MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE
SUMY STATE UNIVERSITY
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Eastern Ukrainian Medical Journal

116, Kharkivska st., Sumy 40007, Ukraine eumj.med.sumdu.edu.ua
e-mail: eumj@med.sumdu.edu.ua ISSN: 2663-5909 (print)/2664-4231 (online)

How to cite: Abaturov O, Nikulina A. Epigenetic influence of long non-coding RNAs on the development of metabolicly associated steatohepatitis. *East Ukr Med J*. 2025;13(3):606-621

DOI: https://doi.org/10.21272/eumj.2025;13(3):606-621

ABSTRACT

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EPIGENETIC INFLUENCE OF LONG NON-CODING RNAS ON THE DEVELOPMENT OF METABOLICLY ASSOCIATED STEATOHEPATITIS

Metabolically associated steatohepatitis (MASH) is a progressive form of metabolically associated fatty liver disease (MAFLD), characterized by lobular liver inflammation. From a diagnostic point of view, lobular liver inflammation in patients with MAFLD is the main pathomorphological sign of the transition of simple hepatic steatosis to steatohepatitis. It has been demonstrated that various long non-coding RNAs play a significant role in the regulation of the response of both the innate and adaptive immune systems, participate in the regulation of proliferation, differentiation and activation of immune cells. Long noncoding RNAs are involved in the development of MAFLD, mainly by providing activity to pro-inflammatory signaling pathways, transcription factors (NF-κB, AP-1) and inflammasomes. Long noncoding RNAs, by regulating the expression level of cytokines (IL-1β, IL-6, TNF-a) and chemokines (CCL2, CXCL1, CXCL5), determine the recruitment of pro-inflammatory immunocytes, local vascular response and, as a consequence, the degree of inflammatory reaction of liver tissue in MAFLD. The state of the lncR transcriptome of structural liver cells, resident and recruited immune cells in the liver determines the likelihood of developing steatohepatitis in MAFLD. The results of deep sequencing of the new generation, carried out in mini-pigs, indicate that the induction of steatohepatitis is accompanied by differential expression of 89 lncRs, the main molecular targets of which are the genes *Ppar*, *Fads2*, *Dgat2*, *Acaa2*, *Cyp2e1*, *Adh4* and *Fos*. Thus, pro-inflammatory and anti-inflammatory lncRs are epigenetic regulators of liver inflammation, which determine the development of MASH and are considered as potential targets for anti-inflammatory drug therapy of patients.

Keywords: *children, obesity, metabolically associated steatohepatitis, long non-coding RNA, literary review.*

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ЕПІГЕНЕТИЧНИЙ ВПЛИВ ДОВГИХ НЕКОДУЮЧИХ РНК НА РОЗВИТОК МЕТАБОЛІЧНО АСОЦІЙОВАНОГО СТЕАТОГЕПАТИТУ

Метаболічно асоційований стеатогепатит (МАСГ) – прогресуюча форма метаболічно асоційованої жирової хвороби печінки (МАЖХП), яка характеризується лобулярним запаленням печінки. Метаболічно асоційований стеатогепатит несе високий ризик як виникнення різноманітних метаболічних порушень, цирозу печінки, гепатоцелюлярної карциноми, так і несприятливого результату захворювання. З точки зору діагностики лобулярне запалення печінки у хворих на МАЖХП є основною патоморфологічною ознакою переходу простого стеатозу печінки до стеатогепатиту. Продемонстровано, що різноманітні довгі некодуючі РНК (long non-coding RNA – lncR) відіграють істотну роль у ругуляції реакції у відповідь як вродженої так і адаптивної імунної системи, беруть участь у регулюванні проліферації, диференціювання та активації імунних клітин, зумовлюють ініціацію й розвиток запалення. Довгі некодуючі РНК беруть участь у розвитку МАСГ, переважно надаючи активності прозапальним сигнальним шляхам, факторам транскрипції (NF-κB, AP-1) та інфламасомам. Довгі некодуючі РНК, регулюючи рівень експресії цитокінів (IL-1β, IL-6, TNF-a) та хемокінів (CCL2, CXCL1, CXCL5), визначають рекрутування прозапальних імуноцитів, місцеву судинну реакцію і, як слідство, ступінь запальної реакції тканини печінки при МАЖХП. Стан транскриптому lncR структурних клітин печінки, резидентних та рекрутованих у печінку імуноцитів визначає ймовірність розвитку стеатогепатиту при МАЖХП. Результати глибокого секвенування нового покоління, проведеного у міні-свиней, свідчать, що індукування стеатогепатиту супроводжується диференційованою експресією 89 lncR, основними молекулярними мішенями яких є гени *Ppar, Fads2, Dgat2, Acaa2, Cyp2e1, Adh4* і *Fos.* Довгі некодуючі РНК характеризуються високим ступенем тканеспецифічності експресії генів, що дозволяє розглядати певні їх сукупності як діагностичні маркери патологічних процесів, локалізованих у конкретних органах та системах. Таким чином, прозапальні та протизапальні lncR є епігенетичними регуляторами запалення печінки, які визначають розвиток МАСГ і розглядаються як потенційні мішені протизапальної медикаментозної терапії хворих.

Ключові слова: *діти, ожиріння, метаболічно асоційований стеатогепатит, довгі некодуючі РНК, літературний огляд.*

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INTRODUCTION

The development of hepatic steatosis in metabolic associated fatty liver disease (MAFLD) at a certain point in the pathogenesis of the disease leads to the initiation of the inflammatory process, which determines the manifestation of steatohepatitis [1, 2, 3]. Metabolic associated steatohepatitis (MASH) is a progressive form of MAFLD, which is characterized by lobular liver inflammation. From a diagnostic point of view, lobular liver inflammation in patients with MAFLD is the main pathomorphological sign of the transition of simple hepatic steatosis to steatohepatitis [4, 5, 6]. Metabolic associated steatohepatitis carries a high risk of both the occurrence of various metabolic disorders, the development of liver cirrhosis, hepatocellular carcinoma, and an unfavorable outcome of the disease [7, 8, 9].

To date, a variety of long non-coding RNAs (lncRs) have been shown to be involved in the regulation of proliferation, differentiation, and activation of immune cells, including monocytes, macrophages, dendritic cells, neutrophils, T cells, and B cells [10, 11]. LncRs are thought to be important regulators of the inflammatory response, exerting their effects by modulating the transcription levels of pro-inflammatory and anti-inflammatory genes, including in the development of steatohepatitis [12, 13, 14]. The state of the lncR transcriptome of liver structural cells, resident, and liver-recruited immunocytes determines the likelihood of developing steatohepatitis in MAFLD [15, 16].

The role of lncR in the development of liver inflammation in patients with MAFLD

Numerous and diverse lncRs are involved in the development of liver inflammation in patients with MAFLD, affecting pro- and anti-inflammatory molecular signaling pathways (Table 1).

The results of next-generation deep sequencing performed in minipigs indicate that the induction of steatohepatitis is accompanied by differential expression of 89 lncRs, the main molecular targets of which are the genes *Ppar*, *Fads2*, *Dgat2*, *Acaa2*, *Cyp2e1*, *Adh4*, and *Fos* [19, 20, 21].

Table 1 – **Long non-coding RNAs associated with the development of MASH** [17, 18]

lncR	**Molecular target**	**Signal cascade and effect of action**
Enhancement of expression		
Gm9795	ERN1	NF-κB and ERK1 signaling pathway, induction of inflammatory response
HOTAIR	SRSF1	NF-κB signaling pathway
HULC	MAPK	JNK signaling pathway, induction of inflammatory response
LeXis		Induction of inflammatory response
lnc18q22.2	BCL family proteins	Apoptosis of hepatocytes
linc00907	miR-942-5p	TAOK1, induction of inflammatory response
lncTNF		NF-κB signaling pathway, induction of inflammatory response
MALAT1	SAA3	mTOR/S6K1 signaling pathway, induction of inflammatory response
NEAT1	miR-129-5p, miR-506	NF-κB signaling pathway, regulation of inflammatory response
Platr4	NLRP3	Reduction of IL-1β and IL-18 activation by inhibiting NLRP3-inflammasome
RUNX1	TLR4, TLR5, NF-κB1, NF-κB2, TNF, ADIPOQ and IL-6	NF-κB signaling pathway, regulation of inflammatory response
NONMMUT010685	XBP1, ACLY	JNK signaling pathway, induction of steatosis and inflammatory response
NONMMUT050689	RIPK1, ACLY	Induction of steatosis and inflammatory response and necroptosis
Reduction of expression		
FLRL2	ARNTL	NF-κB signaling pathway
RUNX1	TLR4, TLR5, NF-κB1, NF-κB2, TNF, ADIPOQ and IL-6	NF-κB signaling pathway, regulation of inflammatory response
SRD5A3-AS1	miR-1205	YAP1 signaling pathway

Pro-inflammatory lncR

Gm9795. The long non-coding RNA Gm9795 is transcribed from the lipid transfer domain-associated StAR pseudogene sequence located on chromosome 10. The expression of lncR Gm9795 is closely associated with the severity of MASH. The Gm9795 transcript promotes the expression of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukins (IL) IL-1β, IL-6, through the activation of NF-κB- and JNK-associated signaling pathways. It has been demonstrated that lncR Gm9795 activates the expression of endoplasmic reticulum to nucleus signaling 1 (ERN1), which is a key molecule of ER-related stress and activates both c-Jun NH2-terminal kinase (JNK) and the transcription factor NF-κB, inducing the inflammatory process (Fig. 1) [22].

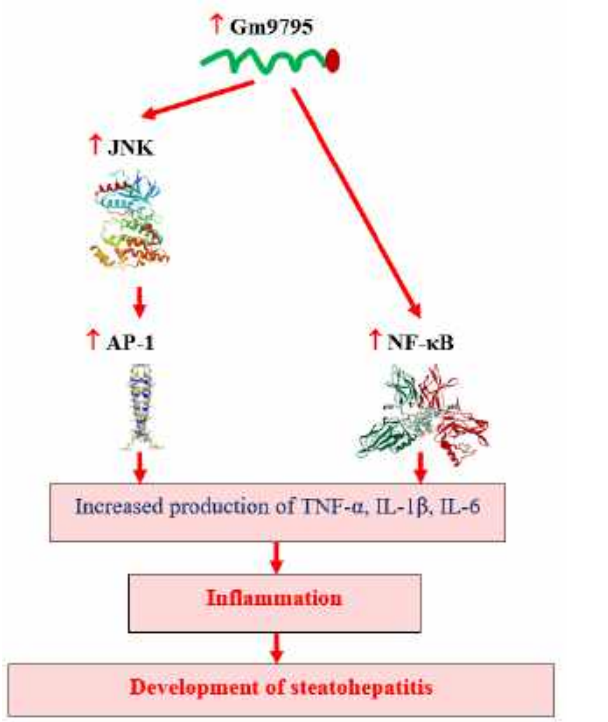

Fig. 1. The role of Gm9795 in the development of MASH

Note: molecular models adapted from the Protein data bank

HOTAIR. It has been demonstrated that HOX transcript antisense RNA (HOTAIR) is highly expressed in HepG2 cells (human hepatocellular carcinoma cell line) treated with free fatty acids (FFA). 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 stabilization of carbohydrate-responsive element-binding protein (ChREBP) mRNA [23]. The ChREBP protein is a major helix-loop-helix leucine zipper transcription factor that 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) [24]. Avisankar Chini et al. [25] 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 MAFLD 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).

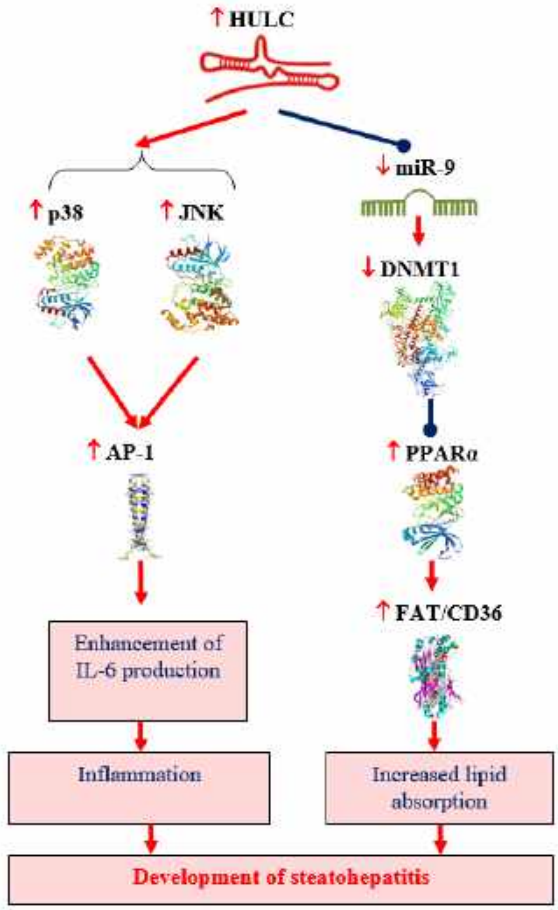

Fig. 2. The role of HULC in the development of MASH

Note**:** Red arrows – activation; blue arrows – inhibition, molecular models adapted from the Protein data bank

Inhibition of both HULC and p38 and JNK kinases improves the histological state of liver tissue in experimental MASH, including reducing signs of steatosis, inflammation and fibrosis [26].

Also, lncR HULC induces methylation of CpG islands of DNA in the miR-9 promoter region by increasing the expression of DNA (cytosine-5) - methyltransferase 1 (DNMT1). Given that miR-9 represses the *PPARA* gene, a decrease in the number of its transcripts leads to activation of PPARα, which contributes to the accumulation of lipids in hepatocytes [27].

LeXis. The 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 [28, 29]. It is necessary to emphasize the special influence of LeXis on the development of inflammatory reactions in the liver tissue of patients with MAFLD. Thus, in patients with MASH, the concentration level of LeXis transcripts in the blood serum is significantly higher than in patients with hepatic steatosis [30].

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 [31]. The serine/threonine protein kinase TAOK1 increases lipopolysaccharide-induced macrophage production of proinflammatory cytokines, such as IL-6, IL-12p40, and TNF-α, by activating mitogen-activated protein kinase MAPK1 [32]. 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) [33].

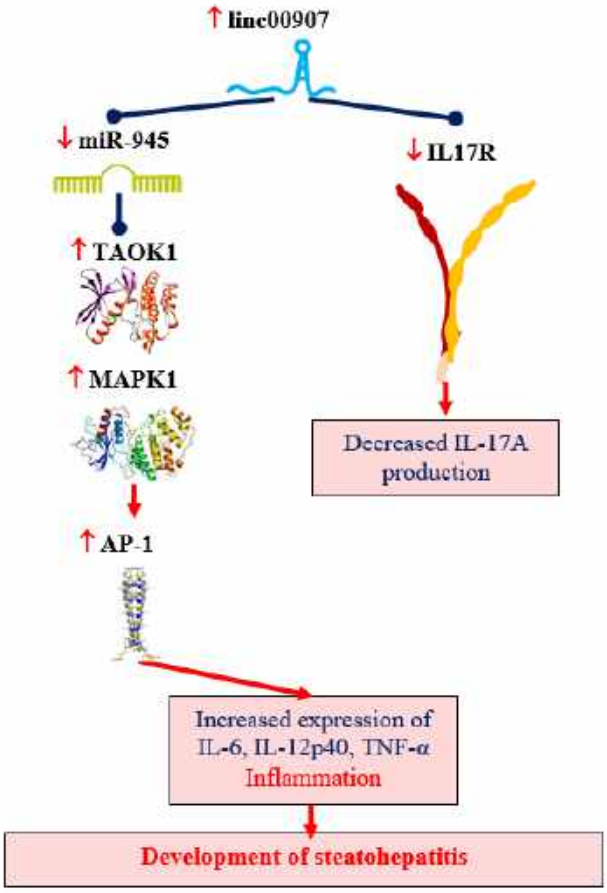

Fig. 3. The role of linc00907 in the development of MASH

Note: Red arrows – activation; blue arrows – inhibition, TAOK1 molecule model adapted from Yu L. et al. [34]

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 after stimulation with pro-inflammatory cytokines TNF-α, IL-1β. Thus, when the TNF-α gene is stimulated in HepG2 cells, the level of expression of the intergenic lncR lncTNF increases almost 20-fold. In liver biopsies of patients with MAFLD, the level of lncTNF expression positively correlates with the degree of lobular liver inflammation. Long non-coding RNA lncTNF activates the transcription factor NF-κB. After activation, 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 pro-inflammatory 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 MAFLD [36].

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 [36]. 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 [37]. 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 [38]. In hepatic stellate cells (HSC) lncR MALAT1 induces the synthesis of the chemokine CXCL5 (ENA-78), which recruits and activates neutrophils to the lesion site (Fig. 4) [39].

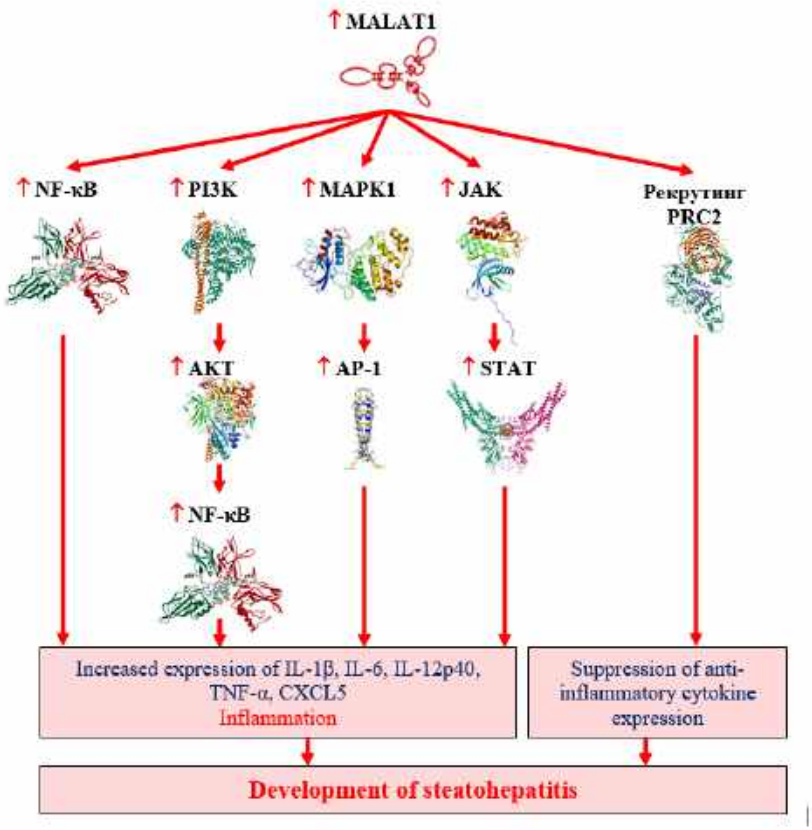

Fig. 4. The role of MALAT1 in the development of MASH
Note**:** molecular models adapted from the Protein data bank

Neutrophils recruited to the liver tissue determine the development of MASH. 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 [40, 41].

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 a member of the hypoxia-inducible factor 1 (HIF1) complex and form a dimer with the aromatic hydrocarbon receptor (AHR), facilitating the interaction of AHR with DNA [42].

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 [43, 44]. 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 [45, 46]. However, the effect of the lncR MALAT1 on ARNT probably does not cause a genetically significant effect, since ARNT expression in liver biopsies of patients with MASH is significantly lower than in healthy people [42]. 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, Christopher Scott and colleagues [42] showed that suppression of ARNT expression is accompanied by increased expression levels of CXCL1 (GROα), monocyte chemoattractant 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 [47].

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. HCG18 has been shown to be involved in the development of steatosis, liver inflammation, and insulin resistance [48].

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 pool of miR-197-3p, which leads to increased expression of the *IL18* gene [49]. It is known that in mice receiving high fat diet (HFD) and humans with MAFLD, the expression of the *IL18* gene, which is actively involved in the development of MASH, is significantly increased (Fig. 5) [50, 51].

NEAT1. Nuclear enriched abundant transcript 1 (homo sapiens (human) nuclear enriched abundant transcript 1 – NEAT1; 3,756 nt URS000075DAEC_9606), the level of expression 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) [52, 53].

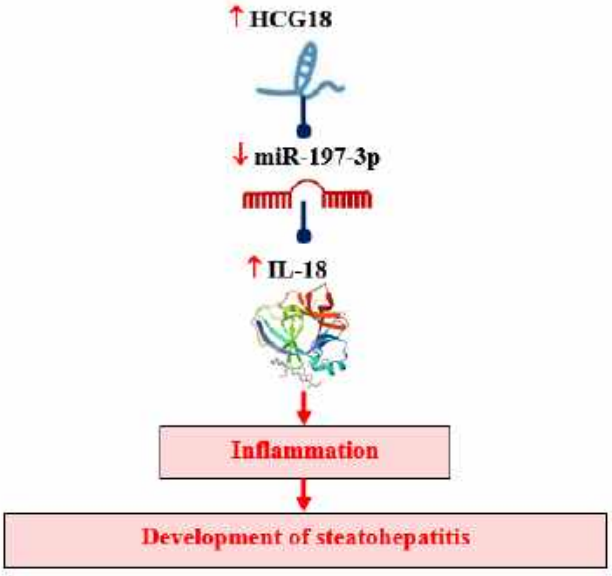

Fig. 5. The role of HCG18 in the development of MASH

Note: Red arrows – activation; blue arrows – inhibition, molecular models adapted from the Protein data bank

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 MAFLD, 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 [54]. It has been shown that macrophages stimulated by 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 [55].

GLI3 activation induces the production of pro-inflammatory cytokines and chemokines by immunocytes: TNF-α, IL-1β, IL-6 and CCL2 [53].

Table 2 – **Target miRs of NEAT1 transcript** [52, 53]

Targeted miRs	Signaling 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	NF-κB activation
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

Sequestration of miR-129-5p by lncR NEAT1 reduces the inhibitory effect 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 [56]. On the other hand, sequestration of miR-129-5p leads to increased expression of the suppressor of cytokine signaling 2 (*SOCS2*) gene [57]. 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 reduction in SOCS2 activity is highly correlated with the degree of liver inflammation during the development of MASH (Fig. 6) [58].

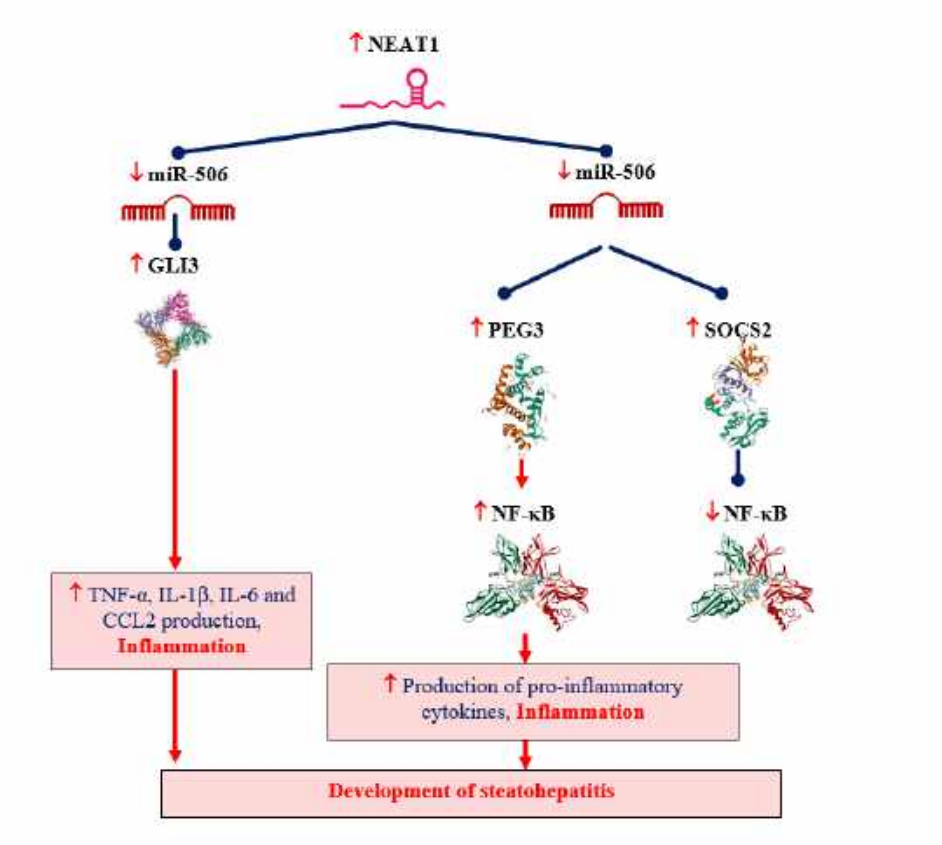

Fig. 6. The role of NEAT1 in the development of MASH

Note**:** Red arrows – activation; blue arrows – inhibition, molecular models adapted from the Protein data bank

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 IBD by regulating the activity of TLR4, TLR5, NF-κB, JNK, TNF, CCL2 and others (Table 3, Fig. 7) [60].

The expression of the lncR RUNX1 increases in the early stages of MAFLD and decreases with the progression of MASH [60].

It has been demonstrated that in the liver tissue of MAFLD, 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].

Table 3 – **Molecular targets of lncR RUNX1 involved in the development of inflammation** [59]

Genes which expression is activated by the lncR RUNX1	**Genes which expression is suppressed by lncR RUNX1**	**Genes which expression is regulated by the lncR RUNX1**
JNK, PKC-E, CEBPB, TNFβ, IL-1β, IL6, IL17A, NOX1, NOX2	*ADIPOR1, ADIPOR2, SOCS3, SIRT1, SPP1, TIMP1*	*TLR4, TLR5, NF-κB*

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 X-box binding protein 1 (x-box binding protein 1 – XBP1) and receptor-interacting protein 1 kinase (RIPK1) genes, respectively [62]. At the same time, data are presented that indicate that the activity of the

XBP1 factor is significantly increased in the 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 promotes the activation of the oligomerization domain that binds nucleotides rich in leucine repeats and pyrin domain 3 (NLR family pyrin domain containing 3 – NLRP3) in steatohepatitis [64].

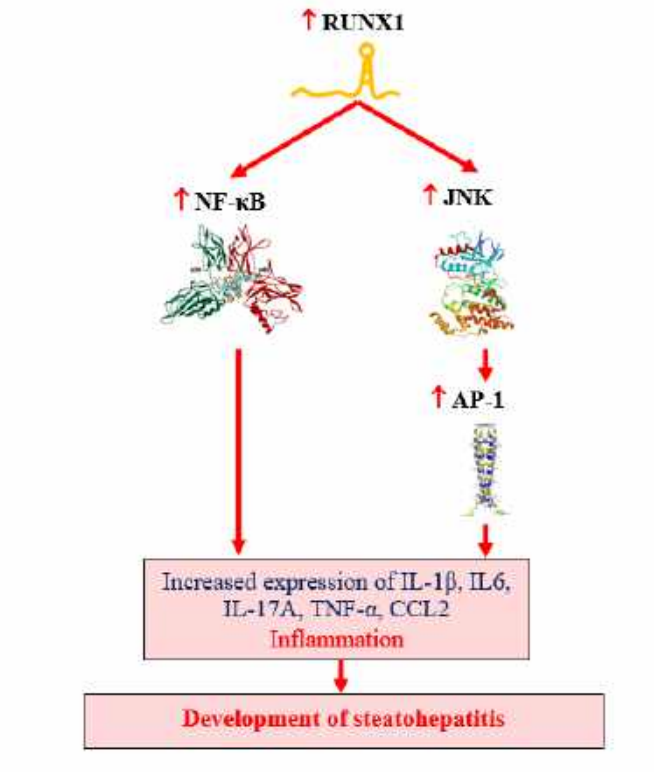

Fig. 7. The role of RUNX1 in the development of MASH

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 via death domain (FADD) induces cell apoptosis; and RIPK1 interaction with RIPK3 induces cell necroptosis [65, 66, 67]. Liang 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 lncR expression NONMMUT010685 and NONMMUT050689 increases the activity of the enzyme ATP citrate lyase (ACLY), which, by converting citrate into acetyl-CoA, promotes the progression of MASH [70].

Anti-inflammatory lncRs

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 IAHD, 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. Knockout 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. Transcript 4, associated with pluripotency (mus musculus pluripotency-associated transcript 4 - Platr4; 2,168 nt URS000075A77E_10090), is highly associated with the development of lobular inflammation in patients with MAFLD. It has been shown that mice fed a methionine-choline-deficient diet (MCD), which induces the development of 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 the lncR Platr4, which in turn suppresses its activity and also inactivates the NLRP3 inflammasome, preventing binding of NF-κB 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, which is associated with a fatty liver (fatty liver-related lncR 2 – FLRL2). A decrease in the expression of lncR FLRL2 in MAFLD leads to the inhibition of the genes of a 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].

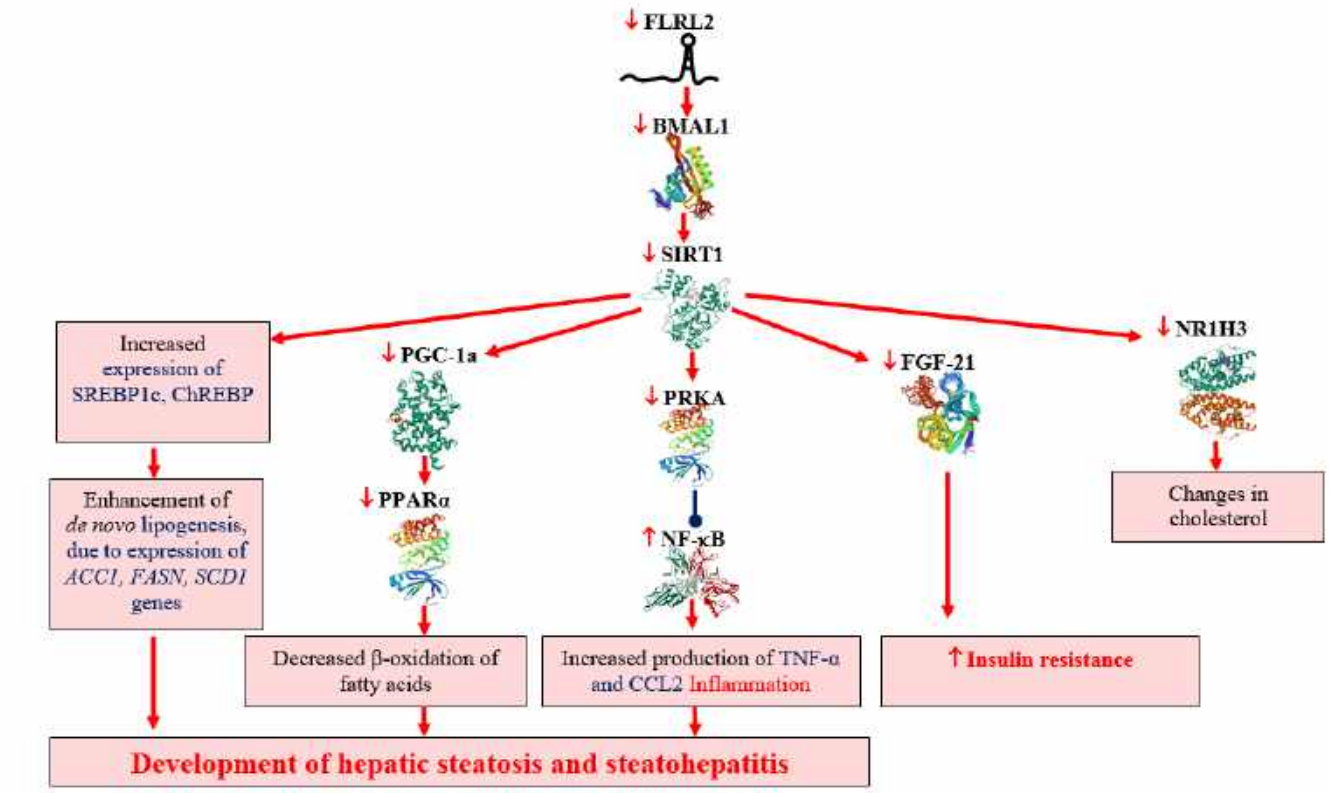

Fig. 8. The role of FLRL2 in the development of hepatic steatosis and MASH

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].

CONCLUSIONS

Inflammation of the liver tissue is a key factor in the development of steatohepatitis in the process of progression of MAFLD [77].

Today, it has been established that lncRs play an essential role in regulating the response of both the innate and adaptive immune systems, determining the initiation and development of inflammation. Temporal analysis has shown that the periodic patterns of fluctuations in the expression of most lncRs in the development of inflammation are the same as those 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 MASH, mainly by providing the activity of pro-inflammatory signaling pathways, transcription factors (NF-κB, AP-1) and inflammasome. Long non-coding RNAs, regulating the level of expression of cytokines

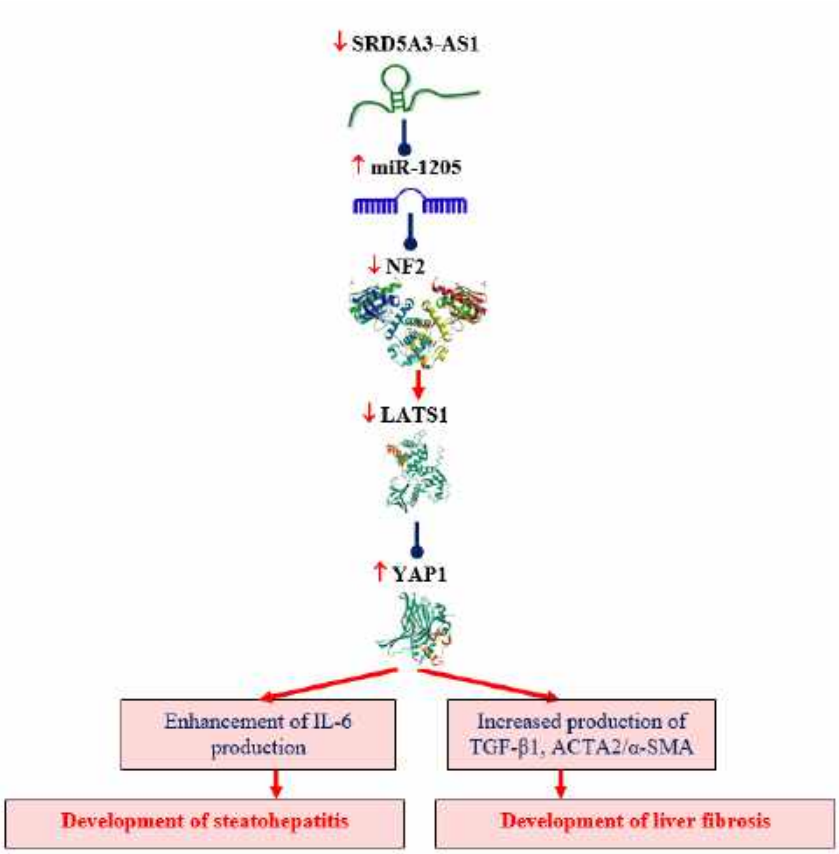

Fig. 9. The role of SRD5A3-AS1 in the development of MASH and liver fibrosis
Note**:** Red arrows – activation; blue arrows – inhibition, molecular models adapted from the Protein data bank

(IL-1β, IL-6, TNF-a) and chemokines (CCL2, CXCL1, CXCL5), determine the recruitment of pro-inflammatory immunocytes, the local vascular reaction and, as a consequence, the degree of inflammatory reaction of liver tissue in MAFLD. Long noncoding RNAs are characterized by a high degree of tissue specificity of gene expression, which allows us to consider certain of their sets as diagnostic markers of pathological processes localized in specific organs and systems. Thus, pro-inflammatory and anti-inflammatory lncRs are epigenetic regulators of liver inflammation that determine the development of MASH, and may be considered as potential targets for anti-inflammatory drug therapy in MASH patients.

PROSPECTS FOR FUTURE RESEARCH

The following fundamental studies may provide a targeted basis for the development of new drugs and technologies for the treatment of steatohepatitis.

AUTHOR CONTRIBUTIONS

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

FUNDING

The study is a fragment of the research work of the Dnipro State Medical University on the topic "Precision approaches to the diagnosis and treatment of somatic and endocrine diseases in children", state registration number 0123U105100.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Received 07.04.2025 ***Accepted 15.06.2025***

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