International Journal of Endocrinology

Огляд
Review

UDC 616.36-003.8:613.25]-092-008.6-008.9-053.2:577.213/.216:57.088.7(048.8) DOI: https://doi.org/10.22141/2224-0721.22.2.2026.1699

A.E. Abaturov, A.O. Nikulina
Dnipro State Medical University, Dnipro, Ukraine

Epigenetic influence of long non-coding steatogenic RNAs on the development of metabolic dysfunction-associated steatotic liver disease

For citation: Mìžnarodnij endokrinologìčnij žurnal. 2026;22(2):222-230. doi: 10.22141/2224-0721.22.2.2026.1699

Abstract. ***Background.*** *Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease in humans, which is caused by changes in the expression level of long non-coding RNAs (lncRs). The aim of this literature review is to present a brief description of the role of steatogenic lncRs in the epigenetic influence on the development of MASLD, analyzing the data of modern scientific literature.* ***Materials and methods.*** *An analysis of 60 literature sources over the past five years was conducted from the databases MEDLINE; Embase; PreMedline In-Process & Other Non-Indexed Citations; The Cochrane Systematic Reviews Database, DARE, NHS EED and HTA databases; Web of Knowledge Science Citation Index; Web of Knowledge ISI Proceedings; CRD databases; BIOSIS, which were selected using the following keywords: long non-coding RNAs, epigenetic regulation, metabolically associated fatty liver disease, metabolic dysfunction-associated steatotic liver disease obesity. PROSPERO CRD420250652980.* ***Results.*** *Increased expression of steatogenic lncRs, such as CCAT1, Gm10804, Gm15622, H19, HOTAIR, lncARSR, NEAT1, PVT1, SRA, Uc.372, is a characteristic feature of the development and progression of hepatic steatosis in MASLD. The development of hepatic steatosis in MASLD is supported by a decrease in the expression level of anti-steatotic lncRs, including AC012668, FLRL2, Gm16551, lncHR1, B4GALT1-AS1/ lncSHGL, MEG3, lncR MRAK052686.* ***Conclusions.*** *Long noncoding RNAs have an unconditional pathogenetic influence on the main mechanisms of the development of hepatic steatosis in MASLD, promoting lipid uptake in hepatocytes, enhancing de novo lipogenesis, inhibiting β-oxidation of fatty acids and lipid export from hepatocytes.*
Keywords: *epigenetic regulation; long noncoding steatogenic RNAs; metabolic dysfunction-associated steatotic liver disease; obesity; literature review*

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is one of the most common chronic liver diseases in the pediatric population, particularly against the background of the global epidemic of childhood obesity. Over the past three decades, the prevalence of obesity among children and adolescents in developed countries has increased 2–3 times, affecting more than 340 million individuals aged 5–19 years [1]. The obesity pandemic is closely linked to the development of metabolic disorders such as insulin resistance, type 2 diabetes mellitus (T2DM), and dyslipidemia, making this issue highly relevant for the entire medical community [2–4].

Long non-coding RNAs (lncRNAs) are important epigenetic regulators that influence transcription, chromatin remodeling, and post-transcriptional processes in hepatocytes, hepatic stellate cells, and macrophages. By modulating key metabolic pathways, lncRNAs act as "sponges" for miRNAs, affect mTOR signaling, ubiquitination, *de novo* lipogenesis, β-oxidation of fatty acids, oxidative stress, inflammation, apoptosis, fibrogenesis, and steatogenesis, and interact with proteins (e.g., CDK1/CYCLIN B1), thereby contributing to the development of steatohepatitis. Dysregulation of lncRNAs observed in patients with MASLD and in animal models allows them to be used as potential biomarkers (in serum or exosomes) and therapeutic targets for future precision therapy [5–7].

The purpose of this literature review is to present a brief description of the role of long non-coding steatogenic RNAs in the epigenetic influence on the development of metabolic dysfunction-associated steatotic liver disease, based on an analysis of data from modern scientific literature.

Для кореспонденції: Нікуліна Анна Олексіївна, доктор медичних наук, доцент, кафедра педіатрії 1 та медичної генетики, Дніпровський державний медичний університет, вул. Володимира Вернадського, 9, м. Дніпро, 49044, Україна; e-mail: anna.nikulina.201381@gmail.com; тел.: +380 (99) 978-16-59
For correspondence: Anna O. Nikulina, MD, DSc, PhD, Associate Professor, Department of Pediatrics 1 and Medical Genetics, Dnipro State Medical University, Volodymyr Vernadsky st., 9, Dnipro, 49044, Ukraine; e-mail: anna.nikulina.201381@gmail.com; phone: +380 (99) 978-16-59
Full list of authors information is available at the end of the article.

Materials and methods

An analysis of 60 literature sources from the past five years was conducted using the databases MEDLINE; Embase; PreMedline In-Process & Other Non-Indexed Citations; The Cochrane Systematic Reviews Database, DARE, NHS EED and HTA databases; Web of Knowledge Science Citation Index; Web of Knowledge ISI Proceedings; CRD databases; BIOSIS. Sources were selected using the following keywords: long non-coding RNAs, epigenetic regulation, metabolically associated fatty liver disease, metabolic dysfunction-associated steatotic liver disease, obesity.

Registration in PROSPERO (National Institute for Health and Care Research) ID652980.

Analysis of the literature

The development of liver steatosis in MASLD is accompanied by increased expression of prosteatotic lncRNAs (Table 1) and reduced activity of antisteatotic lncRNAs such as AC012668, FLRL2, Gm16551, lncHR1, B4GALT1-AS1/lncSHGL, MEG3, and lncR MRAK052686 [8].

Role of steatogenic lncRNAs in the development of liver steatosis in MASLD

Increased expression of steatogenic lncRNAs such as CCAT1, Gm10804, Gm15622, H19, HOTAIR, lncARSR, NEAT1, Uc.372, and others is a characteristic feature of the development and progression of liver steatosis in MASLD.

CCAT1. Colon cancer-associated transcript 1 (homo sapiens colon cancer associated transcript 1 — CCAT1; 2,795 nt URS000075ADFF_9606), a 2795 nt transcript whose expression is significantly elevated on a high-fat diet (HFD), sponges miR-613 (Fig. 1), the molecular target of which is the nuclear liver X receptor alpha (nuclear receptor subfamily 1 group H member 3/liver X receptor alpha — NR1H3/LXRα) [10, 11].

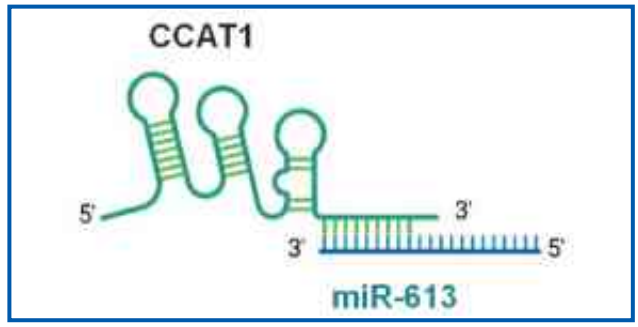

Figure 1. Interaction of lncR CCAT1 with miR-613 [30, modification]

Elevated NR1H3/LXRα expression associated with CCAT1 overexpression in MASLD is accompanied by activation of the carbohydrate-responsive element-binding protein (ChREBP), which senses intracellular carbohydrates and leads to enhanced expression of *de novo* lipogenesis enzyme genes, glycolytic genes, and the microsomal triglyceride transfer protein (MTTP) gene involved in the formation of very low-density lipoproteins (VLDL) from the liver. ChREBP also regulates the production of hepatokines such as fibroblast growth factor 21 (FGF-21) (Fig. 2) [12, 13]. It should be noted that CCAT1 interacts with a very broad spectrum of miRNAs and proteins [14, 15].

Table 1. Long non-coding steatogenic RNAs associated with the development of liver steatosis in MASLD [9, 10]

LncRNA	Effect	Molecular target	Signaling cascade
CCAT1	Enhances lipogenesis	miR-613	miR-613/NR1H3/ChREBP
Gm10804	Promotes lipid accumulation and impaired glucose metabolism		SREBP1c
Gm15622	Promotes lipid accumulation and impaired glucose metabolism	miR-742-3p	SREBP1c
H19	Promotes lipid accumulation and liver fibrosis development	miR-130a	MLXIPL and mTORC1, PPARγ, ↑ACTA2/α-SMA, COL1A1
HCG18	Promotes liver steatosis and insulin resistance	miR-197-3p	HCG18/miR-197-3p
HOTAIR	Promotes lipid accumulation and liver fibrosis development	miR-130b-3p	ROCK1, PRKA
LncARSR	Promotes lipid accumulation and cholesterol biosynthesis in the liver		YAP1 and IRS2/AKT PI3K/AKT/SREBP1c AKT/SREBP-2/HMGCR
LncPRYP4	Promotes steatohepatitis development		RPS4Y
MALAT1	Promotes liver steatosis development	miR-206	ARNT/PPARα/CD36 CXCL5, SREBP-1c
NEAT1	Stimulates lipogenesis, lipid accumulation, inflammatory response, and fibrosis development	miR-139-5p miR-212-5p miR-140 miR-146a-5p miR-506	PRKA/SREBP c-Jun/SREBP1c GRIA3 Hh signaling pathway mTORC1/S6K1
PVT1	Promotes lipid accumulation and insulin resistance development	miR-20a-5p	LncPVT1/miR-20a-5p
SRA	Reduces β-oxidation of fatty acids	FoxO1	PPARγ
Uc.372	Promotes lipid accumulation	miR-195/ miR-4668	miR-195/miR-4668

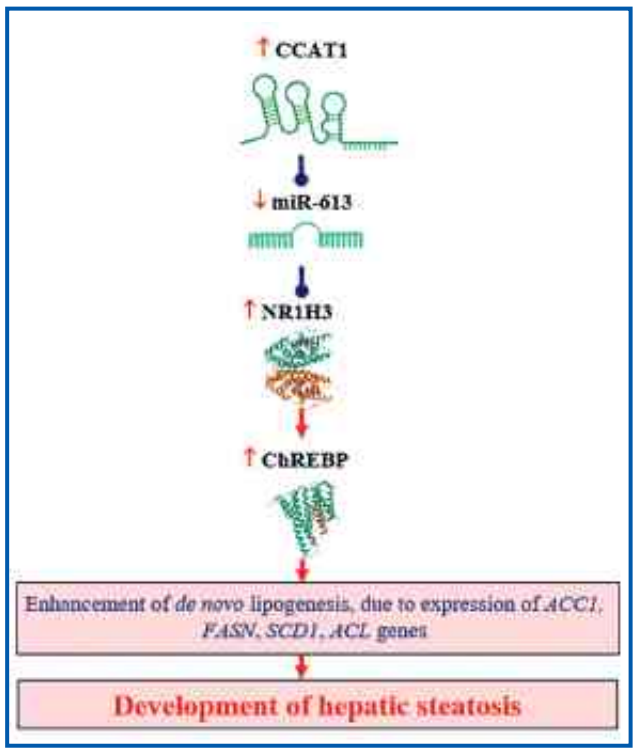

Figure 2. The role of lncR CCAT1 in the development of hepatic steatosis in MASLD

Notes (hereinafter): red arrows — activation; blue arrows — inhibition; molecular models adapted from the Protein data bank.

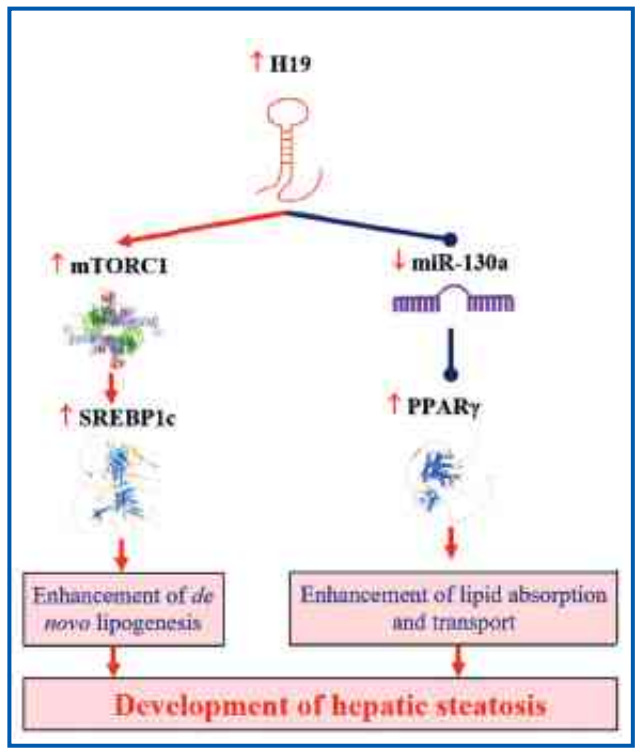

Figure 3. The role of lncR H19 in the development of hepatic steatosis in MASLD

Gm10804, Gm15622. Long non-coding RNAs Gm10804 (mus musculus predicted gene 10804, transcript variant 1; 2,247 nt URS000075D186_10090) and Gm15622 (mus musculus predicted gene 15622; 1,464 nt URS0000780065_10090), whose expression increases in HFD-induced MASLD, promote activation of: 1) sterol regulatory element-binding protein 1c (SREBP1c) in hepatocytes, thereby contributing to lipid accumulation through induction of the fatty acid synthase (FASN) gene; and 2) phosphoenolpyruvate carboxykinase 1 (PCK1/PEPCK1) and glucose-6-phosphatase (G6P), causing enhanced gluconeogenesis. The lncRNA Gm15622 exerts its effect by sponging miR-742-3p. It is believed that Gm10804 and Gm15622 may serve as novel diagnostic biomarkers for MASLD and as therapeutic targets for disease treatment [16, 17].

H19. The H19 gene is located on human chromosome 11p15.5 in a conserved imprinted gene cluster H19-IGF2, which contains the adjacent reciprocally imprinted insulin-like growth factor-2 (IGF-2) gene. The H19 gene consists of five exons separated by small introns and produces a spliced, capped, and polyadenylated RNA primarily located in the cytoplasm. The long non-coding RNA H19 (homo sapiens H19 imprinted maternally expressed transcript; 2,315 nt URS00026A1E43_9606) is maternally expressed, actively produced during embryonic development, and suppressed after birth. Thus, lncRNA H19 is almost undetectable in adult human liver [6, 18]. Increased H19 expression is driven by factors such as free fatty acids, glucagon, and reduced folate concentrations. Folate deficiency, including that resulting from hyperglycemia, leads to hypomethylation of the H19 gene promoter, promoting increased transcription. LncRNA H19 inactivates S-adenosylhomocysteine hydrolase (SAHH) and inhibits methylation of the hepatocyte nuclear factor 4 alpha (HNF4A) gene promoter, enhancing its expression and stimulating gluconeogenic genes PCK1/PEPCK1 and G6P [19, 20].

It has been demonstrated that lncRNA H19 promotes liver steatosis in MASLD by activating the lipogenic transcription factor MLXIP (MLX interacting protein-like), which causes phosphorylation of mTORC1 [21]. Increased H19 production contributes to MASLD progression, while H19 gene deletion reduces triglyceride content in hepatocytes. It is believed that lncRNA H19 sponges miR-130a, which inhibits mRNA of peroxisome proliferator-activated receptor gamma 2 (PPARG2) (Fig. 3). Reduced inhibitory effect of miR-130a promotes PPARγ activation, ensuring lipid accumulation in hepatocytes [22, 23].

Increased H19 production is also associated with activation of hepatic stellate cells (HSC) and liver fibrosis development [24, 25].

HOTAIR. Mice on an HFD exhibit significantly elevated levels of HOX transcript antisense RNA (homo sapiens HOX transcript antisense RNA — HOTAIR; 2,273 nt URS00026A23F2_9606), which can bind to various chromatin-modifying complexes. The HOTAIR gene is located on human chromosome 12q13.13 [26–28]. The primary mechanism of HOTAIR action is suppression of gene transcription through recruitment of the Polycomb repressive complex 2 (PRC2) and lysine-specific demethylase 1A (KDM1A) to chromatin at target gene promoters. Recruitment of PRC2 and KDM1A leads to methylation of histone H3K27 sites and demethylation of H3K4 sites, resulting in gene silencing. LncRNA HOTAIR also binds miR-130b-3p, which suppresses expression of Rho-associated coiled-coil containing pro-

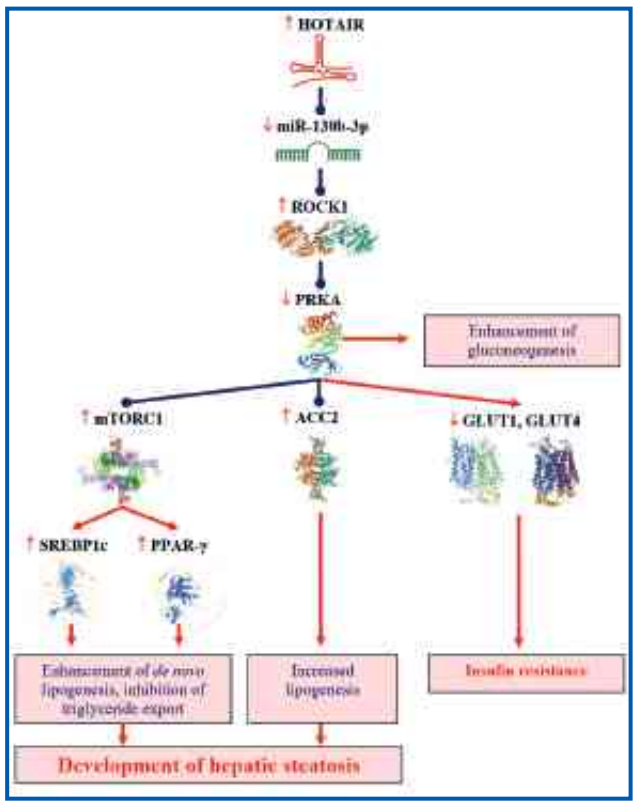

Figure 4. The role of lncR HOTAIR in the development of hepatic steatosis in MASLD

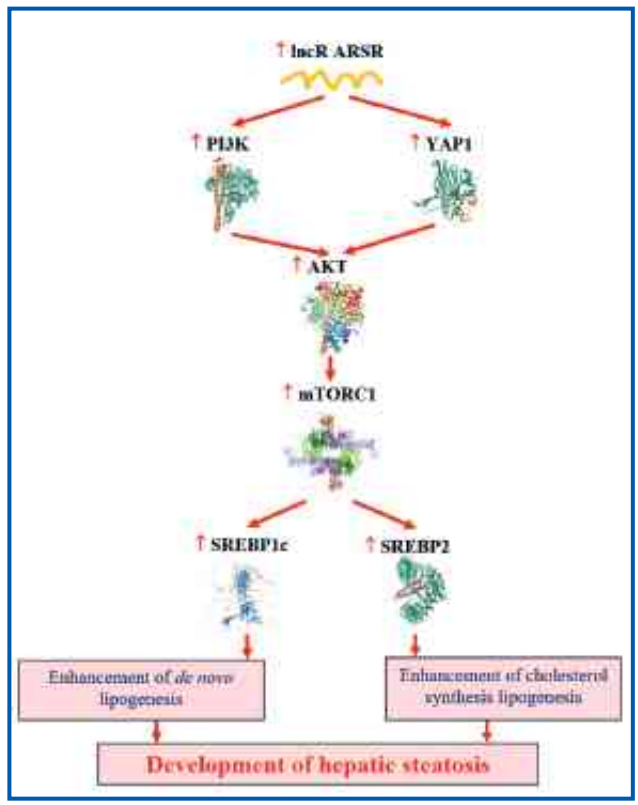

Figure 5. The role of lncARSR in the development of hepatic steatosis in MASLD

tein kinase 1 (ROCK1). The serine/threonine kinase ROCK1 reduces phosphorylation and activity of AMP-activated protein kinase (PRKA), thereby stimulating lipogenic signaling pathways and gluconeogenesis, contributing to the development and progression of insulin resistance (Fig. 4) [26–30].

LncARSR. The long non-coding RNA activated in renal cell carcinoma with sunitinib resistance (lncARSR; 1,187 nt URS00026A271B_9606) is more actively expressed in patients with MASLD, in experimental animals on HFD, and in cell cultures treated with fatty acids, including oleic, palmitic, and stearic acids. Overexpression of lncARSR in hepatocytes of experimental mice leads to elevated lipid levels in both serum and liver tissue. LncARSR has been shown to activate the PI3K/AKT-associated signaling pathway, which induces SREBP factors and yes-associated protein 1 (YAP1). Activation of SREBP1c stimulates lipogenesis enzymes, leading to triglyceride accumulation in the liver [31–33]. LncARSR overexpression also increases the rate of *de novo* cholesterol synthesis in the liver. At the molecular level, YAP1 in mouse liver activates the PI3K/AKT pathway, enhancing expression of insulin receptor substrate 2 (IRS2). It is suggested that lncARSR, by activating the PI3K/AKT pathway, increases expression of SREBP-2, the primary activator of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) transcription (Fig. 5) [34].

LncARSR, by reducing phosphorylation of the transcriptional coactivator and mechanosensor YAP1, affects the IRS2/AKT pathway and induces lipid accumulation in hepatocytes [32].

MALAT1. The metastasis-associated lung adenocarcinoma transcript 1 gene (homo sapiens metastasis associated lung adenocarcinoma transcript 1 — MALAT1; 8,779 nt URS0000A77400_9606) is located on chromosome 11q13.1. The 3'-end of MALAT1 forms a unique triple-helical structure that protects it from 3'-5' exonucleases. The long MALAT1 transcript is localized in the nucleus, while the small tRNA-like MALAT1 is in the cytoplasm [35–37].

MALAT1, whose expression significantly increases during liver steatosis development, directly interacts with SREBP1c, enhancing its activity and inhibiting ubiquitination [38]. Palmitate has been shown to induce MALAT1 generation and Srebp1c expression in HepG2 human hepatocellular carcinoma cells and primary mouse hepatocytes. MALAT1 overexpression in HepG2 cells increases lipid accumulation, whereas Malat1 knockout in experimental animals is associated with reduced triglyceride content in hepatocytes. Suppression of Srebp1c expression reduces elevated intracellular triglyceride and cholesterol levels previously induced by MALAT1. MALAT1 also induces obesity by activating PPARG mRNA expression. Malat1 knockout significantly suppresses adipogenesis [39].

MALAT1 can interact with miR-206, which blocks expression of Rock1 and aryl hydrocarbon receptor nuclear translocator (ARNT) mRNA [40]. miR-206, affecting the ROCK1/PRK signaling pathway, inhibits lipid synthesis in the liver in MASLD [41]. The transcription factor ARNT participates in lipid uptake and synthesis. Specifically, ARNT suppresses PPARA gene transcription, reducing PPARα receptor activity and inhibiting expression of fatty acid translocase (FAT/CD36), which is involved in lipid uptake by hepatocytes (Fig. 6) [42, 43].

Thus, excessive MALAT1 production contributes to MASLD development.

NEAT1. One of the most studied lncRNAs involved in MASLD pathogenesis is nuclear enriched abundant transcript 1 (homo sapiens nuclear enriched abundant transcript 1 — NEAT1; 3,756 nt URS000075DAEC_9606), a transcript of the multiple endocrine neoplasia (MEN) type 1 locus that stimulates lipid accumulation, *de novo* lipogenesis, inflammatory response, and fibrosis development [44]. In experimental animals with MASLD on HFD, NEAT1 expression is significantly elevated; it interacts with several target miRNAs: miR-22, miR-29b, miR-122, miR-129-5p, miR-139-5p, miR-140, miR-148a, miR-212-5p, miR-146a-5p, miR-342, miR-506, which regulate liver lipid metabolism.

Sequestration of miR-139-5p by NEAT1 promotes activation of c-Jun and SREBP1c and, consequently, lipogenic enzymes such as acetyl-CoA carboxylase 1 (ACC1) and FASN, leading to increased lipid content in hepatocytes. Overexpression of miR-139-5p reduces lipid accumulation through direct interaction with c-Jun. Isolated inhibition of c-Jun expression suppresses SREBP1c and reduces lipid accumulation activity [45]. NEAT1-dependent reduction in functional miR-140 may also enhance MASLD progression via SREBP1c activation [46]. In patients with MASLD, elevated NEAT1 and glutamate ionotropic receptor AMPA type subunit 3 (GRIA3) levels are observed alongside reduced miR-212-5p generation. NEAT1 directly suppresses miR-212-5p expression, leading to enhanced GRIA3 activity and accelerated lipid accumulation in hepatocytes [47]. miR-212-5p directly inhibits expression of FASN and stearoyl-CoA desaturase 1 (SCD1) genes as well as triglyceride accumulation, whereas miR-212-5p silencing produces opposite effects in primary mouse hepatocytes. Reduced inhibitory effect of miR-212-5p in MASLD leads to increased lipid accumulation [48]. NEAT1 also promotes lipid accumulation by sequestering miR-146a-5p, resulting in ROCK1 expres-

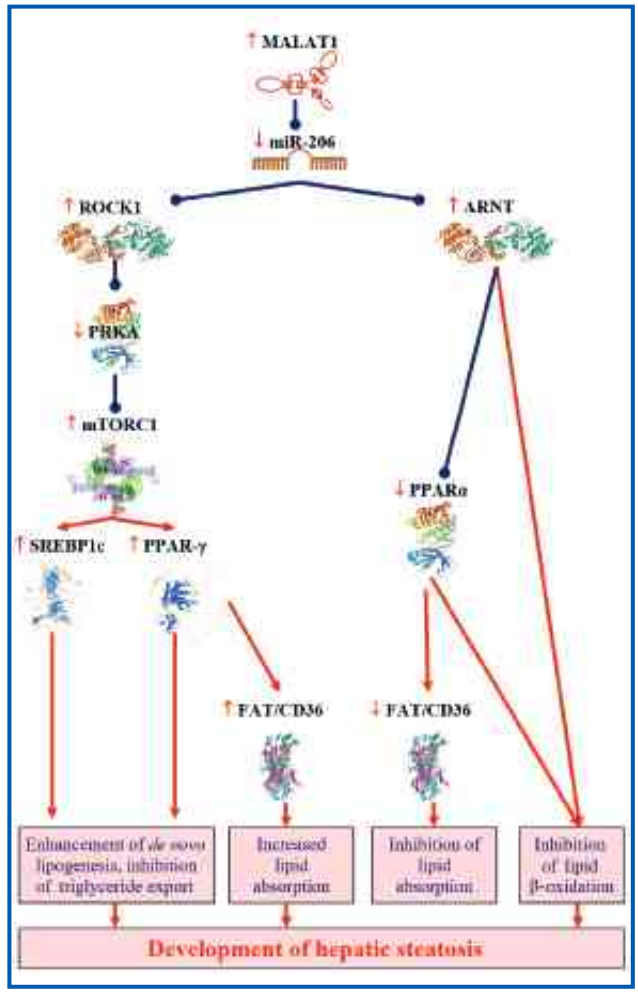

Figure 6. The role of lncR MALAT1 in the development of hepatic steatosis in MASLD

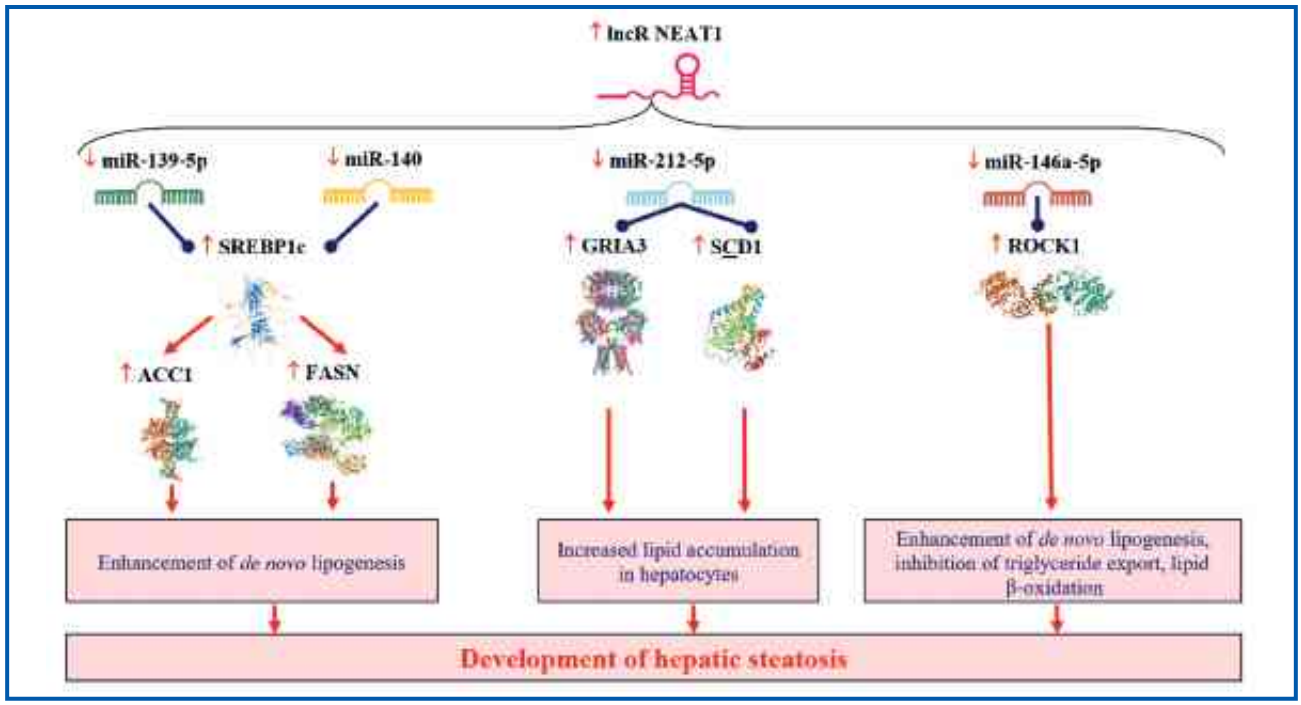

Figure 7. The role of lncR NEAT1 in the development of hepatic steatosis in MASLD

Note: molecular models adapted from the Protein data bank.

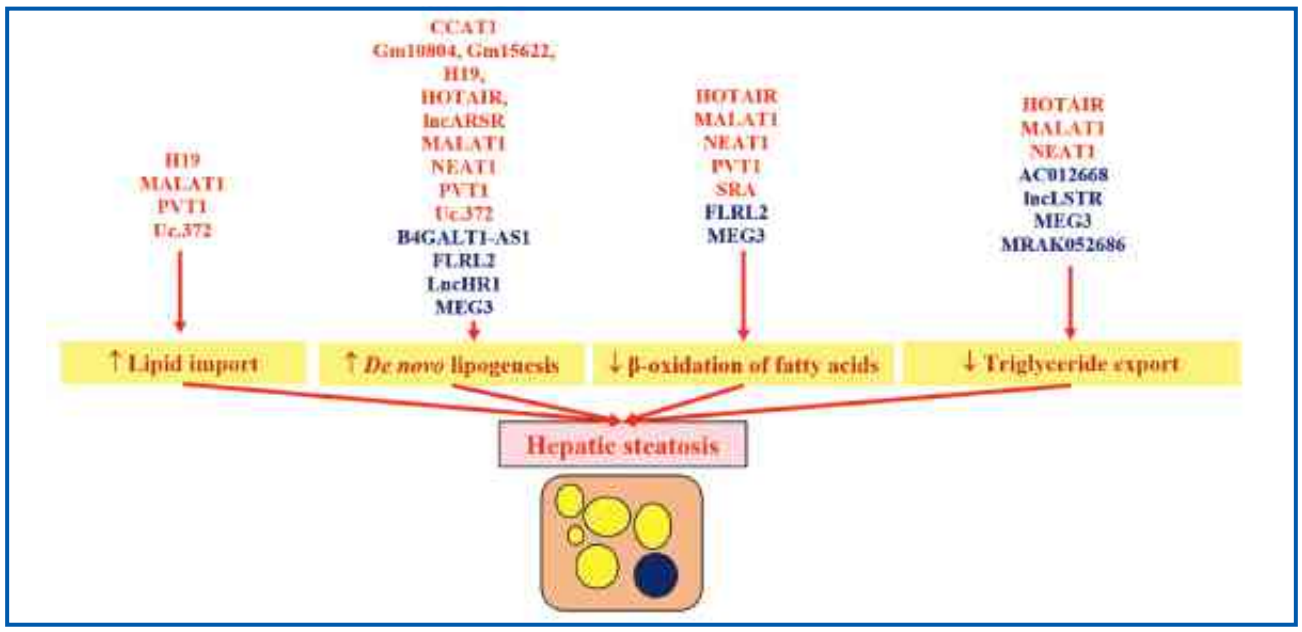

Figure 8. The influence of lncR on the main molecular pathways of the pathogenesis of hepatic steatosis in MASLD

Notes: red color highlights pro-steatosis lncRs, the expression level of which is increased in MASLD; dark blue color highlights anti-steatosis lncRs, the expression level of which is decreased in MASLD.

sion activation and suppression of AMP-activated protein kinase (PRKA). Knockout of Neat1 and Rock1 genes and miR-146a-5p overexpression inhibit lipid accumulation in hepatocytes via activation of the PRKA-associated pathway and suppression of SREBP factors. Active PRKA phosphorylates and inhibits acetyl-CoA carboxylase 1 (ACC1) and enhances β-oxidation of fatty acids. Active ACC1 catalyzes the conversion of acetyl-CoA to malonyl-CoA, which allosterically inhibits carnitine palmitoyltransferase-1 (CPT1), responsible for transferring fatty acyl groups from acyl-CoA to carnitine for transport from the cytosol to mitochondria for β-oxidation (Fig. 7) [49].

NEAT1 also regulates lipid metabolism and promotes inflammatory response and liver tissue fibrosis by inhibiting miR-506, whose molecular target is GLI family zinc finger 3 (GLI3) [50].

PVT1. Plasmacytoma variant translocation 1 (homo sapiens plasmacytoma variant translocation 1 — PVT1; 1,952 nt URS00026A27F2_9606) inhibits the functional activity of miR-20a-5p, suppressing lipid uptake and β-oxidation of fatty acids while promoting lipid synthesis. The molecular target of miR-20a-5p is FAT/CD36. Increased FAT/CD36 activity due to reduced miR-20a-5p inhibition elevates lipid uptake by hepatocytes in MASLD [51]. Elevated PVT1 transcript levels combined with low miR-20a-5p expression are considered highly diagnostic biomarkers for MASLD [52].

SRA. Steroid receptor RNA activator (homo sapiens steroid receptor RNA activator — SRA; 875 nt URS00001A8152_9606) is encoded by the SRA1 gene on chromosome 5q31.3. SRA1 produces several non-coding RNA transcripts of varying lengths and also generates mRNA encoding a protein of 236/237 amino acids [53]. SRA suppresses expression of adipose triglyceride lipase (ATGL) by inhibiting the transcriptional activity of forkhead box O1 (FoxO1) in an insulin-independent manner, thereby reducing β-oxidation of fatty acids. Interestingly, SRA is highly expressed in white adipose tissue and functions as a coactivator of PPARγ receptor transcription [54].

Uc.372. The ultraconserved lncRNA Uc.372 inhibits maturation of miR-195/miR-4668, inducing expression of genes associated with lipid synthesis and uptake, such as ACC1, FASN, SCD1, and FAT/CD36. Elevated Uc.372 expression observed in MASLD mediates lipid accumulation in the liver [55–57].

Conclusions

Thus, lncRNAs exert a pathogenetic influence on the main mechanisms of liver steatosis development in MASLD, promoting lipid uptake into hepatocytes, enhancing *de novo* lipogenesis, inhibiting β-oxidation of fatty acids, and impairing lipid export from hepatocytes (Fig. 8).

References

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. Lancet. 2017 Dec 16;390(10113):2627-2642. doi: 10.1016/S0140-6736(17)32129-3.

2. European Association for the Study of the Liver; European Association for the Study of Diabetes; European Association for the Study of Obesity. EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD): Executive Summary. Diabetologia. 2024 Nov;67(11):2375-2392. doi: 10.1007/s00125-024-06196-3.

3. Faienza MF, Farella I, Khalil M, Portincasa P. Converging Pathways between Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) and Diabetes in Children. Int J Mol Sci. 2024 Sep

14;25(18):9924. doi: 10.3390/ijms25189924.

4. Panganiban J, Kehar M, Ibrahim SH, et al. Metabolic dysfunction-associated steatotic liver disease (MASLD) in children with obesity: An Obesity Medicine Association (OMA) and expert joint perspective 2025. Obes Pillars. 2025 Feb 1;14:100164. doi: 10.1016/j.obpill.2025.100164.

5. Yang L, Li P, Yang W, et al. Integrative Transcriptome Analyses of Metabolic Responses in Mice Define Pivotal LncRNA Metabolic Regulators. Cell Metab. 2016 Oct 11;24(4):627-639. doi: 10.1016/j.cmet.2016.08.019.

6. DiStefano JK, Gerhard GS. Long Noncoding RNAs and Human Liver Disease. Annu Rev Pathol. 2022 Jan 24; 17:1-21. doi: 10.1146/annurev-pathol-042320-115255.

7. Alipoor B, Nikouei S, Rezaeinejad F, Malakooti-Dehkordi SN, Sabati Z, Ghasemi H. Long non-coding RNAs in metabolic disorders: pathogenetic relevance and potential biomarkers and therapeutic targets. J Endocrinol Invest. 2021 Oct;44(10):2015-2041. doi: 10.1007/s40618-021-01559-8.

8. Abaturov OE, Nikulina AO. Characterization of anti-steatogenic long noncoding RNAs and their epigenetic influence on the development of metabolic fatty liver disease - a systematic review. Eur J Clin Exp Med. 2025;23(3):767-775. doi: 10.15584/ejcem.2025.3.16.

9. Shi N, Sun K, Tang H, Mao J. The impact and role of identified long noncoding RNAs in nonalcoholic fatty liver disease: A narrative review. J Clin Lab Anal. 2023 Jun;37(11-12):e24943. doi: 10.1002/jcla.24943.

10. Zeng Q, Liu CH, Wu D, Jiang W, Zhang N, Tang H. LncRNA and circRNA in Patients with Non-Alcoholic Fatty Liver Disease: A Systematic Review. Biomolecules. 2023 Mar 20;13(3):560. doi: 10.3390/biom13030560.

11. Huang F, Liu H, Lei Z, et al. Long noncoding RNA CCAT1 inhibits miR-613 to promote nonalcoholic fatty liver disease via increasing LXRžtranscription. J Cell Physiol. 2020 Dec;235(12):9819-9833. doi: 10.1002/jcp.29795.

12. Leti F, DiStefano JK. Long Noncoding RNAs as Diagnostic and Therapeutic Targets in Type 2 Diabetes and Related Complications. Genes (Basel). 2017 Aug 22;8(8):207. doi: 10.3390/genes8080207.

13. Tang Z, Li X, Zheng Y, Liu J, Liu C, Li X. The role of competing endogenous RNA network in the development of hepatocellular carcinoma: potential therapeutic targets. Front Cell Dev Biol. 2024 Jan 31;12:1341999. doi: 10.3389/fcell.2024.1341999.

14. Liau XL, Salvamani S, Gunasekaran B, et al. CCAT 1- A Pivotal Oncogenic Long Non-Coding RNA in Colorectal Cancer. Br J Biomed Sci. 2023 Mar 21;80:11103. doi: 10.3389/bjbs.2023.11103.

15. Liu Z, Chen Q, Hann SS. The functions and oncogenic roles of CCAT1 in human cancer. Biomed Pharmacother. 2019 Jul;115:108943. doi: 10.1016/j.biopha.2019.108943.

16. Li T, Huang X, Yue Z, Meng L, Hu Y. Knockdown of long non-coding RNA Gm10804 suppresses disorders of hepatic glucose and lipid metabolism in diabetes with non-alcoholic fatty liver disease. Cell Biochem Funct. 2020 Oct;38(7):839-846. doi: 10.1002/cbf.3495.

17. Ma M, Duan R, Shen L, et al. The lncRNA Gm15622 stimulates SREBP-1c expression and hepatic lipid accumulation by sponging the miR-742-3p in mice. J Lipid Res. 2020 Jul;61(7):1052-1064. doi: 10.1194/jlr.RA120000664.

18. Busscher D, Boon RA, Juni RP. The multifaceted actions of the lncRNA H19 in cardiovascular biology and diseases. Clin Sci (Lond). 2022 Aug 12;136(15):1157-1178. doi: 10.1042/CS20210994.

19. Zhou J, Yang L, Zhong T, et al. H19 lncRNA alters DNA methylation genome wide by regulating S-adenosylhomocysteine hydrolase. Nat Commun. 2015 Dec 21;6:10221. doi: 10.1038/ncomms10221.

20. Zhang N, Geng T, Wang Z, et al. Elevated hepatic expression of H19 long noncoding RNA contributes to diabetic hyperglycemia. JCI Insight. 2018 May 17;3(10):e120304. doi: 10.1172/jci.insight.120304.

21. Wang H, Cao Y, Shu L, et al. Long non-coding RNA (lncRNA) H19 induces hepatic steatosis through activating MLXIPL and mTORC1 networks in hepatocytes. J Cell Mol Med. 2020 Jan;24(2):1399-1412. doi: 10.1111/jcmm.14818.

22. Liu J, Tang T, Wang GD, Liu B. LncRNA-H19 promotes hepatic lipogenesis by directly regulating miR-130a/PPARž axis in non-alcoholic fatty liver disease. Biosci Rep. 2019 Jul 15;39(7):BSR20181722. doi: 10.1042/BSR20181722.

23. Liao J, Chen B, Zhu Z, et al. Long noncoding RNA (lncRNA) H19: An essential developmental regulator with expanding roles in cancer, stem cell differentiation, and metabolic diseases. Genes Dis. 2023 Mar 24;10(4):1351-1366. doi: 10.1016/j.gendis.2023.02.008.

24. Zhu J, Luo Z, Pan Y, et al. H19/miR-148a/USP4 axis facilitates liver fibrosis by enhancing TGF-žsignaling in both hepatic stellate cells and hepatocytes. J Cell Physiol. 2019 Jun;234(6):9698-9710. doi: 10.1002/jcp.27656.

25. Sun Y, Liu C, Guo X, et al. Identification of the c-Jun/H19/miR-19/JNK1 cascade during hepatic stellate cell activation. Clin Transl Med. 2023 Mar;13(3):e1106. doi: 10.1002/ctm2.1106.

26. Lee GH, Peng C, Park SA, et al. Citrus Peel Extract Ameliorates High-Fat Diet-Induced NAFLD via Activation of AMPK Signaling. Nutrients. 2020 Mar 1;12(3):673. doi: 10.3390/nu12030673.

27. Guo B, Cheng Y, Yao L, et al. LncRNA HOTAIR regulates the lipid accumulation in non-alcoholic fatty liver disease via miR-130b-3p/ROCK1 axis. Cell Signal. 2022 Feb;90:110190. doi: 10.1016/j.cellsig.2021.110190.

28. Ferro A, Saccu G, Mattivi S, et al. Extracellular Vesicles as Delivery Vehicles for Non-Coding RNAs: Potential Biomarkers for Chronic Liver Diseases. Biomolecules. 2024 Feb 26;14(3):277. doi: 10.3390/biom14030277.

29. Landry T, Shookster D, Huang H. Tissue-Specific Approaches Reveal Diverse Metabolic Functions of Rho-Kinase 1. Front Endocrinol (Lausanne). 2021 Feb 9;11:622581. doi: 10.3389/fendo.2020.622581.

30. Zaky YA, Rashad MW, Zaater MA, El Kerdawy AM. Discovery of dual rho-associated protein kinase 1 (ROCK1)/apoptosis signal-regulating kinase 1 (ASK1) inhibitors as a novel approach for non-alcoholic steatohepatitis (NASH) treatment. BMC Chem. 2024 Jan 3;18(1):2. doi: 10.1186/s13065-023-01081-3.

31. Zhang M, Chi X, Qu N, Wang C. Long noncoding RNA lncARSR promotes hepatic lipogenesis via Akt/SREBP-1c pathway and contributes to the pathogenesis of nonalcoholic steatohepatitis. Biochem Biophys Res Commun. 2018 Apr 30;499(1):66-70. doi: 10.1016/j.bbrc.2018.03.127.

32. Chi Y, Gong Z, Xin H, Wang Z, Liu Z. Long noncoding RNA lncARSR promotes nonalcoholic fatty liver disease and hepatocellular carcinoma by promoting YAP1 and activating the IRS2/AKT pathway. J Transl Med. 2020 Mar 13;18(1):126. doi: 10.1186/s12967-020-02225-y.

33. Li N, Li X, Ding Y, et al. SREBP Regulation of Lipid Metabolism in Liver Disease, and Therapeutic Strategies. Biomedicines. 2023 Dec 12;11(12):3280. doi: 10.3390/biomedicines11123280.

34. Huang J, Chen S, Cai D, Bian D, Wang F. Long noncoding RNA lncARSR promotes hepatic cholesterol biosynthesis via modulating

Akt/SREBP-2/HMGCR pathway. Life Sci. 2018 Jun 15;203:48-53. doi: 10.1016/j.lfs.2018.04.028.

35. Ji P, Diederichs S, Wang W, et al. MALAT-1, a novel noncoding RNA, and thymosin beta4 predict metastasis and survival in early-stage non-small cell lung cancer. Oncogene. 2003 Sep 11;22(39):8031-41. doi: 10.1038/sj.onc.1206928.

36. Tufail M. The MALAT1-breast cancer interplay: insights and implications. Expert Rev Mol Diagn. 2023 Jul-Dec;23(8):665-678. doi: 10.1080/14737159.2023.2233902.

37. Piórkowska K, Zygmunt K, Hunter W, Wrzblewska K. MALAT1: A Long Non-Coding RNA with Multiple Functions and Its Role in Processes Associated with Fat Deposition. Genes (Basel). 2024 Apr 10;15(4):479. doi: 10.3390/genes15040479.

38. Yan C, Chen J, Chen N. Long noncoding RNA MALAT1 promotes hepatic steatosis and insulin resistance by increasing nuclear SREBP-1c protein stability. Sci Rep. 2016 Mar 3;6:22640. doi: 10.1038/srep22640.

39. Han J, Shen L, Zhan Z, et al. The long noncoding RNA MALAT1 modulates adipose loss in cancer-associated cachexia by suppressing adipogenesis through PPAR-γ. Nutr Metab (Lond). 2021 Mar 10;18(1):27. doi: 10.1186/s12986-021-00557-0.

40. Xiang J, Deng YY, Liu HX, Pu Y. LncRNA MALAT1 Promotes PPARα/CD36-Mediated Hepatic Lipogenesis in Nonalcoholic Fatty Liver Disease by Modulating miR-206/ARNT Axis. Front Bioeng Biotechnol. 2022 Jun 13; 10: 858558. doi: 10.3389/fbioe.2022.858558.

41. Chen X, Tan QQ, Tan XR, Li SJ, Zhang XX. Circ_0057558 promotes nonalcoholic fatty liver disease by regulating ROCK1/AMPK signaling through targeting miR-206. Cell Death Dis. 2021 Aug 26;12(9):809. doi: 10.1038/s41419-021-04090-z.

42. Bougarne N, Weyers B, Desmet SJ, et al. Molecular Actions of PPARα in Lipid Metabolism and Inflammation. Endocr Rev. 2018 Oct 1;39(5):760-802. doi: 10.1210/er.2018-00064.

43. Chen S, Sun S, Feng Y, et al. Diosgenin attenuates nonalcoholic hepatic steatosis through the hepatic FXR-SHP-SREBP1C/PPARα/CD36 pathway. Eur J Pharmacol. 2023 Aug 5;952:175808. doi: 10.1016/j.ejphar.2023.175808.

44. Wang Z, Li K, Huang W. Long non-coding RNA NEAT1-centric gene regulation. Cell Mol Life Sci. 2020 Oct;77(19):3769-3779. doi: 10.1007/s00018-020-03503-0.

45. Jin SS, Lin CJ, Lin XF, Zheng JZ, Guan HQ. Silencing lncRNA NEAT1 reduces nonalcoholic fatty liver fat deposition by regulating the miR-139-5p/c-Jun/SREBP-1c pathway. Ann Hepatol. 2022 Mar-Apr;27(2):100584. doi: 10.1016/j.aohep.2021.100584.

46. Sun Y, Song Y, Liu C, Geng J. LncRNA NEAT1-MicroRNA-140 axis exacerbates nonalcoholic fatty liver through interrupting AMPK/SREBP-1 signaling. Biochem Biophys Res Commun. 2019 Aug 20;516(2):584-590. doi: 10.1016/j.bbrc.2019.06.104.

47. Hu MJ, Long M, Dai RJ. Acetylation of H3K27 activated lncRNA NEAT1 and promoted hepatic lipid accumulation in non-alcoholic fatty liver disease via regulating miR-212-5p/GRIA3. Mol Cell Biochem. 2022 Jan;477(1):191-203. doi: 10.1007/s11010-021-04269-0.

48. Guo Y, Yu J, Wang C, et al. miR-212-5p suppresses lipid accumulation by targeting FAS and SCD1. J Mol Endocrinol. 2017 Oct;59(3):205-217. doi: 10.1530/JME-16-0179.

49. Chen X, Tan XR, Li SJ, Zhang XX. LncRNA NEAT1 promotes hepatic lipid accumulation via regulating miR-146a-5p/ROCK1 in nonalcoholic fatty liver disease. Life Sci. 2019 Oct 15;235:116829. doi: 10.1016/j.lfs.2019.116829.

50. Jin SS, Lin XF, Zheng JZ, Wang Q, Guan HQ. lncRNA NEAT1 regulates fibrosis and inflammatory response induced by nonalcoholic fatty liver by regulating miR-506/GLI3. Eur Cytokine Netw. 2019 Sep 1;30(3):98-106. doi: 10.1684/ecn.2019.0432.

51. Wang X, Ma Y, Yang LY, Zhao D. MicroRNA-20a-5p Ameliorates Non-alcoholic Fatty Liver Disease via Inhibiting the Expression of CD36. Front Cell Dev Biol. 2020 Dec 3;8:596329. doi: 10.3389/fcell.2020.596329.

52. Zhang H, Niu Q, Liang K, Li X, Jiang J, Bian C. Effect of LncPVT1/miR-20a-5p on Lipid Metabolism and Insulin Resistance in NAFLD. Diabetes Metab Syndr Obes. 2021 Nov 23;14:4599-4608. doi: 10.2147/DMSO.S338097.

53. Sheng L, Ye L, Zhang D, Cawthorn WP, Xu B. New Insights Into the Long Non-coding RNA SRA: Physiological Functions and Mechanisms of Action. Front Med (Lausanne). 2018 Sep 6;5:244. doi: 10.3389/fmed.2018.00244.

54. Shabgah AG, Norouzi F, Hedayati-Moghadam M, Soleimani D, Pahlavani N, Navashenaq JG. A comprehensive review of long non-coding RNAs in the pathogenesis and development of non-alcoholic fatty liver disease. Nutr Metab (Lond). 2021 Feb 23;18(1):22. doi: 10.1186/s12986-021-00552-5.

55. Guo J, Fang W, Sun L, et al. Ultraconserved element uc.372 drives hepatic lipid accumulation by suppressing miR-195/miR4668 maturation. Nat Commun. 2018 Feb 9;9(1):612. doi: 10.1038/s41467-018-03072-8.

56. Chen X, Ma H, Gao Y, et al. Long non-coding RNA AC012668 suppresses non-alcoholic fatty liver disease by competing for microRNA miR-380-5p with lipoprotein-related protein LRP2. Bioengineered. 2021 Dec;12(1):6738-6747. doi: 10.1080/21655979.2021.

57. Qian W, Liu Z, Zhang W, et al. Targeting steroid receptor RNA activator as a novel therapeutic strategy for myocardial hypertrophy. Biochem Pharmacol. 2025 Oct;240:117121. doi: 10.1016/j.bcp.2025.117121.

Received 10.01.2026
Revised 17.02.2026
Accepted 25.02.2026

Information about authors

Aleksandr Abaturov, MD, DSc, PhD, Professor, Honored Worker of Science and Technology of Ukraine, Head of the Department of Pediatrics 1 and Medical Genetics, Dnipro State Medical University, Dnipro, Ukraine; e-mail: alexandrabaturov56@gmail.com; https://orcid.org/0000-0001-6291-5386

Anna O. Nikulina, MD, DSc, PhD, Associate Professor, Department of Pediatrics 1 and Medical Genetics, Dnipro State Medical University, Dnipro, Ukraine; e-mail: anna.nikulina.201381@gmail.com; phone: +380 (99) 978-16-59; https://orcid.org/0000-0002-8617-9341

Conflicts of interests. Authors declare the absence of any conflicts of interests and own financial interest that might be construed to influence the results or interpretation of the manuscript.

Information about funding. The study has no separate additional funding. Conducted within the framework of the research theme of the Department of Pediatrics 1 and Medical Genetics of the Dnipro State Medical University on the topic: "Precision approaches to the diagnosis and treatment of somatic and endocrine diseases (No. 0123U105100)".

Authors' contribution. A. Abaturov — conceptualization, methodology, validation, formal analysis, investigation, resources, original draft preparation, review and editing, visualization, supervision, project administration; A. Nikulina — conceptualization, validation, formal analysis, investigation, resources, review and editing, visualization, supervision.

Абатуров О.Є., Нікуліна А.О.
Дніпровський державний медичний університет, м. Дніпро, Україна

Епігенетичний вплив довгих некодуючих стеатогенних РНК на розвиток стеатотичної хвороби печінки, асоційованої з метаболічною дисфункцією

Резюме. ***Актуальність.*** Стеатотична хвороба печінки, асоційована з метаболічною дисфункцією (metabolic dysfunction-associated steatotic liver disease — MASLD), є найпоширенішим хронічним захворюванням печінки в людей, що зумовлене зміною рівня експресії довгих некодуючіх РНК (long non-coding RNA — lncR). ***Метою*** цього огляду було надати короткий опис ролі стеатогенних lncR в епігенетичному впливі на розвиток MASLD шляхом аналізу даних сучасної наукової літератури. ***Матеріали та методи.*** Проведено аналіз 60 літературних джерел за останні п'ять років із баз даних MEDLINE; Embase; PreMedline In-Process & Other Non-Indexed Citations; The Cochrane Systematic Reviews Database, DARE, NHS EED and HTA databases; Web of Knowledge Science Citation Index; Web of Knowledge ISI Proceedings; CRD databases; BIOSIS, які були відібрані за ключовими словами: довгі некодуючі РНК; епігенетична регуляція; метаболічно асоційована жирова хвороба печінки; стеатотична хвороба печінки, асоційована з метаболічною дисфункцією; ожиріння. PROSPERO CRD420250652980. ***Результати.*** Посилення експресії стеатогенних lncR, як-от CCAT1, Gm10804, Gm15622, H19, HOTAIR, lncARSR, NEAT1, PVT1, SRA, Uc.372 та інші, є характерною ознакою розвитку й прогресування стеатозу печінки при MASLD. Розвиток стеатозу печінки при MASLD підтримується зниженням рівня експресії антистеатозних lncR, зокрема AC012668, FLRL2, Gm16551, lncHR1, B4GALT1-AS1/lncSHGL, MEG3, lncR MRAK052686 та інших. ***Висновки.*** Довгі некодуючі РНК мають безумовний патогенетичний вплив на основні механізми розвитку стеатозу печінки при MASLD, обумовлюючи поглинання ліпідів у гепатоцитах, посилюючи *de novo* ліпогенез, пригнічуючи β-окиснення жирних кислот та експорт ліпідів із гепатоцитів.

Ключові слова: епігенетична регуляція; довгі некодуючі стеатогенні РНК; стеатотична хвороба печінки, асоційована з метаболічною дисфункцією; ожиріння; огляд літератури