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Epigenetic influence of long non-coding RNAs on the development of metabolic-associated steatohepatitis

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Abstract. ***Background.*** *Long non-coding RNAs (lncR) are characterized by a high degree of tissue-specific gene expression, allowing certain combinations to be considered as diagnostic markers of metabolic-associated steatohepatitis (MASH). The purpose of this literature review is to present current data on the role of long non-coding RNAs in the epigenetic influence on the development of metabolic-associated steatohepatitis, based on analysis of contemporary scientific literature.* ***Materials and methods.*** *An analysis of 76 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, and BIOSIS. Sources were selected using the keywords: long non-coding steatogenic RNAs, epigenetic regulation, metabolically associated fatty liver disease, metabolic dysfunction-associated steatotic liver disease, obesity. PROSPERO registration: CRD420250652980.* ***Literature analysis.*** *Temporal analysis showed that periodic fluctuations in the expression of most lncR lead to both inflammation development and production of pro-inflammatory cytokines. Inhibition of the transcription factor NF-κB suppresses the expression activity of most pro-inflammatory lncR. Long non-coding RNAs participate in the development of MASH primarily by activating pro-inflammatory signaling pathways, transcription factors (NF-κB, AP-1), and inflammasomes. By regulating the expression levels of cytokines (IL-1β, IL-6, TNF) and chemokines (CCL2, CXCL1, CXCL5), lncR determine the recruitment of pro-inflammatory immune cells, local vascular response, and, consequently, the degree of inflammatory reaction in liver tissue in metabolic dysfunction-associated steatotic liver disease.* ***Conclusions.*** *Pro-inflammatory and anti-inflammatory lncR are epigenetic regulators of liver inflammation that determine the development of MASH and may be considered potential targets for anti-inflammatory pharmacotherapy in patients with MASH.*

Keywords: *children; obesity; metabolic-associated steatohepatitis; long non-coding RNAs; literature review*

Introduction

The development of liver steatosis in metabolic dysfunction-associated steatotic liver disease (MASLD) at a certain stage of pathogenesis leads to the initiation of an inflammatory process, which determines the manifestation of steatohepatitis. Metabolic-associated steatohepatitis (MASH) is a progressive form of MASLD characterized by lobular liver inflammation. From a diagnostic perspective, lobular liver inflammation in MASLD patients is the main pathomorphological feature marking the transition from simple steatosis to steatohepatitis [1–5]. Metabolic-associated steatohepatitis carries a high risk of various metabolic disturbances, liver cirrhosis, hepatocellular carcinoma, and adverse disease outcomes [6–9].

Currently, it has been demonstrated that various long non-coding RNAs (lncR) are involved in regulating the proliferation, differentiation, and activation of immune cells, including monocytes, macrophages, dendritic cells, neutrophils, T-cells, and B-cells [10]. Long non-coding RNA are considered important regulators of the inflammatory response, exerting their effects by modulating the transcription levels of pro- and anti-inflammatory genes, including during the development of steatohepatitis [11–14]. The lncR transcriptome

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profile in liver structural cells, resident liver immune cells, and recruited immune cells determines the likelihood of steatohepatitis development in MASLD [15–17].

Aim. To present current data on the role of long non-coding RNAs in the epigenetic influence on the development of metabolic-associated steatohepatitis based on analysis of contemporary scientific literature.

Materials and methods

An analysis of 76 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 — NIHR) ID652980, CRD420250652980.

Literature analysis: role of lncRNAs in liver inflammation development in MASLD

Numerous and diverse lncR are involved in the development of liver tissue inflammation in MASLD patients, influencing pro- and anti-inflammatory molecular signaling pathways (Table 1).

Next-generation deep sequencing results in minipigs indicate that induction of steatohepatitis is accompanied by differential expression of 89 lncR, whose primary molecular targets are the genes *Ppar*, *Fads2*, *Dgat2*, *Acaa2*, *Cyp2e1*, *Adh4*, and *Fos* [20].

Pro-inflammatory lncRNAs

Gm9795. The long non-coding RNA Gm9795 is transcribed from a pseudogene sequence of the lipid transfer domain associated with StAR, located on chromosome 10. Gm9795 expression is closely linked to MASH severity. The Gm9795 transcript promotes the expression of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukins IL-1β, and IL-6 through activation of NF-κB- and JNK-associated signaling pathways. It has been shown that Gm9795 activates the expression of endoplasmic reticulum-to-nucleus signaling protein 1 (ERN1), a key molecule in ER stress that activates both c-Jun NH2-terminal kinase (JNK) and the transcription factor NF-κB, inducing inflammation (Fig. 1) [21].

HOTAIR. It has been demonstrated that in HepG2 cells treated with free fatty acids (FFA), the HOX transcript antisense RNA (HOTAIR) is highly expressed. Knockout of the HOTAIR gene leads to a decrease in the activity of inflammation induced by FFA. It is believed that the lncR HOTAIR promotes the development of the inflammatory process in the liver by recruiting the serine and arginine rich splicing factor 1 (SRSF1), which contributes to the stabili-

Table 1. Long non-coding RNAs associated with MASH development [18, 19]

lncRNA	Molecular target	Signaling cascade and effect
Increased expression		
Gm9795	ERN1	NF-κB and ERK1 signaling pathway, induction of inflammation
HOTAIR	SRSF1	NF-κB signaling pathway
HULC	MAPK	JNK signaling pathway, induction of inflammation
LeXis	–	Induction of inflammation
lnc18q22.2	BCL family proteins	Hepatocyte apoptosis
linc00907	miR-942-5p	TAOK1, induction of inflammation
lncTNF	–	NF-κB signaling pathway, induction of inflammation
MALAT1	SAA3	mTOR/S6K1 signaling pathway, induction of inflammation
NEAT1	miR-129-5p, miR-506	NF-κB signaling pathway, regulation of inflammation
Platr4	NLRP3	Reduced IL-1β and IL-18 activation via NLRP3 inflammasome inhibition
RUNX1	TLR4, TLR5, NF-κB1, NF-κB2, TNF, ADIPOQ, IL-6	NF-κB signaling pathway, regulation of inflammation
NONMMUT010685	XBP1, ACLY	JNK signaling pathway, induction of steatosis and inflammation
NONMMUT050689	RIPK1, ACLY	Induction of steatosis, inflammation, and necroptosis
Decreased expression		
FLRL2	ARNTL	NF-κB signaling pathway
RUNX1	TLR4, TLR5, NF-κB1, NF-κB2, TNF, ADIPOQ, IL-6	NF-κB signaling pathway, regulation of inflammation
SRD5A3-AS1	miR-1205	YAP1 signaling pathway

zation of the carbohydrate-responsive element-binding protein (ChREBP) mRNA [21]. The ChREBP protein is the main helix-loop-helix leucine zipper transcription factor, which primarily mediates glucose homeostasis in the body. ChREBP has also been shown to mediate the inflammatory response by promoting the production of several proinflammatory cytokines (TNF-α, IL-1β, and IL-6) [22]. A. Chini et al. [24] provided compelling evidence that the lncR HOTAIR plays a critical role in the activation of macrophages and their production of proinflammatory cytokines during the innate immune response.

HULC. It has been shown that the development of MASH in patients with MASLD is accompanied by increased expression of long non-coding RNA, the expression level of which increases in hepatocellular carcinoma (homo sapiens (human) hepatocellular carcinoma up-regulated long non-coding RNA — HULC; 434 nt URS00026A1D8A_9606), the gene of which is located in the p24.3 region of chromosome 6. It is believed that the expression of lncR HULC induces the MAPK (mitogen-activated protein kinases)-associated signaling pathway (Fig. 2).

Inhibition of both HULC and p38/JNK kinases improves histological liver status in experimental MASH, including reduced steatosis, inflammation, and fibrosis [25].

HULC also induces CpG island methylation in the miR-9 promoter via increased DNA methyltransferase 1 (DNMT1) expression. Since miR-9 inhibits *PPARA*, reduced miR-9 leads to PPARα activation and lipid accumulation in hepatocytes [26].

LeXis. A long noncoding RNA sequence, the expression of which in the liver is induced by the liver X receptor (liver-expressed liver X receptor (LXR) induced sequence — LeXis) is associated with cholesterol metabolism and the development of hepatic steatosis in mice. The long noncoding RNA LeXis represses the expression of genes involved in cholesterol biosynthesis by interacting with the ribonucleoprotein RALY, which is a member of the heterogeneous nuclear ribonucleoprotein (hnRNP) family, a large family of RNA-binding proteins. The ribonucleoprotein RALY binds to specific coding and noncoding RNAs, including mammalian translational mRNAs. It has been shown that the lncR LeXis disrupts the binding of the ribonucleoprotein RALY to the translated mRNAs of cholesterologenic genes in mouse hepatocytes, which inhibits translation activity [26, 27]. It is necessary to emphasize the special influence of LeXis on the development of inflammatory reactions in liver tissue in patients with MASLD. Thus, in patients with MASH, the concentration level of LeXis transcripts in the blood serum is significantly higher than in patients with hepatic steatosis [28].

linc00907. Long intergenic non-protein coding RNA linc00907 (homo sapiens (human) long intergenic non-protein coding RNA 907; 1,865 nt URS000075B00D_9606) functions as a competing endogenous RNA (ceRNA), which sequesters miR-945 and leads to the amplification of its target gene TAO kinase 1 (TAOK1). It has been demonstrated that linc00907 expression is significantly increased in patients with MASH. Overexpression of linc00907 is accompanied by increased intracellular lipid accumulation and the development of liver inflammation [29]. The serine/threonine protein kinase TAOK1 increases lipopolysaccha-

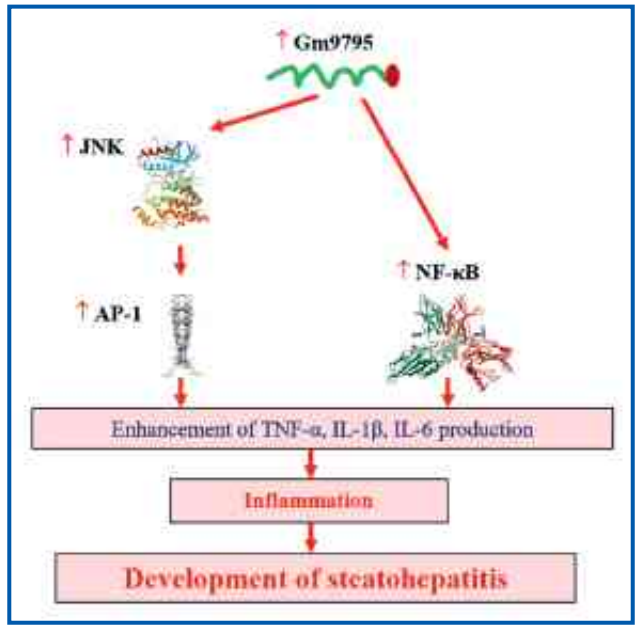

Figure 1. Role of Gm9795 in MASH development
Note: molecular models adapted from the Protein Data Bank.

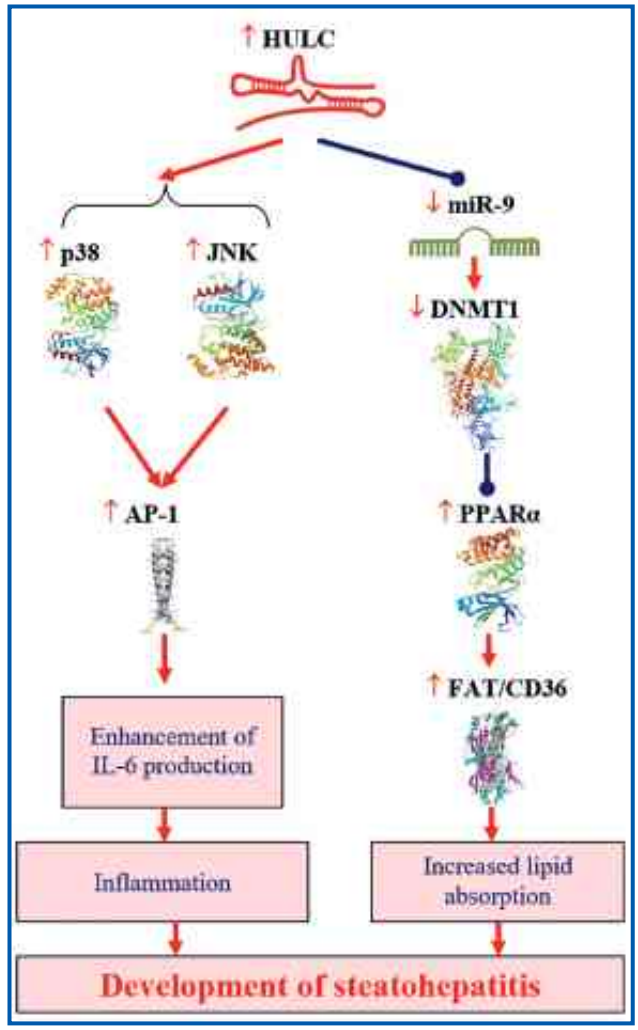

Figure 2. Role of HULC in MASH development
Notes: red arrows — activation; blue — inhibition. Molecular models adapted from the Protein Data Bank.

ride-induced macrophage production of proinflammatory cytokines, such as IL-6, IL-12p40, and TNF-α, by activating the mitogen-activated protein kinase MAPK1 [30]. At the same time, TAOK1, by preventing the interaction of the IL-17 receptor with the adaptor protein 1 (ACT 1 adaptor protein — ACT1/TRAF3IP2), suppresses the development of IL-17-associated inflammation (Fig. 3) [31].

lncTNF. It has been demonstrated that the expression of the lncTNF gene (lncR gene tumor necrosis factor-alpha; RP11-91K9.1) is significantly increased in HepG2 cells (a human hepatocellular carcinoma cell line) after stimulation with pro-inflammatory cytokines TNF-α, IL-1β. Thus, when the TNF-α gene is stimulated in HepG2 cells (a human hepatocellular carcinoma cell line), the level of expression of the intergenic lncR lncTNF increases by about 20 times. In liver biopsies of patients with MASLD, the level of lncTNF expression positively correlates with the degree of lobular liver inflammation. The long non-coding RNA lncTNF activates the transcription factor NF-κB. Once activated, the transcription factor NF-κB induces the expression of a wide range of genes involved in the regulation of proliferation, differentiation, survival, as well as genes encoding proinflammatory cytokines, chemokines, and adhesion molecules. Knockout of the lncTNF gene is accompanied by a decrease in the activity of the transcription factor NF-κB and a decrease in the expression of the genes A20 and IκBα, which determine the effectiveness of the action of the NF-κB factor. It is suggested that lncTNF may be a new target for drug control of liver inflammation in MASLD [34].

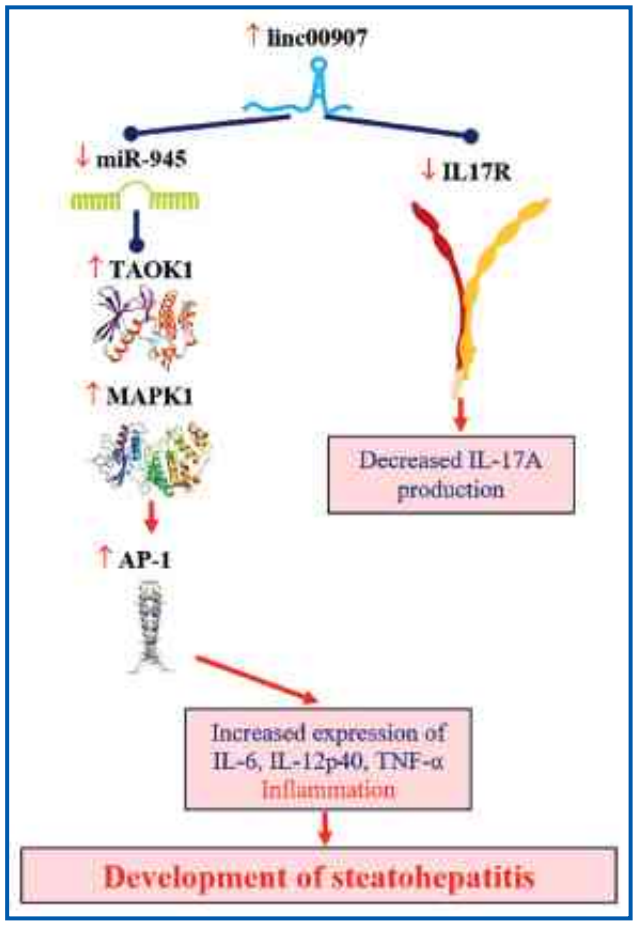

Figure 3. Role of linc00907 in MASH development

Notes: red arrows — activation; blue — inhibition. TAOK1 model adapted from L. Yu et al. [33].

MALAT1. Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is involved in the regulation of various pro-inflammatory pathways, such as NF-κB, PI3K/AKT, MAPK, JAK/STAT [35]. Hyperglycemia and high serum free fatty acid levels induce overexpression of the MALAT1 transcript, which is a key partner for the polycomb repressive complex 2 (PRC2), which inhibits the expression of anti-inflammatory genes. The MALAT1 transcript binds to enhancer of zeste polycomb homolog 2 (EZH2), which is a catalytic subunit of the PRC2 repressive complex, which leads to histone methylation of anti-inflammatory genes, repression of their transcription, and transcription [36]. The MALAT1 transcript activates the expression of serum amyloid antigen 3 (SAA3), which stimulates the production of pro-inflammatory cytokines TNF-α and IL-6 by endothelial cells, which can lead to the development of cardiovascular disorders [37]. In HSC lncR MALAT1 induces the synthesis of the chemokine CXCL5 (ENA-78), which recruits and activates neutrophils to the lesion site (Fig. 4) [38].

Neutrophils recruited to the liver tissue determine the development of MAS. In particular, activated neutrophils produce activated oxygen-containing metabolites (AOMs), which cause direct damage to hepatocytes. AOMs also recruit and activate macrophages, which enhance inflammatory effects in the liver tissue and contribute to the excitation of HSCs, which induces the development of liver fibrosis. Neutrophils release neutrophil proteins, such as lipocalin-2-LCN2, myeloperoxidase (MPO), and neutrophil elastase (NE), which contribute to the development of liver inflammation [39, 40].

The long noncoding RNA MALAT1 inactivates miR-206, which suppresses the expression of the aryl hydrocarbon receptor nuclear translocator (ARNT) gene. The ARNT phosphoprotein can be part of the hypoxia-inducible factor 1 (HIF1) complex and form a dimer with the aromatic hydrocarbon receptor (aryl hydrocarbon receptor (AHR)), facilitating the interaction of AHR with DNA [41].

Activation of the ARNT phosphoprotein is accompanied by a significant decrease in the activity of PPARα receptors, which have a pronounced anti-inflammatory effect, increasing the expression of the inhibitory component IκBα, thereby preventing the translocation of the p50/p65 transcription factor NF-κB into the nucleus [42, 43]. It has been shown that in primary hepatocytes and human hepatoma cells, PPARα receptor agonists suppress IL-1-induced expression of C-reactive protein and IL-6 fibrinogen. A decrease in the activity of PPARα receptors is associated with increased production of pro-inflammatory cytokines [44, 45]. However, the effect of lncR MALAT1 on ARNT probably does not cause a genetically significant effect, since ARNT expression in liver biopsies of patients with MAH is significantly lower than in healthy people [41]. It has been demonstrated that decreased ARNT activity is associated with the development of steatohepatitis, and AHR activation is associated with anti-inflammatory effects. Thus, C. Scott and colleagues [41] showed that suppression of ARNT expression is accompanied by increased expression levels of CXCL1 (GROα), monocyte che-

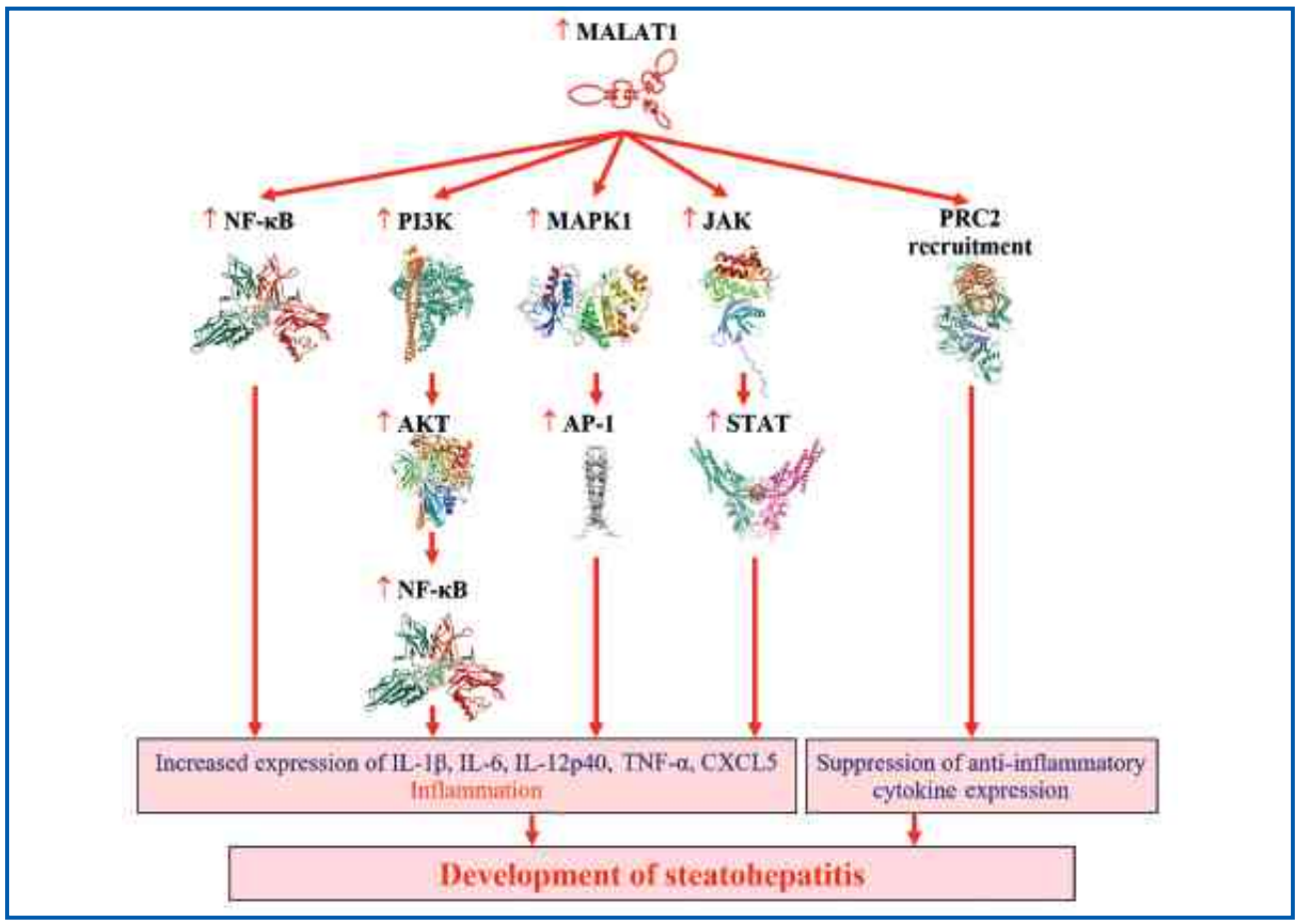

Figure 4. Role of MALAT1 in MASH development

moattractant protein 1 (MCP1/CCL2), TNF-α and TGF-β1 mRNA, contributing to the transformation of hepatic steatosis. It has been shown that increased activity of the AHR signaling pathway causes activation of the transcription factor Foxp3 in naive T cells, inducing their differentiation into regulatory T cells, and in mice with a knockout of the *Ahr* gene, portal fibrosis and liver inflammation develop already at the age of three weeks [46].

HCG18. Aberrant expression of the human leukocyte antigen complex group 18 (HCG18; 6,820 nt URS000075CE1F_9606) lncR is closely associated with the clinicopathological characteristics of numerous diseases and contributes to their progression. It has been shown that HCG18 may be involved in the development of steatosis, liver inflammation, and insulin resistance [47].

The key molecular target of HCG18 is miR-197-3p, which suppresses the production of the main proximal proinflammatory interleukin — IL-18. Thus, an increase in the representation of HCG18 causes a decrease in the miR-197-3p pool, which leads to increased expression of the *IL18* gene [48]. It is known that in mice receiving HFD and people with MASLD, the expression of the *IL18* gene, which is actively involved in the development of MASH (Fig. 5) [49, 50].

NEAT1. Nuclear enriched abundant transcript 1 (homo sapiens (human) nuclear enriched abundant transcript 1 — NEAT1; 3,756 nt URS000075DAEC_9606), the expression level of which increases in the case of the development of MASH. It is known that the expression level of lncR NEAT1 is significantly increased in numerous inflammatory and autoimmune diseases. The amount of lncR NEAT1 is directly proportional to the concentration of pro-inflammatory cytokines in the blood serum of patients. The NEAT1 transcript, interacting with numerous miRs, regulates the activity of various pro-inflammatory signaling pathways (Table 2) [51, 52].

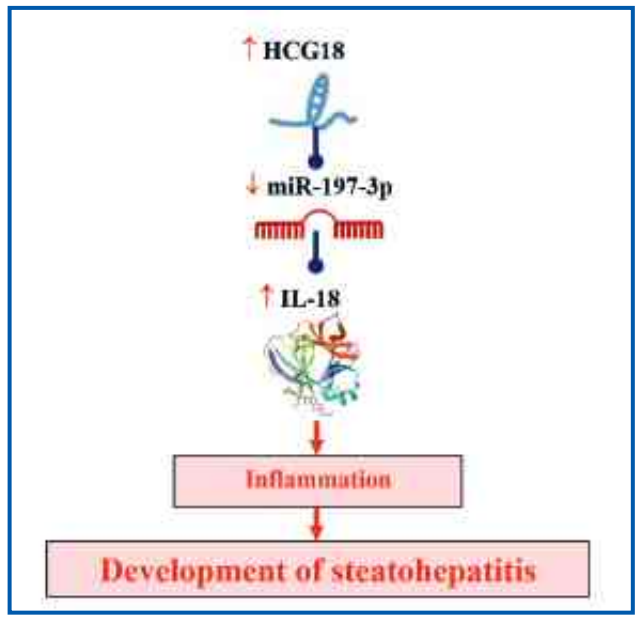

Figure 5. Role of HCG18 in MASH development

In MASH, the lncR NEAT1, acting as a ceRNA, directly interacts with and sequesters miR-129-5p and miR-506, which are involved in the regulation of the inflammatory process. It has been demonstrated that during the progression of MASLD, there is an increase in the number of NEAT1 transcripts and a proportional decrease in the level of miR-506, one of the targets of which is the protein 3 of the zinc finger family domain (GLI family zinc finger 3 — GLI3). Overexpression of miR-506 suppresses the expression of GLI3, and a decrease in the expression of miR-506 promotes the activation of GLI3 [53]. It has been shown that macrophages stimulated with lipopolysaccharide, in the absence of the Gli3 factor, secrete significantly lower amounts of TNF-α and CCL2 compared to wild-type macrophages. The Gli3 factor promotes the transmission of excitation from the TLR3 and TLR4 receptors via the TRIF-IRF3 signaling pathway [54]. GLI3 activation induces the production of pro-inflammatory cytokines and chemokines by immunocytes: TNF-α, IL-1β, IL-6 and CCL2 [53]. Sequestration of miR-129-5p by lncR NEAT1 reduces the inhibitory effect

Table 2. Target miRNAs of NEAT1 transcript [51, 52]

Target miRNA	Signaling pathway	Pathway effect (secretion)
miR-9-5p	SLC26A2	IL-4, IL-6, IL-13
miR-17-5p	TLR4	TNF-α, IL-1β, IL-6
miR-21		IL-4, IL-6, IL-10, IL-17
miR-22-3p		TNF-α, IL-1β, IL-6, IL-8
miR-23a	MDM2/SIRT6	TNF-α, IL-1β, IL-6
miR-27a-3p	TAB3	TNF-α, IL-1β, IL-6
miR-30c-5p	TCF7	TNF-α, IL-1β, IL-6
miR-31-5p	POU2F1	TNF-α, IL-1β, IL-6
miR-124		TNF-α, IL-1β, IL-6, IL-17
miR-124		TNF-α, IL-1β, IL-6, IL-17
miR-124	NF-κB	TNF-α, IL-1β, IL-6
miR-125	MCEMP1	TNF-α, IL-1β, IL-6
miR-125a-5p	TRAF6/TAK1	TNF-α, IL-1β, IL-4, IL-6, IL-10
miR-128		TNF-α, IL-1β, IL-6
miR-129		IL-1β, IL-6
miR-129-5p	PEG3	Activation of the NF-κB
miR-129-5p	SOCS2	TNF-α, IL-1β, IL-6
miR-139	PUMA	TNF-α, IL-1β, IL-6
miR-144-3p		TNF-α, IL-1β, IL-6
miR-146b	TRAF6/NF-κB	TNF-α, IL-1β, IL-6, IFN-γ
miR-148b-3p	ICAM-1	TNF-α, IL-6, sICAM-1
miR-181a	GPD1L	TNF-α, IL-1β, IL-6, IL-8, COX-2
miR-193a-3p	SOX5	TNF-α, IL-1β, IL-6, IL-8
miR-193a-3p	TLR4/NF-κB	TNF-α, IL-1β, IL-6, IL-8
miR204-5p	PI3K-AKT	TNF-α, IL-7, IL-12a, IL-17a
miR-211	PI3K/AKT	TNF-α, IL-6, IL-10, CCL2
miR-216b	MAP2K6	TNF-α, IL-6, IL-10
miR-342-3p		TNF-α, IL-1β, IL-6, COX-2
miR-34c	NLRP3	IL-1β
miR-370-3p	IRAK2	TNF-α, IL-1β, IL-6, IL-8
miR-370-3p	TSP-1	TNF-α, IL-1β, IL-6, IL-8
miR-377–3p		TNF-α, IL-6, IFN-γ
miR-377-3p	ITGA6	IL-1β
miR-410-3p	YY1	TNF-α
miR-506	GLI3	TNF-α, IL-1β, IL-6, CCL2
miR-590-3p		TNF-α, IL-1β, IL-6, IL-9
miR-944	TRIM37	TNF-α, IL-1β, IL-6

of miR-129-5p on the paternally expressed 3 (PEG3) gene, which activates the transcription factor NF-κB, inducing the development of the inflammatory process [55]. On the other hand, sequestration of miR-129-5p leads to increased expression of the suppressor of cytokine signaling 2 (SOCS2) gene [56]. The suppressor protein SOCS2 is one of the classic negative regulators of cytokine signaling. Overexpression of SOCS2 in macrophages suppresses inflammatory activity and cell apoptosis by inhibiting the NF-κB-associated signaling pathway and inflammasome formation, while knockout of the SOCS2 gene in macrophages causes excessive activation of the transcription factor NF-κB. The level of decrease in SOCS2 activity is highly correlated with the degree of liver inflammation during the development of MASH (Fig. 6) [57, 58].

In addition, lncR NEAT1 may act as a scaffold during the assembly of NLRC3- and NLRP4-inflammasomes, thereby promoting the recruitment, maturation, and stabilization of caspase-1 in activated macrophages [59].

Thus, the effect of NEAT1 overexpression on the activity of liver lobular inflammation depends on the level of miR-129-5p and miR-506 generation.

RUNX1. Transcription factor 1, related to Runt (homo sapiens (human) Runt-related transcription factor 1 — RUNX1; 1,502 nt URS000075E3D1_9606) plays a significant role in the development of liver inflammation in MASLD by regulating the activity of TLR4, TLR5, NF-κB, JNK, TNF, CCL2 and others (Table 3, Fig. 7) [60].

The expression of lncR RUNX1 is increased in the early stages of MASLD and decreases as MASH progresses [60].

It has been demonstrated that in liver tissue in MASLD, the main generators of lncR RUNX1 are hepatic endothelial cells. The level of lncR RUNX1 expression in these cells correlates with the severity of MASH. RUNX1 transcripts, the generation of which is induced by hepatic steatosis, increase the expression of adhesion and angiogenic molecules (VEGFA, VEGFR1, VEGFR2) [61].

NONMMUT010685, NONMMUT050689. The development of MASH is associated with an increase in the expression level of lncR NONMMUT010685 (mus musculus long non-coding RNA NONMMUT010685.2; 2,096 nt URS00009C54B5_10090), NONMMUT050689 (mus musculus long non-coding RNA NONMMUT050689.2; 623 nt URS00009BED89_10090), which inhibit the expression of the X-box binding protein 1 (XBP1) and receptor-interacting protein 1 kinase (RIPK1) genes, respectively [62]. At the same time, data are presented indicating that the activity of the XBP1 factor is significantly increased in liver tissues of patients with MASH. Knockout of the *Xbp1* gene leads to a decrease in lipid accumulation in mouse hepatocytes, and drug inhibition of Xbp1 activity prevents the development of steatohepatitis and fibrosis in experimental animals [63]. It has also been shown that XBP1 contributes to the activation of the oligomerization domain that binds nucleotides rich in

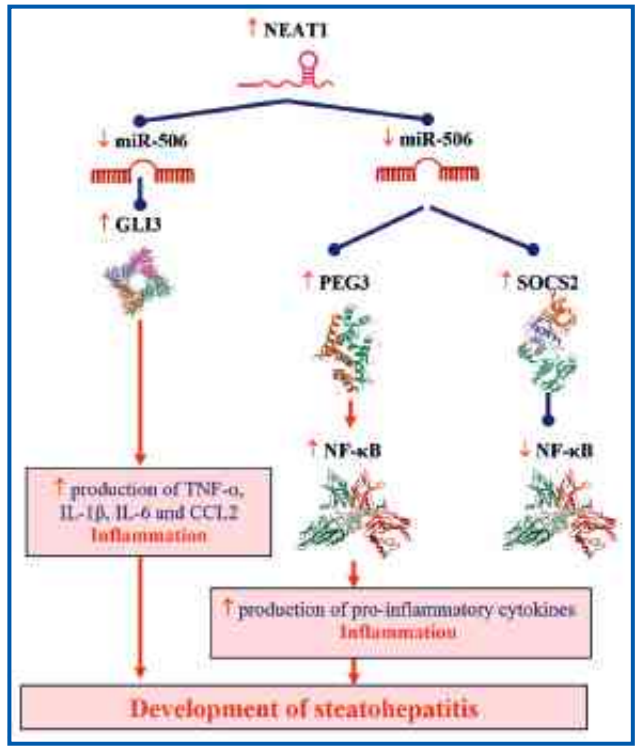

Figure 6. Role of NEAT1 in MASH development

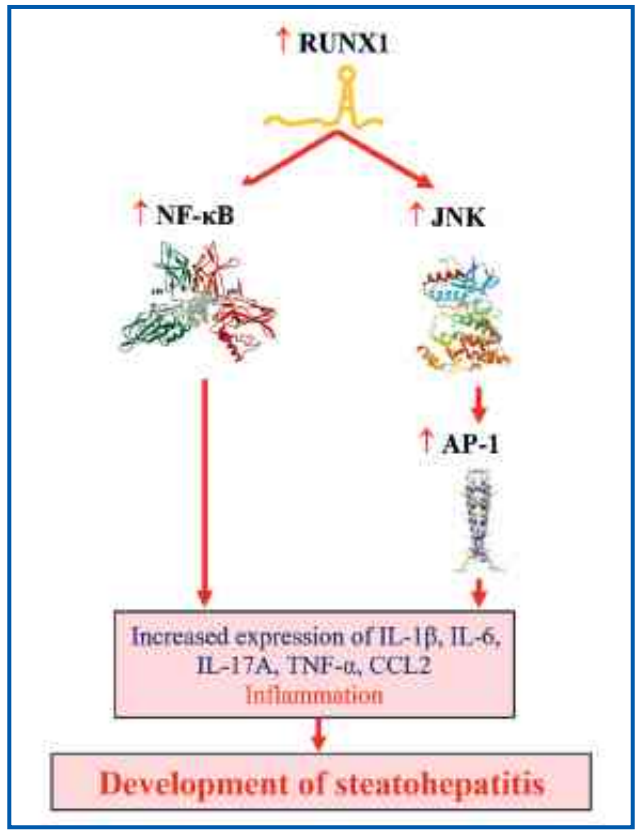

Figure 7. Role of RUNX1 in MASH development

Table 3. Molecular targets of lncRNA RUNX1 involved in inflammation [60]

Genes activated by lncR RUNX1	Genes suppressed by lncR RUNX1	Genes regulated by lncR RUNX1
JNK, PKC-E, CEBPB, TNFβ, IL1β, IL6, IL17A, NOX1, NOX2	*ADIPOR1, ADIPOR2, SOCS3, SIRT1, SPP1, TIMP1*	*TLR4, TLR5, NF-κB1*

leucine repeats and pyrin domain 3 (NLR family pyrin domain containing 3 — NLRP3) in steatohepatitis [64]. RIPK1 is known to be a determining component of the signaling pathways of inflammation, apoptosis and necroptosis. The interaction of RIPK1 with TGF-β-activated kinase 1 (TAK1) leads to the activation of the transcription factor NF-κB and the development of inflammation; RIPK1 interaction with the Fas adaptor protein associated with the death domain (FADD) induces cell apoptosis; and RIPK1 interaction with RIPK3 induces cell necroptosis [65–67]. L. Tao and colleagues [68] demonstrated that RIPK1 is highly expressed in human liver macrophages in MASH, and that its kinase activity largely determines the development of steatohepatitis in mice. Moreover, drug inhibition of RIPK1 kinase activity prevents the development of steatohepatitis [69].

On the other hand, activation of the expression of lncR NONMMUT010685 and NONMMUT050689 increases the activity of the enzyme ATP citrate lyase (ACLY), which, by converting citrate to acetyl-CoA, promotes the progression of MASH [70].

Anti-inflammatory lncRNAs

Lnc18q22.2. The expression of the liver-specific long noncoding RNA lnc18q22.2 (RP11-484N16.1), whose gene is located on chromosome 18, is significantly increased in patients with MASH, and the level of expression is directly related to the degree of lobular liver inflammation. The long noncoding RNA lnc18q22.2 is involved in mRNA translation, redox reactions, and the process of hepatocyte apoptosis. Knockdown of the lnc18q22.2 gene is accompanied by a sharp decrease in the expression of antiapoptotic genes, including genes of the BCL family proteins, which leads to a decrease in cell viability or a lethal phenotype in liver cell lines. The increased expression of lnc18q22.2 in the liver in MASH is associated with genes involved in the negative regulation of apoptosis, inhibiting apoptosis and necrosis of hepatocytes. It is believed that the increased expression of lnc18q22.2 is a component of a protective mechanism that protects liver tissue by inhibiting hepatocyte apoptosis [71]. It has also been confirmed that lnc18q22.2 has a pronounced oncogenic effect and plays a crucial role in enhancing the proliferation and migration of hepatocellular carcinoma cells [72].

Platr4. Mus musculus pluripotency-associated transcript 4 (Platr4; 2,168 nt URS000075A77E_10090) is highly associated with the development of lobular inflammation in MASLD patients. It has been shown that mice fed a methionine-choline-deficient diet (MCD), which induces steatohepatitis, have an increased expression of the lncR Platr4, which is associated with the functioning of the transcription factor NF-κB. The activated transcription factor NF-κB in MASH controls the expression of lncR Platr4, which in turn suppresses its activity and inactivates the NLRP3 inflammasome, preventing NF-κB from binding to κB sites on the promoters of target genes, including *Nlrp3* and *Asl*. The lncR Platr4 also has the ability to remove the NF-κB/Rxrα complex from the cell nucleus. Thus, overexpression of Platr4 leads to inhibition of the activity of the transcription factor NF-κB and the NLRP3 inflammasome, which leads to a decrease in the conversion of pro-IL-1β and pro-IL-18 to their active forms [73].

FLRL2. The development of MASH is accompanied by a decrease in the expression of long non-coding RNA 2 associated with fatty liver (fatty liver-related lncR 2 — FLRL2).

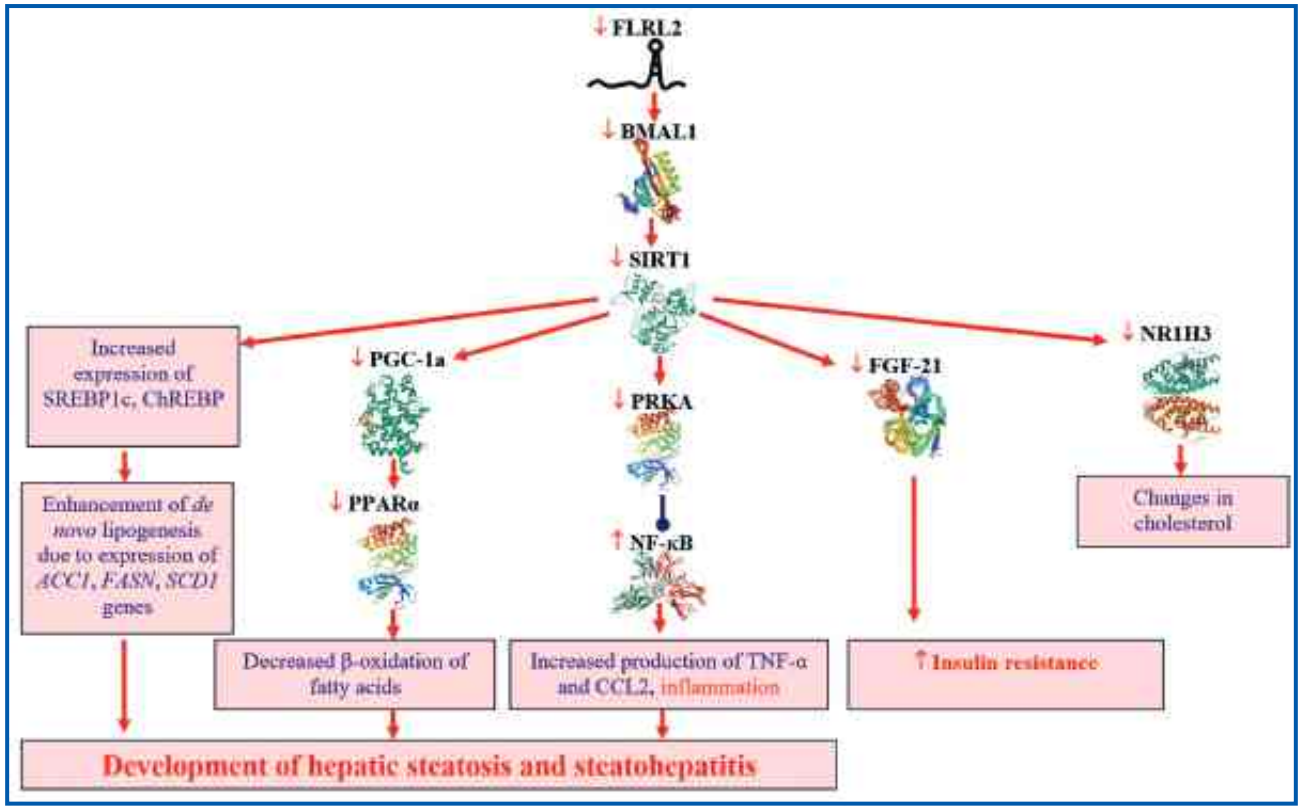

Figure 8. Role of FLRL2 in liver steatosis and MASH development

A decrease in the expression of lncR FLRL2 in MASLD leads to the inhibition of the genes of the protein similar to the nuclear translocator AHR (basic helix-loop-helix ARNT like 1 — BMAL1) and sirtuin (sirtuin 1 — SIRT1). Insufficient expression of SIRT1 leads to activation of lipogenic genes, transcription factor NF-κB, release of cytokine TNF-α and chemokine CCL2, development of ER-related stress, decreased activity of peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PPARGC1A/PGC-1α), PPARα receptors, serine/threonine AMP-activated protein kinase (PRKA), nuclear receptor subfamily 1 group H member 3/liver X receptor alpha (NR1H3/LXRα), and expression of FGF-21 (Fig. 8) [74, 75].

SRD5A3-AS1. Antisense RNA transcript 1 of the steroid 5 alpha-reductase 3 gene (lncR steroid 5 alpha-reductase 3 — SRD5A3-AS1), the expression of which is reduced in the development of MASH, exerts its influence on the innate immune system through miR-1205. Low expression of lncR SRD5A3-AS1 is accompanied by an increase in the number of functionally active miR-1205, which suppress the expression of moesin-ezrin-radixin like (MERLIN) tumor suppressor (NF2) and, as a result, contribute to a decrease in the activity of large tumor suppressor kinase 1 (LATS1). Low levels of LATS1 mediate the activation of yes-associated protein 1 (YAP1), which leads to the production of IL-6, supporting the inflammatory process in the liver tissue. YAP1 also induces the development of liver fibrosis by causing the production of TGF-β1, α-actin of smooth muscle myocytes (actin alpha 2, smooth muscle — ACTA2/α-SMA) (Fig. 9) [76].

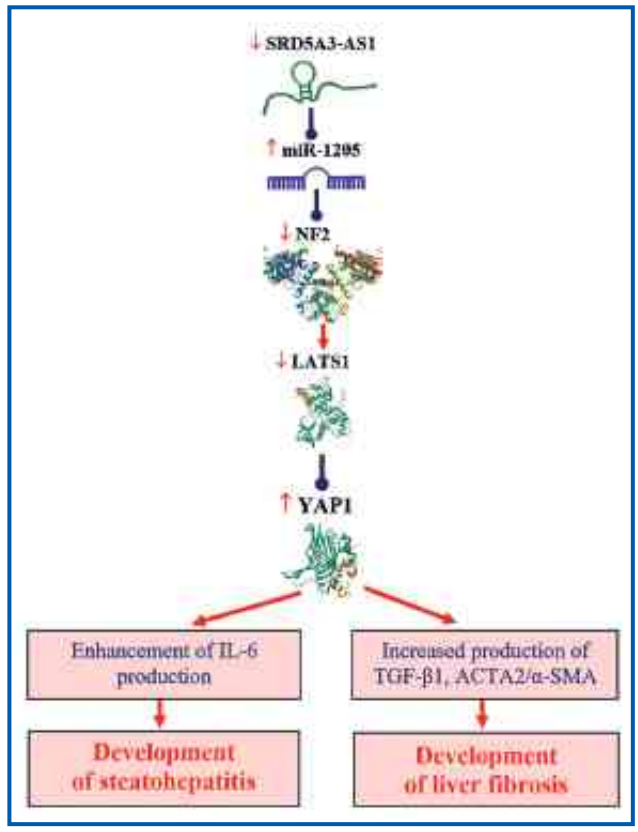

Figure 9. Role of SRD5A3-AS1 in MASH and liver fibrosis development

Conclusions

Inflammation of liver tissue is a key factor in the development of steatohepatitis in the progression of MASLD. It has been established that lncRs play a significant role in regulating the response of both the innate and adaptive immune systems, leading to the initiation and development of inflammation. Temporal analysis showed that periodic patterns of fluctuations in the expression of most lncRs lead to both the development of inflammation and the expression of pro-inflammatory cytokines. Inhibition of the transcription factor NF-κB suppresses the expression activity of most pro-inflammatory lncRs. Long non-coding RNAs are involved in the development of MASLD, mainly by providing the activity of pro-inflammatory signaling pathways, transcription factors (NF-κB, activator protein 1) and inflammasomes. Long noncoding RNAs, regulating the expression level of cytokines (IL-1β, IL-6, TNF-α) and chemokines (CCL2, CXCL1, CXCL5), determine the recruitment of proinflammatory immunocytes, local vascular response and, as a consequence, the degree of inflammatory reaction of liver tissue in MASLD. Long noncoding RNAs are characterized by a high degree of tissue specificity of gene expression, which allows us to consider certain of their aggregates as diagnostic markers of pathological processes localized in specific organs and systems. Thus, proinflammatory and anti-inflammatory lncRs are epigenetic regulators of liver inflammation that determine the development of MASH and can be considered as potential targets for anti-inflammatory drug therapy of patients with MASH.

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Епігенетичний вплив довгих некодуючих РНК на розвиток метаболічно асоційованого стеатогепатиту

Резюме. ***Актуальність.*** Довгі некодуючі РНК (long non-coding RNA — lncR) характеризуються високим ступенем тканиноспецифічної експресії генів, що дозволяє розглядати певні їх сукупності як діагностичні маркери метаболічно асоційованого стеатогепатиту (metabolic-associated steatohepatitis — MASH). ***Метою*** цього огляду є надати сучасні дані щодо ролі довгих некодуючих РНК в епігенетичному впливі на розвиток метаболічно асоційованого стеатогепатиту шляхом аналізу даних сучасної наукової літератури. ***Матеріали та методи.*** Проведено аналіз 76 літературних джерел баз даних MEDLINE, Embase, PreMedline In-Process & Other Non-Indexed Citations, The Cochrane Systematic Reviews Database, DARE, NHS EED та HTA, Web of Knowledge Science Citation Index, Web of Knowledge ISI Proceedings, CRD, BIOSIS за останні п'ять років, які були відібрані за ключовими словами: довгі некодуючі стеатогенні РНК; епігенетична регуляція; метаболічно асоційована жирова хвороба печінки; стеатотична хвороба печінки, асоційована з метаболічною дисфункцією; ожиріння. PROSPERO CRD420250652980. ***Аналіз літератури.*** Темпоральний аналіз показав, що періодичні флуктуації експресії більшості lncR призводять до розвитку як запалення, так і продукції прозапальних цитокінів. Інгібування фактора транскрипції NF-κB пригнічує активність експресії більшості прозапальних lncR. Довгі некодуючі РНК беруть участь у розвитку MASH переважно шляхом активації прозапальних сигнальних шляхів, факторів транскрипції (NF-κB, AP-1) та інфламасом. Довгі некодуючі РНК, регулюючи рівень експресії цитокінів (IL-1β, IL-6, TNF) та хемокінів (CCL2, CXCL1, CXCL5), визначають рекрутинг прозапальних імуноцитів, місцеву судинну реакцію і, як наслідок, ступінь запальної реакції тканини печінки при стеатотичній хворобі печінки, асоційованій із метаболічною дисфункцією. ***Висновки.*** Прозапальні й протизапальні lncR є епігенетичними регуляторами запалення печінки, що визначають розвиток MASH і можуть розглядатися як потенційні мішені протизапальної медикаментозної терапії хворих на MASH.

Ключові слова: діти; ожиріння; метаболічно асоційований стеатогепатит; довгі некодуючі РНК; огляд літератури