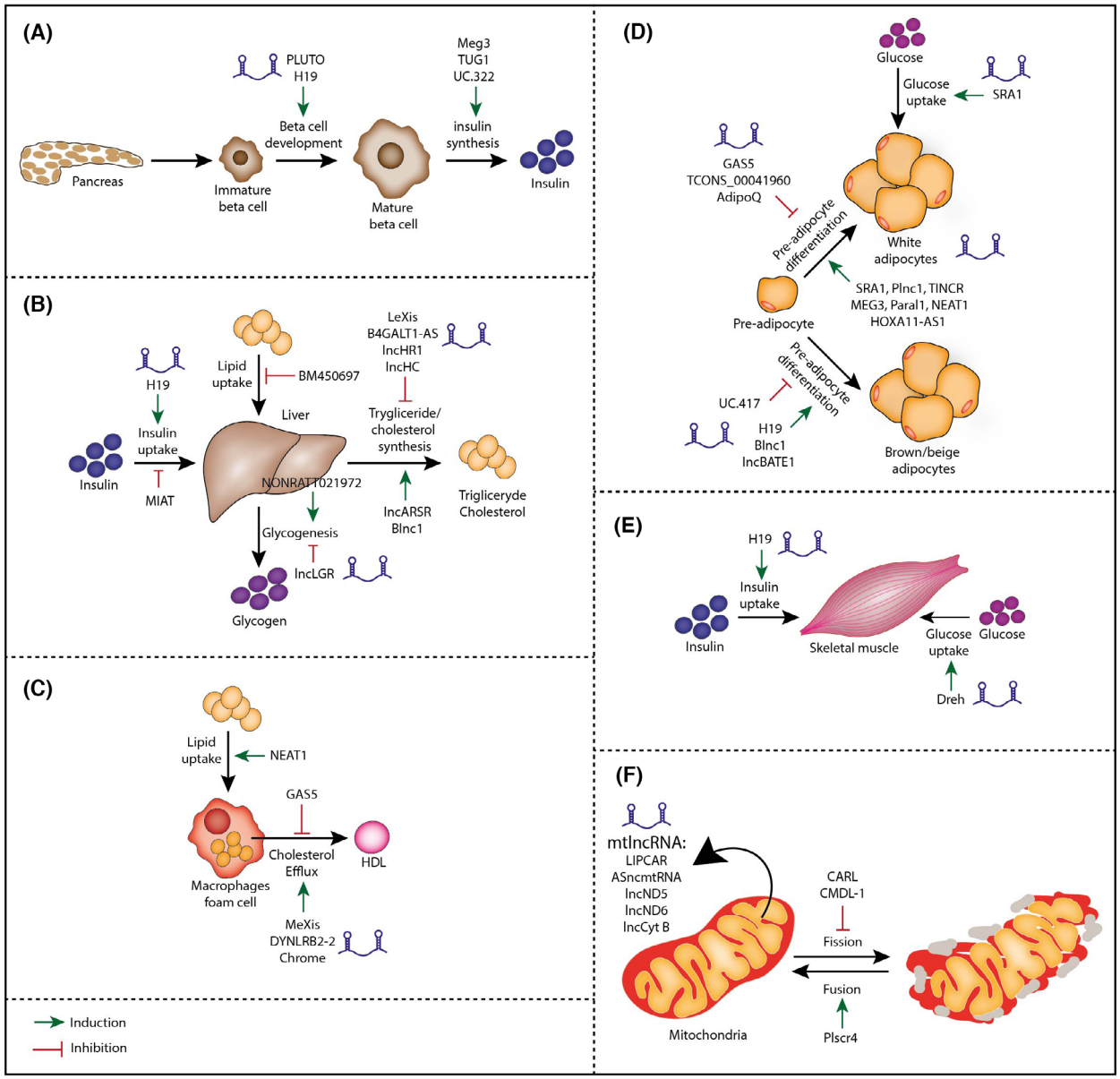

Fig. 3. LncRNA-mediated tissue-specific metabolic processes. An overview of lncRNAs affecting metabolic or mitochondrial function in various tissues, as described in the text. lncRNAs inhibit or induce metabolic processes, including (A) β-cell development and insulin synthesis in the pancreas, (B) insulin uptake, glycogenesis, and triglyceride metabolism in the liver, (C) lipid uptake and cholesterol efflux in macrophages, (D) preadipocyte differentiation in adipose tissue, (E) insulin and glucose uptake in skeletal muscle, (F) and mitochondrial function.

blood mononuclear cells (PBMCs) from patients with type 2 diabetes [75], indicative of its role in glucose metabolism. Meg3 suppressed the expression of inhibitory transcription factors *Rad21*, *Smc3*, and *Sin3a*, *via* enhancer of zeste homolog 2 (*EZH2*)-driven H3K27 methylation in pancreatic β-cells, leading to increased expression of a key factor in insulin biosynthesis, *MafA*, *in vivo* and *in vitro* (Fig. 3) [76]. The absence of *Meg3* contributes to the development of diabetic microvascular complications [77]. *Meg3* expression is downregulated in the retinas of STZ-induced diabetic mice and endothelial cells upon high glucose exposure. *Meg3* knockdown induces retinal capillary degeneration, microvascular leakage, and inflammation *in vivo*. *In vitro*, *Meg3* knockdown impairs retinal endothelial cell proliferation, migration, and tube formation. This endothelial effect of *Meg3* is mediated by the activation of phosphatidylinositol-3-kinase (*PI3K*)/*Akt* signaling [77]. In contrast, inhibition of *Meg3* augments endothelial cell sprouting and improves perfusion in the hind limb ischemia model [78]. In addition, *Meg3* is upregulated in hepatocytes of mice fed with a high-fat diet [79]. The knockdown of *Meg3* decreases the expression of *FoxO1* and its downstream targets phosphoenolpyruvate carboxykinase and the glucose-6-phosphatase and improves glucose tolerance and insulin sensitivity in liver tissue [80]. The discrepancy in the role of *Meg3* in regulating glucose metabolism in different tissues is unclear.

Another lncRNA regulating glucose metabolism is *TUG1*, a highly enriched lncRNA in the pancreas, which has been shown to maintain pancreatic β-cell function. Knockdown of *TUG1* induces apoptosis of and decreases insulin secretion in β-cells *in vitro* and *in vivo* [81]. lncRNA ultraconserved 322 (*uc.322*) is also highly expressed in pancreatic tissue, where it induces the expression of the insulin transcription factors *PDX1*, and thereby promoting insulin secretion [82]. LncRNA myocardial infarction associated transcript (*MIAT*) or *Gomafu*, a nuclear-enriched lncRNA, promotes hepatic insulin resistance by acting as a *miR-139* sponge and de-represses the expression of its target gene *FoxO1*, which plays an important role in gluconeogenesis and glucose production in hepatocytes [83]. Another lncRNA playing a role in hepatic glucose metabolism is lncRNA hepatic glucokinase (*GCK*) repressor (*lncLGR*). *LncLGR* is induced by fasting in mice. Overexpression of *lncLGR* to mimic fasting suppresses *GCK* expression and reduces hepatic glycogen content. *lncLGR* binds to nuclear ribonucleoprotein L, a transcriptional repressor of *GCK*, thereby establishing a lncRNA-mediated mechanism that regulates hepatic *GCK* expression and glycogen deposition [84]. lncRNA *NONRATT021972* shows increased levels in the liver of diabetic rats, which is associated with an increase in blood glucose levels. The knockdown of *NONRATT021972* enhances *Akt* phosphorylation, hepatic glucokinase expression, and hepatic glycogen synthesis (Fig. 3) [85].

Several lncRNAs exert their functions in adipocyte glucose metabolism. LncRNA steroid receptor RNA activator 1 (*SRA1*) was the first lncRNA identified to regulate adipogenesis [86]. *SRA1* binds to *PPARγ* in 3T3-L1 adipocytes and enhances *PPARγ* expression and transcriptional activity. SRA1 also increases CCAAT/enhancer-binding protein-α (*C/EBPα*) expression and other adipocyte genes and promotes glucose uptake and phosphorylation of *Akt* and *FOXO1* in response to insulin [86]. In contrast, another study shows that *SRA1* silencing improved insulin sensitivity and glucose tolerance *in vivo* (Fig. 3) [87]. lncRNA *slincRAD* also displays a pivotal function in the adipose tissue. *slincRAD* downregulation impairs the development of adipose tissue, leading to abnormal glucose and lipid metabolism and generating a thin phenotype in mice [88].

In addition to the pancreas, liver, and adipocytes, lncRNAs play a pivotal role in regulating glucose metabolism in other tissues. lncRNA *Dreh* regulates glucose metabolism in skeletal muscles. The absence of *Dreh* in myotubes reduces glucose concentrations in the culture medium and increases glucose transport, while in C2C12 skeletal muscle cells it increases glucose transporter 4 (*GLUT4*) protein levels [89]. Furthermore, lncRNA *ANRIL* or *CDKN2B-AS1* has been described as a genetic risk factor for coronary artery disease [90], and its expression level is associated with left ventricular (LV) dysfunction after myocardial infarction (MI) [91]. In a mechanistic study using HEK293T and HeLa cells, knockdown of *ANRIL* decreases the expression of *ADIPOR1*, *TMEM258*, and *VAMP3*, which are important genes in the regulation of glucose and fatty acid metabolism. *ANRIL* acts as a scaffold forming complexes with several molecular components acting as transcriptional activators or repressors. *ANRIL* recruits and interacts with PRC1 and PRC2 leading to the silencing of the *INK4b-INK4a* locus [92]. LncRNA metastasis associated with lung adenocarcinoma transcript 1 (*MALAT1*), which has been renamed to nuclear-enriched noncoding transcript 2 due to its enrichment in the nucleus, plays an important role in the progression of insulin resistance and diabetic microvascular complications [93]. *MALAT1* was upregulated in PBMCs from patients with diabetes [75]. *MALAT1* promotes proinflammatory phenotype

of endothelial cells treated with high glucose [94] and its expression is significantly upregulated in the retinas of STZ-induced diabetic rats. *MALAT1* activates *p38/MAPK* signaling pathway to dysregulate retinal endothelial cell function, which leads to pathological microvascular growth under diabetic conditions [93]. LncRNA growth arrest-specific 5 (*GAS5*), another nuclear-enriched lncRNA, is associated with the prevalence of diabetes. Decreased *GAS5* levels in patient serum were associated with the increased risk of diabetes [95]. *GAS5* is also involved in the regulation of wound healing in diabetic patients with foot ulcer (DFU). *GAS5* is downregulated in the skin tissues of DFU patients along with the expression of *HIF1A*. Mechanistically, *GAS5* induces *HIF1A* expression by interacting with *TAF15*. *GAS5* overexpression promotes cell proliferation, tubule formation, and wound healing in HUVECs exposed to hyperglycemia [96].

Long noncoding RNAs in lipid metabolism

Dysregulation of lipid metabolism is a well-known risk factor for cardiovascular diseases. In atherosclerosis, for instance, lipid disorders promote lipoprotein accumulation within the arterial wall [97]. Accumulation of triglycerides within hepatocytes leads to the development of nonalcoholic fatty liver disease (NAFLD), the most prevalent chronic liver disease in developed countries, which is closely associated with increased risk of type II diabetes, atherosclerosis, and other cardiovascular events [98,99]. LncRNAs regulate cholesterol and triglyceride metabolism, lipid transport, and bile acid excretion, and dysregulation of their expression profile has been associated with the development of cardiometabolic diseases.

Long noncoding RNAs in cholesterol and triglyceride metabolism

Cholesterol and triglyceride synthesis is an important part of lipid metabolism. lncRNAs participate in regulating transcription factor sterol regulatory element-binding proteins (*SREBP*), which controls the expression of enzymes required for cholesterol, triacylglycerol, and fatty acid biosynthesis. LncRNA activated in renal cell carcinoma with sunitinib resistance (*lncARSR*) induces the expression of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (*HMGCR*), the rate-limiting enzyme of cholesterol synthesis, and promotes hepatic cholesterol biosynthesis *in vivo*. Mechanistically, *lncARSR* activates the *PI3K/Akt* pathway, increasing the expression of mature SREBP2, a key transcription factor of HMGCR [100]. *lncARSR* contributes to the development of NAFLD and nonalcoholic steatohepatitis (NASH). The expression of *lncARSR* increased both in NAFLD patients and a NASH mouse model, and in hepatocytes exposed to fatty acids. *LncARSR* induced hepatic lipogenesis by promoting SREBP1c expression *via* activation of the *PI3K/Akt/mTOR* pathway [101].

Another lncRNA, brown fat lncRNA 1 (*Blnc1*), augments the induction of *SREBP1c* in primary hepatocytes and increases the expression of triacylglycerol biosynthesis genes, leading to the progression of hepatic steatosis and insulin resistance through LXR activation. Mechanistically, *Blnc1* interacts with *EDF1,* which acts in concert with LXR transcriptional complex to activate the lipogenic gene program [102]. LncRNA *MALAT1* also plays a role to induce lipid accumulation in the liver, which might in turn contribute to LV dysfunction in patients with MI as its expression is upregulated in the circulation of these patients presenting with co-morbidities, including diabetes and hypercholesterolemia [91]. *MALAT1* expression increases in hepatocytes exposed to palmitate and in the liver of ob/ob mice, promoting hepatic steatosis and insulin resistance. *MALAT1* silencing suppresses palmitate-induced lipid accumulation and the increase of nuclear *SREBP1c* protein in HepG2 cells. Mechanistically, *MALAT1* forms a complex with *SREBP1c*, inhibiting its ubiquitination, thereby increasing the stability of the nuclear *SREBP1c* protein [103]. LncRNA *H19* plays also a pivotal role in regulating lipid metabolism. *H19* expression is upregulated in hepatocytes exposed to fatty acids and in high-fat diet-induced fatty liver models. *H19* functions as a lipid sensor by interacting with the RNA-binding polypyrimidine tract-binding protein 1 (*PTBP1*) to modulate hepatic metabolic homeostasis. *H19* RNA interacts with PTBP1 to facilitate its association with *SREBP1c* mRNA and protein, leading to increased stability and nuclear transcriptional activity. Silencing of H19 prevents high-fat and high-sucrose diet-induced steatosis [104]. Further, H19 was upregulated in oleic acid-induced steatosis and high-fat diet-induced NAFLD. *H19* activation induces lipid accumulation by upregulating both the MLXIPL transcriptional network and the *mTORC1* signaling axis, including *SREBP* (Fig. 3) [105]. In contrast, *H19* suppresses the levels of cardiac inflammatory cytokines in high-fat diet-fed mice by inhibiting *miR-29a*, leading to de-repression of its target gene *IGF-1* [106], and alleviates cardiac defects by inhibiting mitochondrial apoptosis [107]. *H19* also inhibits excessive mitophagy by limiting *Pink1* mRNA

translation, thus alleviating cardiac damage that occurs during obesity [108]. The effect of *H19* in promoting steatosis in the liver while protecting against high-fat diet-induced inflammation in the heart seems conflicting and may be due to the tissue type-selective function of this lncRNA.

Other lncRNAs, such as *lncHR1*, inhibit *SREBP1c* in the liver. *lncHR1* overexpression inhibits the activation of *SREBP1c* and fatty acid synthase and decreases triglyceride synthesis and lipid droplet formation in hepatocytes exposed to oleic acid and high-fat diet-fed mice [109]. LncRNA liver-expressed liver X receptor (LXR)-induced sequence (*LeXis*) is a chromatin-associated lncRNA whose expression is upregulated in the liver of mice fed with a Western diet. *LeXis* interacts with ribonucleoprotein RALY and inhibits RALY-mediated recruitment of RNA polymerase II to the promoters of cholesterol biosynthesis genes, including *SREBF2* and *HMGCR*, promoting a reduction in serum and hepatic cholesterol levels [110]. The potential of LeXis as a gene therapy has been tested on an atherosclerotic model. En face lesion analysis on low-density lipoprotein receptors (*LDLR*) knockout animals treated with AAV8 vector expressing *LeXis* showed significantly reduced atherosclerotic burden as compared with control mice [111]. LncRNA *B4GALT1-AS1* and its mouse homolog *lncSHGL* have been shown to be downregulated in obese mice and patients with NAFLD. Overexpression of *lncSHGL* in the hepatocytes reduces triglyceride content and alleviates hyperglycemia, insulin resistance, and steatosis in obese diabetic mice *via* activation of the *PI3K/Akt* pathway and inhibition of *mTOR/SREBP1c* [112]. *Lnc-HC* also targets *SREBP1c* and is implicated in NAFLD [99]. *Lnc-HC* negatively regulates hepatocyte cholesterol metabolism by reducing *Cyp7a1* and ATP-binding cassette transporter (*Abca1*) expression. Furthermore, *lnc-HC* downregulates *PPARγ* mRNA and protein levels and suppresses hepatocyte lipid droplet formation. Silencing of *lnc-HC* induces *PPARγ* expression and increases triglyceride levels, an effect that seems to be mediated by *miR-130b-3p* expression (Fig. 3) [113].

Long noncoding RNAs in lipid efflux

Lipid efflux and reverse cholesterol transport play an important role in lipid homeostasis to remove and transfer excess lipids from the intracellular compartment. One of the key proteins in cholesterol efflux is the membrane-bound transporter *Abca1*, which transports excess cholesterol from cells to the corresponding apolipoprotein. LncRNA *MeXis* is one of the lncRNAs that induces Abca1 gene expression. Silencing of *MeXis in vivo* leads to a reduction of Abca1 expression. Further, loss of function of *MeXis* in mouse bone marrow alters chromosome architecture at the Abca1 locus, impairs macrophage cholesterol efflux, and accelerates the development of atherosclerosis. Mechanistically, *MeXis* interacts with and guides promoter binding of the transcriptional co-activator *DDX17*, leading to induction of the LXR-dependent transcription of *Abca1* in macrophages [114]. LncRNA *DYNLRB2-2* was induced by oxidized LDL, which leads to *Abca1*-mediated cholesterol efflux and inhibits inflammation *via* G protein-coupled receptor 119 in THP-1 macrophage-derived foam cells [115]. Another lncRNA promoting *Abca* activity is lncRNA cholesterol homeostasis regulator of miRNA expression (*Chrome*), a primate-specific lncRNA that is elevated in the plasma and atherosclerotic plaques from CAD patients. Chrome promotes cholesterol efflux and high-density lipoprotein (HDL) biogenesis by inhibiting a set of functionally related miRNAs that repress genes in those pathways. Conversely, *Chrome* knockdown in human hepatocytes and macrophages increases the levels of *miR-27b, miR-33a, miR-33b, and miR-128*, thereby reducing the expression of their target gene and associated biological functions [116]. Another lncRNA, *AC096664*.3, mediates LDL-induced cholesterol accumulation *via* the *PPARγ-Abcg1* pathway. Oxidized LDL decreases *AC096664.3* levels in vascular smooth muscle cells and THP-1 macrophages, leading to reduced Abcg1 expression. Downregulation of *AC096664.3* decreases *Abcg1* level through inhibition of *PPARγ* expression [117]. Other lncRNAs display a negative effect on Abca1. LncRNA *GAS5*, for instance, inhibits the expression of *Abca1* by binding to *EZH2*, which promotes triple methylation of lysine 27 in the *Abca1* promoter region. *GAS5* is highly expressed in THP-1 macrophage-derived foam cells in coronary heart disease and its silencing increases cholesterol efflux and inhibits intracellular lipid accumulation in THP-1 macrophage-derived foam cells and in homozygous apolipoprotein E knockout mice (Fig. 3) [118].

Lipoprotein also plays an important role in regulating lipid metabolism by binding and transporting lipids to various tissues. Two antisense lncRNAs, *APOA1-AS and APOA4-AS*, regulate the formation and function of lipoproteins. *APOA1-AS* is a negative transcriptional regulator of *APOA1*, the major component of HDL. Downregulation of *APOA1-AS* promotes *ApoA1* gene expression through the recruitment of suppressor of zeste 12 homolog and the histone-modifying enzyme lysine-specific demethylase 1 to the

ApoA1 promoter [119]. *APOA4-AS* is a regulator of *APOA4*, a major component of HDL and triglyceride-rich lipoprotein particles, and controls liver triglyceride secretion. The expression of *APOA4-AS* and *APOA4* is abnormally upregulated in ob/ob mice and patients with hepatic steatohepatitis. *APOA4-AS* knockdown reduced *APOA4* expression, leading to a decrease in serum triglyceride content and total cholesterol in ob/ob mice. Mechanistically, *APOA4-AS* directly interacts with an RNA-binding protein human antigen R (*HuR*), and stabilizes *APOA4* mRNA [120].

Long noncoding RNAs in lipid uptake and excretion

LDLR in the liver plays a vital role in ingesting and removing LDL particles from circulation. When accumulated in the blood, LDL undergoes oxidative modifications allowing its cellular uptake by CD36 and scavenger receptors. lncRNA *BM450697* acts as a regulator of LDLR in hepatocytes. *BM450697* decreases LDLR mRNA levels by inhibiting the interactions of RNA polymerase II and *SREBP1a* at the LDLR gene promoter [121]. Lncrna *NEAT1* expression significantly increases in THP-1 macrophages treated with oxidized LDL. *NEAT1* downregulation in THP-1 cells inhibited CD36 mRNA expression and decreased Oil-Red staining levels, total cholesterol, and triglyceride content through the modulation of *miR-342-3p* (Fig. 3) [122].

Excess lipid excretion is regulated by bile acid metabolism. Nuclear farnesoid X receptors (*FXR*) control genes that are involved in bile acid synthesis, including Cyp8b1 and Cyp7a1 [123]. LncRNA liver-specific triglyceride regulator (*lncLSTR*), displays an essential function in lipid homeostasis through regulating the bile acid pathway. Mice with a liver-specific depletion of *lncLSTR* display a reduction in plasma triglyceride levels. *LncLSTR* forms a complex with TDP-43 to enhance the expression of Cyp8b1, an enzyme in the bile acid synthesis pathway, leading to a reduction in *apoC2* expression through the FXR-mediated pathway. *lncLSTR* depletion enhances *apoC2*, leading to activation of lipoprotein lipase and increased plasma triglyceride clearance. Thus, *lncLSTR* maintains systemic lipid homeostasis through the regulation of the *TDP-43*/*FXR*/*apoC2*-dependent pathway [124].

Long noncoding RNAs in adipogenesis

Adipogenesis is the process by which preadipocytes develop into mature white, brown, or beige adipocytes, contributing to both lipid storage and clearance. Disturbance of this biological process underlies the development of cardiovascular risk factors, such as obesity, which promotes insulin resistance and atherosclerosis [125]. Transcriptomic analysis of primary preadipocytes, brown and white adipocytes revealed differential expression of hundreds of lncRNAs, indicating their vital role in adipogenesis. These lncRNAs may interact with the promoters of key adipogenic transcription factors, such as *PPARγ* and *C/EBPα* [126]. In white adipocyte differentiation, lncRNA *SRA1* promotes preadipocyte differentiation to white adipocyte *via* its binding to *PPARγ* and co-activates *PPARγ*-dependent gene expression [86]. Another lncRNA promoting adipocyte differentiation is *Plnc1*. *Plnc1* is enriched in adipose tissue and its expression increases in the adipose tissue of obese mice. *Plnc1* knockdown reduces *PPARγ*, *C/EBPα*, and adipocyte protein 2 expressions, preventing differentiation of ST2 adipogenic cell line and bone marrow stromal cells into mature adipocytes. *Plnc1* inhibits methylation of the CpG region in the promoter region of *PPARγ2* and thus enhances its transcriptional activity and thereby increases PPARγ2 transcription [127]. lncRNA terminal differentiation-induced ncRNA (*TINCR*) regulates differentiation of human adipose tissue-derived mesenchymal stem cells by acting as a ceRNA for *miR-31* to target *C/EBPα* [128]. Similarly, *Meg3* promotes 3T3-L1 preadipocyte differentiation by acting as a *miR-217* sponge [129]. Antisense lncRNA *PU.1AS* also regulates adipogenesis by forming an RNA duplex with *PU.1* mRNA and inhibiting *PU.1* mRNA translation [130]. In addition, *Paral1* and *NEAT1* also positively regulate adipogenesis of white adipocytes. *Paral1*, in particular, acts through interaction with the paraspeckle component and hnRNP-like RNA-binding protein 14 (*RBM14*/*CoAA*) to guide *PPARγ* to promote adipogenic gene expression [131,132]. Furthermore, LncRNA *HOXA11-AS1* was upregulated in patients with obesity. Silencing of *HOXA11-AS1* suppresses adipocyte differentiation, leading to reduced transcription of adipogenic genes, including *C/EBPα, DGAT2, CIDEC*, and *perilipin* [133]. Another lncRNA, *AC092159.2*, is positively associated with body mass index (BMI) and obesity. Overexpression of this lncRNA promotes adipocyte differentiation by inducing transcription of transmembrane protein 18 (*TMEM18*) (Fig. 3) [134].

Conversely, *GAS5* displays an inhibitory effect on the adipogenesis of 3T3-L1 cells through its repressive effect on *miR-21a-5p*, leading to improved expression of *PTEN*. LncRNA *TCONS_00041960* has also been shown to suppress adipogenesis of rat bone marrow

mesenchymal stem cells by acting as a ceRNA, which forms a complex with *miR-125a-3p* and *miR-205-5p* to regulate anti-adipogenic gene glucocorticoid-induced leucine zipper (*GILZ*) and *Runx2*, respectively, leading to *PPARγ* inhibition and repression of adipocyte differentiation [135]. lncRNA *AdipoQ-AS*, inhibits adipogenesis by translocating from the nucleus to the cytoplasm to form complex with *adiponectin* (*AdipoQ*) mRNA to suppress the mRNA translation in mouse primary preadipocytes and adipose tissues of mice fed with high-fat diet [136]. Obese mice have a low level of *lnc-U90926* in subcutaneous and visceral adipose tissue. Upregulation of *lnc-U90926* inhibits 3T3-L1 adipocyte differentiation by suppressing mRNA levels of *PPARγ2*, fatty acid-binding protein 4 (*FABP4*), and *adipoQ* (Fig. 3) [137].

Brown and beige adipose tissues are responsible for thermogenesis and are regulated by several key transcription factors, including *PPARγ*, *PPARγ* coactivator 1α (*PGC1α*), *C/EBPβ*, PR domain-containing 16 (*PRDM16*), and early B-cell factor 2 (*EBF2*) [138,139]. *De novo* reconstruction of human adipose transcriptome shows approximately 900 lncRNAs that are specifically detected in brown adipose tissue (BAT), 169 of which are conserved human lncRNAs that regulate their adjacent mRNAs [140]. *H19*, for instance, shows inverse correlations with BMI in humans. *H19* expression in BAT increases upon cold activation and decreases in obesity. *H19* promotes oxidative metabolism and mitochondrial respiration in brown but not white adipocytes. *In vivo*, *H19* protects against diet-induced obesity and improves insulin sensitivity and mitochondrial biogenesis, whereas loss of *H19* promotes weight gain. Mechanistically, *H19* recruits paternally expressed gene (*PEG*)-inactivating *H19-MBD1* complexes and acts as BAT-selective *PEG* gatekeeper [141]. *Blnc1* and several key transcriptional regulators of BAT, including *EBF2* and *PPARγ*, are highly expressed during brown adipocyte differentiation [142]. *Blnc1* forms a ribonucleoprotein complex with nuclear ribonucleoprotein U (*hnRNPU*) and *EBF2* or zinc finger and BTB domain-containing 7b to promote thermogenic gene program, leading to brown and beige adipocyte differentiation [142,143]. *lncBATE1* is enriched in BAT and the loss of *lncBATE1* reduces BAT-selective gene expression in primary brown adipocytes through interaction with *hnRNPU* [144]. *lncBATE10*, another BAT-enriched lncRNA, promotes full brown fat differentiation and white fat browning program by decoying *Celf1* from *PGC1α*, protecting *PGC-1a* mRNA from repression by *Celf1* [145]. Another lncRNA acting as a negative regulator of brown and beige adipocyte differentiation is lncRNA *uc.417*, which impairs adipogenesis and thermogenic gene program in brown adipocytes by inhibiting phosphorylation of *p38* mitogen-activated protein kinase (*MAPK*), which is essential for BAT activation (Fig. 3) [146].

LncRNAs affecting mitochondrial function and structure

Mitochondria regulate various cellular processes, including oxidative phosphorylation, biosynthetic pathways, redox homeostasis, ion exchange, and programmed cell death. Mitochondrial dysfunction underlies the impairment of cardiac and vascular cells, leading to the development of various cardiovascular pathologies [147–149]. Deranged glucose and lipid metabolism can disturb mitochondrial structure and function. Disturbed mitochondrial homeostasis induced by aging or impaired glucose and lipid metabolism is considered a major driver of cardiac cell senescence. Aged mitochondria produce less ATP and form excessive reactive oxygen species (ROS) with detrimental effects on cells [150,151]. Mitochondrial fission and fusion are important processes in mitochondrial homeostasis and a disrupted balance between those two is observed in many age-related diseases [152]. Genes involved in fission are dynamin-related protein 1 (*Drp1*) and mitochondrial fission 1 protein (*Fis1*) while the mitofusin genes (*Mfn1* and *Mfn2*) and *OPA1* are responsible for outer and inner mitochondrial membrane fusion, respectively. In cardiomyocytes, lncRNA *Plscr4* regulates this process *via* downregulating the expression of *miR-214*. This in turn leads to a moderate increase in *Mfn2* expression and a protection against angiotensin II-induced mitochondrial dysfunction. Disrupting this balance by inhibition of *Mfn2* can lead to cardiac hypertrophy *in vitro* and *in vivo* [153]. Another lncRNA that changes mitochondrial morphology is Cardiac apoptosis-related lncRNA (*CARL*), which can suppress mitochondrial fission and apoptosis in cardiomyocytes *via* the miR-539/prohibitin 2 (phb2) axis. *CARL* can directly bind to and inhibit *miR-539* from suppressing its downstream target *Phb2*. The prohibitin genes are localized in the inner mitochondrial membrane (IMM) and play a role in maintaining the shape of mitochondria [154].

Cardiomyocyte mitochondrial dynamic related lncRNA 1 (*CMDL*-1) is another lncRNA involved in maintaining mitochondrial biology. It was downregulated in cardiomyocytes after treatment with doxorubicin, a chemotherapeutic agent that often leads to cardiac toxicity. This lncRNA regulates post-transcriptional

modification by enhancing phosphorylation of fission protein *Drp1* at Serine-637, leading to the deactivation of this protein. Overexpressing this lncRNA in cardiomyocytes prevents mitochondrial fission and apoptosis induced by doxorubicin treatment (Fig. 3) [155]. The lncRNA cytoplasmic endogenous regulator of oxidative phosphorylation 1 (*Cerox1*) is a post-transcriptional regulator of mitochondrial complex I catalytic activity [156]. This lncRNA binds to *miR-488-3p*, which regulates multiple electron transport chain proteins, and blocks the effect of this miRNA. Therefore, increased *Cerox1* expression leads to increased levels of complex 1 proteins and enzymatic activity, and decreases ROS production [156]. Another lncRNA enriched in cardiomyocytes and regulating mitochondrial function is lncRNA cardiomyocyte enriched transcript (*Caren*) [157]. This lncRNA was upregulated in the hearts of aged mice of 24-months old. *In vivo* studies revealed lower levels of *Caren* in mice that underwent TAC surgery compared with sham control, while overexpression resulted in resistance to developing heart failure (HF). Proteomics of *Caren* overexpressing and knockdown mice compared with corresponding littermates revealed metabolic pathways as the most enriched. The number of mitochondria in the heart and mitochondrial DNA (mtDNA) content was significantly higher in *Caren* overexpressing mice, while *Caren* deficient mice had reduced respiratory chain capacity. Caren decreases the translation of an mRNA transcribed from a distant gene encoding for *Hint1* protein, which activates the ataxia telangiectasia mutated (*ATM*)-DNA damage response (DDR) pathway and reduces mitochondrial respiratory capacity in cardiomyocytes. Hence, *Caren* maintains cardiac function by inactivating the DDR and activating mitochondrial biogenesis [157]. With mitochondrial dysfunction as one of the hallmarks of aging, these lncRNAs may serve as a potential therapeutic target in age-related pathologies such as CVD.

Mitochondrial DNA-transcribed lncRNAs

All lncRNAs described so far are transcribed from the nuclear DNA. However, lncRNAs transcribed from mitochondrial DNA (mtlncRNAs) also play a role in CVD and aging. Most of the mtlncRNAs are antisense transcripts of mitochondrial transcribed genes since the number of noncoding regions on the mtDNA is relatively small [158]. LncRNA predicting cardiac remodeling (*LIPCAR*), for instance, plays a role in several cardiac pathologies. It was first described as a predictor for survival in HF patients [159]. In patients with type 2 diabetes it is inversely associated with LV diastolic dysfunction [160]. A functional study in atrial fibrillation (AF) showed that LIPCAR regulates AF by modulating the *TGFβ* pathway and upregulating *LIPCAR* in arterial fibroblast increased cell viability and proliferation [161]. *ASncmtRNA-2* is another mtlncRNA that plays a role in CVD [162]. ASncmtRNA-2 was upregulated in the aortas of old mice and in human umbilical vein endothelial cells undergoing replicative senescence. Interestingly, the expression of *miR-4485* and *miR-1973*, which show perfect homology to the double-strand region of ASncmtRNA-2 and partly originate from a mitochondrial transcript, was also induced in replicative senescence. Overexpression of *ASncmtRNA-2* in endothelial cells resulted in the accumulation of cells in G2/M phase. Therefore, it is plausible that this lncRNA plays a role in cardiovascular senescence by participating in cell cycle arrest through the production of *miR-4485* and *miR-1973*. Deep sequencing analysis also revealed the presence of 3 other mtlncRNAs in human tissues, namely *lncND5*, *lncND6,* and *lncCyt B* [158]. The functional role of these mtlncRNAs is not known yet. Since these are antisense transcripts of mitochondrial genes, it is suggested that they play a role in the regulation of expression of mitochondrial transcribed genes or in nuclear-mitochondrial communication (Fig. 3).

Conclusions

LncRNAs play a key role in regulating a wide range of metabolic processes. These metabolic lncRNAs (metaboLncs) can regulate glucose metabolism by modulating β-cell development and thereby insulin production and secretion, and glucose uptake. They also modulate cholesterol and triglyceride synthesis, lipid uptake, efflux and excretion, adipose tissue development, bile acid synthesis, and mitochondrial function. metaboLncs display their metabolic function not only in major metabolic tissues, such as pancreas, liver, skeletal muscle, and adipocytes, but also in the main cardiovascular cell types, including cardiomyocytes, endothelial cells, and vascular smooth muscle cells. metaboLnc dysregulation contributes to various metabolic disorders such as insulin resistance, NASH, NAFLD, obesity, and type 2 diabetes, leading to complications including chronic wounds, retinopathy, atherosclerosis, myocardial infarction, heart failure, and other CVD. One lncRNA can regulate different metabolic processes or mitochondrial functions in different tissues and these regulatory functions can be protective or detrimental in different cell types. It is plausible that opposite functional effects depend on the disease model used, but they could also be due to

the tissue-specific functions of a given lncRNA. This is of importance when lncRNA therapeutics are considered to specifically target a lncRNA only in the particular tissue of interest. Most lncRNAs are transcribed in the nucleus and some are transported into mitochondria to regulate various mitochondrial functions. Interestingly, some lncRNAs are encoded by mtDNA, the so-called mtlncRNAs, showing how diverse these noncoding transcripts are and how they may regulate metabolic processes to maintain homeostasis in the cardiovascular system. Lastly, as many metaboLncs have proven functional involvement in metabolic disorders, their potential as therapeutic targets or biomarkers is likely. Small molecules targeting lncRNAs and RNA interference using antisense oligonucleotides or small-interfering RNAs are promising therapeutic strategies for the treatment of metabolic disorders and should therefore be further investigated in the near future.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Localization, function, targets and related pathologies of metaboLncs.